Foodborne diseases in Switzerland: understanding the burden of illness pyramid to improve Swiss infectious disease surveillance

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ii Executive summary

Background Infectious diseases cause a considerable burden to population health worldwide. Different types of surveillance systems have been implemented to assess changes in disease frequency, to identify outbreaks, and to detect newly emerging diseases aiming at early detection of epidemics, disease control and prevention. Passive surveillance systems are mostly used, measuring the 'incidence of notified cases' rather than the incidence (frequency) of disease at population level. Foodborne pathogens, for example, do not always cause disease in infected individuals. Sick individuals – mostly presenting with acute gastroenteritis (AG) – do not always seek healthcare. Of those approaching a physician, aetiology of disease is investigated only in a fraction of patients. Finally, not all cases with a positive laboratory finding for a notifiable pathogen might be reported to the surveillance system. This "loss" of cases along the so-called burden of illness pyramid – from infection to actual notification in the surveillance system –, or the factor of underestimation, depends on the pathogen and the local health (care) system.
Two surveillance systems are implemented in Switzerland which are important for infectious disease surveillance and early detection: the National Notification System for Infectious Diseases (NNSID) and the Swiss Sentinel Surveillance Network (*Sentinella*). The NNSID is based on the Epidemics Act and is the only mandatory surveillance system in Switzerland covering the entire nation and involving all physicians and diagnostic laboratories. The Epidemics Act defines which observations have to be reported to the NNSID and stipulates the time frame for reporting. *Sentinella* is a network where information from a subset of voluntarily participating physicians is collected to study diseases and health issues at the primary care level.
It was estimated that 31 foodborne hazards caused 33 million Disability Adjusted Life Years (DALYs) and 600 million cases of illness worldwide in 2010. In European countries, the incidence of AG was estimated at 0.3–1.5 disease episodes per person-year. *Campylobacter* spp. is the most frequent, notifiable, bacterial foodborne disease, both in the European Union (EU) and in Switzerland and showed increasing trends in the past decade. In contrast, *Salmonella* spp. notifications were decreasing in the EU and in Switzerland while enterohaemorrhagic *Escherichia coli*

(EHEC) notifications were increasing in Switzerland but remained stable in the EU.
In Switzerland, information on foodborne diseases is mostly restricted to data obtained through the NNSID. Many factors contribute to underestimation and hence, it is unclear how well notification rates reflect disease incidence.

Objectives This work aimed at contributing to a better understanding of the burden of illness pyramid for foodborne infections in Switzerland and, thus, contributing to improve infectious disease surveillance and control. It sought to investigate the frequency of cases of foodborne disease or AG at different levels of the burden of illness pyramid. Further, it should describe trends and understand factors leading to case registration. Finally, a better understanding of disease epidemiology will lead to improvements in early disease detection and control.

Methods This research work consisted of several projects characterising different levels of the burden of illness pyramid from its tip to the wide (population) base. In a first step, notification data of *Campylobacter*, *Salmonella* and hepatitis A were analysed to describe trends since 1988. Considering that the number of tests conducted can (strongly) influence the number of cases detected, we studied the trend in the proportion of positive tests out of all tests performed – the positivity rate – for *Campylobacter*, *Salmonella* and EHEC over a 10-year period. Personnel of diagnostic laboratories was consulted to assess current laboratory practices, focussing on the diagnosis of EHEC infections. Furthermore, we conducted a qualitative study among Swiss general practitioners (GPs) to understand physicians' approaches towards anamnesis (including diagnosis) and treatment of AG in general and campylobacteriosis in particular. Subsequently, these findings were complemented by a study within *Sentinella*, where the number of patient consultations due to AG at primary care level was assessed. Physicians reported all first consultations due to AG including information on hospitalisation, stool diagnostics, treatment and inability to work.
Findings of the aforementioned studies, expert consultations and publicly available data were used to explore healthcare costs for AG and campylobacteriosis in Switzerland for the first time. Four distinct patient management models were defined for which frequency and individual case management costs were estimated. Extrapolations of these results were used to assess total direct healthcare costs for Switzerland. Finally, bringing together all study results of the above-mentioned stud-

ies, we identified the need to understand the burden of AG at the basis – at the level of the general population. Therefore, a study protocol to investigate the lowest level of the burden of illness pyramid – the incidence and aetiology of AG at population-level – was developed.

Results *Campylobacter* case notifications increased between 1988 and 2013 while *Salmonella* case notifications decreased. Highest case numbers for *Campylobacter* were recorded in 2012 with 8'480 cases. For *Salmonella*, peak levels were observed in 1992 with 7'806 cases. While showing inverse long-term trends, both pathogens follow a similar seasonality pattern with higher case numbers during summer months. In winter, a short but pronounced peak over Christmas and New Year was observed for *Campylobacter*. Positivity rates for *Campylobacter* increased from 2003 to 2012 while they decreased for *Salmonella*. At the same time, the number of tests conducted increased for both pathogens. Hepatitis A case notifications decreased between 1988 and 2016 in Switzerland, similar to *Salmonella*. The strongest decline was observed in the early 1990's, starting even before active immunisation was introduced in 1992. At the same time, there was a shift in reported risk exposures for hepatitis A: Intravenous drug use was the most frequently mentioned risk exposure at the beginning of reporting while, more recently, contaminated food and beverages were mentioned predominantly as possible sources of infection. Notification forms and content were changed multiple times during this 29-year period.
Laboratory experts unanimously think that the increase in EHEC notifications which is observed in the NNSID can be explained by the introduction of multiplex gastrointestinal PCR panels. Those panels also test for EHEC while traditional culture-based stool testing mostly considered *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. only. Nevertheless, there was also an increase in positivity rate observed for EHEC from 2007 to 2016 apart from an increase in testing frequency.
Preliminary analysis of surveillance data on testing frequency, which was collected since the implementation of the new Epidemics Act in 2016, reveals several issues regarding data quality related to the complex and heterogeneous "laboratory landscape" in Switzerland.
AG case management of Swiss GPs is diverse. Nevertheless, four distinct strategies could be identified. The majority of patients is managed with a "wait & see" approach based on the knowledge that AG is usually self-limiting. Two of the four approaches include microbiological investigation (stool testing), with antibiotic treatment started either before or after availability of stool test results. Swiss GPs perceive AG and

campylobacteriosis as diseases of minor importance in their daily work but acknowledge that they can be disturbing and debilitating for the individual patient. Surveillance of AG in *Sentinella* revealed that 8.5% of AG patients received antibiotic therapy, for 12.3% stool testing was initiated and 86.3% of employees were not able to work. Extrapolation of case numbers suggested an incidence of AG at primary care level of 2'146 first consultations per 100'000 inhabitants in Switzerland in 2014. Direct healthcare costs of AG and campylobacteriosis in Switzerland were estimated at €29–45 million in 2012. Of these, €8.3 million were attributed to the 8'480 laboratory-confirmed campylobacteriosis patients registered in the NNSID. It was estimated that 233'000–629'000 patients consulted a physician without further stool testing resulting in healthcare costs of €9.0–24.2 million in 2012. Work-loss and other non-healthcare costs associated with AG and campylobacteriosis were not assessed in this study. However, this socio-economic burden will be explored in more detail in an upcoming study on the **bu**rden of **g**astroenteritis in **S**witzerland ("BUGS study"). The BUGS study was developed to explore the "true" incidence, burden of disease, aetiology and socio-economic impact of AG in Switzerland; to finally understand the entire burden of AG at population level and the level of underestimation of cases notified to the NNSID. BUGS is a prospective cohort study weekly following up individuals of the general population during a 52-week period. Furthermore, the presence of four pathogenic bacteria (*Campylobacter*, *Salmonella*, *Shigella* and EHEC) and of bacteria harbouring selected antibiotic resistances (fluoroquinolone, extended-spectrum β-lactamase (ESBL), carbapenemase and mobilised colistin resistance-1 (mcr-1)) is assessed in cohort participants during an asymptomatic period.

Conclusions The NNSID is a useful and stable surveillance system and health system component which is well accepted by stakeholders. Surveillance data from the NNSID suggest increasing trends for *Campylobacter* and EHEC and decreasing trends for *Salmonella* and hepatitis A. Our complementary research studies come to the same conclusion even though trends might appear more pronounced (EHEC) or attenuated (*Salmonella*) in the notification system than the true incidence due to changes in diagnostic procedures. Hence, from what we know we cannot fully explain the increase of *Campylobacter* and EHEC seen in the notification system. Therefore, an increase in disease incidence or an outbreak must be considered from an epidemiological perspective. Furthermore, underestimation is probably substantial. Cases seen in the NNSID are more likely to be severe, have co-morbidities or present with

well-known risk factors. Assessing all factors contributing to underestimation on a regular basis is hardly possible. Instead, complementary research such as the proposed BUGS study are needed.
The information on disease trends and individual cases obtained through the NNSID should be restricted to the minimum (with high data quality) rather than expanded to keep the system as simple and responsive as possible, providing reliable information. This enables the system to stay alert to and be prepared for a rapid response in the event of changing case numbers. Maintaining systems like *Sentinella* and fostering strategic research partnerships for action is important to be able to react immediately once an outbreak or a change in disease epidemiology is suspected. Pathways to provide good evidence for public health policy and distribute information to stakeholders should be established.

iii Zusammenfassung

Hintergrund Infektionskrankheiten verursachen weltweit eine beträchtliche Krankheitsbürde. Um Änderungen in der Häufigkeit von bekannten sowie neuen Infektionskrankheiten festzustellen und Ausbrüche einzudämmen, werden verschiedene Überwachungssysteme eingesetzt. Passive Überwachungssysteme sind am weitesten verbreitet. Diese passiven Überwachungssysteme messen nicht die effektive Krankheitshäufigkeit – die Inzidenz in der Bevölkerung, sondern vielmehr die "Inzidenz der gemeldeten Fälle". So zeigen beispielsweise Personen, die mit durch Lebensmittel übertragenen Krankheitserregern infiziert sind, nicht immer Symptome – sie sind asymptomatische Träger. Symptomatische Personen wiederum – die Erkrankung äussert sich dabei meistens in Form einer akuten Gastroenteritis – melden sich nicht immer beim Arzt. Wird ein Arzt aufgesucht, wird die Ursache der Erkrankung zudem nur bei einem Bruchteil der Patienten mittels weiterführender Labor-Untersuchungen abgeklärt. Und letztlich führt ein positiver Laborbefund einer meldepflichtigen Krankheit nicht immer zu einer Meldung an das Überwachungssystem. Die Dunkelziffer, d.h. wie viele Fälle entlang dieser sogenannten Krankheitspyramide – auf dem Weg von der Infektion bis zur Erfassung der Krankheitsepisode im Meldesystem – verloren gehen, hängt sehr vom Pathogen und vom jeweiligen Gesundheitssystem ab.
Die Schweiz betreibt zwei Systeme zur Früherkennung und Überwachung von Infektionskrankheiten: das obligatorische Meldesystem für Infektionskrankheiten und das "Swiss Sentinel Surveillance Network", kurz *Sentinella*. Das obligatorische Meldesystem für Infektionskrankheiten stützt sich auf das Epidemiengesetz und ist das einzige obligatorische Überwachungssystem für Infektionskrankheiten der Schweiz, welches die gesamte Bevölkerung abdeckt und das alle Ärzte und diagnostischen Laboratorien zur Meldung verpflichtet. Das Epidemiengesetz regelt, welche Beobachtungen zu melden und welche Meldefristen dabei einzuhalten sind. *Sentinella* ist ein Netzwerk, in dem eine Gruppe aus freiwillig teilnehmenden Ärztinnen und Ärzten Konsultationen zu bestimmten Themen meldet und somit eine Charakterisierung des Krankheitsgeschehens auf Ebene der Grundversorgung erlaubt.
Im Jahr 2010 verursachten 31 von Lebensmitteln ausgehende Gefährdungen für die Gesundheit weltweit 33 Millionen sogenannte 'Disability

Adjusted Life Years (DALYs)' und rund 600 Millionen Erkrankungen. Die Inzidenz akuter Gastroenteritis wurde in europäischen Ländern auf 0.3–1.5 Krankheitsepisoden pro Person und Jahr geschätzt. Sowohl in der Europäischen Union (EU) als auch in der Schweiz ist *Campylobacter* spp. der häufigste, meldepflichtige, bakterielle Erreger, der durch Lebensmittel übertragen werden kann. Die Fallzahlen nahmen dabei im letzten Jahrzehnt stetig zu. Im Gegensatz dazu nahmen die Fallzahlen von *Salmonella* spp. in der EU und der Schweiz ab. Die Anzahl Meldungen von enterohämorrhagischen *Escherichia coli* (EHEC)-Infektionen war in der EU grösstenteils konstant, während sie in der Schweiz zunahm. Zurzeit verfügbare Informationen zu lebensmittelbedingten Infektionskrankheiten beschränken sich in der Schweiz mehrheitlich auf Informationen aus dem obligatorischen Meldesystem. Die Dunkelziffer der Erkrankungen, die durch zahlreiche Faktoren beeinflusst wird, ist unbekannt. Eine Aussage, inwiefern die Melderaten die wahre Inzidenz der Erkrankungen in der Allgemeinbevölkerung widerspiegeln, ist daher nicht möglich.

Ziele Im Rahmen dieser Dissertation soll ein besseres Verständnis der Krankheitspyramide am Beispiel von lebensmittelbedingten Infektionen erarbeitet werden. Die Erkenntnisse sollen dazu beitragen, die Überwachung und Kontrolle von Infektionskrankheiten in der Schweiz zu verbessern. Zu diesem Zweck wird die Häufigkeit von Fällen lebensmittelbedingter Erkrankungen oder akuter Gastroenteritiden auf verschiedenen Stufen der Krankheitspyramide untersucht. Es werden Trends beschrieben und Faktoren identifiziert, welche schlussendlich zur Meldung eines Krankheitsfalles führen. Die daraus gewonnenen Erkenntnisse helfen die Früherkennung und Kontrolle von Infektionskrankheiten zu verbessern.

Methodik Diese Forschungsarbeit besteht aus mehreren Projekten, welche sich unterschiedlichen Stufen der Krankheitspyramide, von der Spitze bis zur Basis, widmen. In einem ersten Schritt wurden Meldedaten zu *Campylobacter*, *Salmonella* und Hepatitis A untersucht, um deren Entwicklung seit 1988 zu beschreiben. Die Entwicklung des Anteils positiver Testresultate unter allen durchgeführten Tests wurde analysiert, da die Anzahl durchgeführter Tests einen grossen Einfluss auf die Anzahl identifizierter Fälle haben kann. Diese sogenannte "Positivitätsrate" von *Campylobacter*, *Salmonella* und EHEC wurde über einen Zeitraum von jeweils 10 Jahren untersucht. Mitarbeitende aus Diagnostiklaboratorien wurden zu ihrem Vorgehen bei der Stuhlproben-Diagnostik befragt, insbesondere im Hinblick auf die Diagnostik von EHEC. Des Weiteren wurde eine qualitative Studie durchgeführt, um das Vorgehen der Ärzte

bei der Anamnese (und der damit verbundenen Diagnostik) und Behandlung von akuten Gastroenteritiden (mit Fokus auf Campylobacteriose) in der Schweiz zu verstehen. Diese Erkenntnisse wurden im Anschluss durch eine Studie im *Sentinella*-Meldesystem ergänzt, in der die Anzahl Patienten untersucht wurde, welche aufgrund von akuter Gastroenteritis einen Hausarzt aufsuchen. Dazu haben Ärztinnen und Ärzte alle Erstkonsultationen aufgrund einer akuten Gastroenteritis gemeldet. Die Meldungen beinhalteten Informationen zur Hospitalisierung, Stuhldiagnostik, Behandlung und Arbeitsunfähigkeit des jeweiligen Patienten.
Gesundheitskosten, die durch akute Gastroenteritis und Campylobacteriose in der Schweiz entstehen, wurden basierend auf Resultaten aus den vorangegangenen Studien, Expertenmeinungen und öffentlich verfügbaren Daten geschätzt und erstmals publiziert. Es wurden dafür vier Patientenmodelle definiert, für welche jeweils deren Häufigkeit und die individuellen Behandlungskosten geschätzt wurden. Mittels Hochrechnung wurden so die direkten Gesundheitskosten, die durch akute Gastroenteritis und Campylobacteriose entstehen, quantifiziert. Basierend auf den Ergebnissen der oben genannten Studien wurde schliesslich deutlich, wie wichtig es ist, die Basis der Krankheitspyramide für akute Gastroenteritiden zu verstehen. Deshalb wurde ein Studienprotokoll entwickelt, um die Krankheitshäufigkeit (Inzidenz) von akuter Gastroenteritis auf Populationsebene zu untersuchen sowie deren Ätiologie abzuklären.

Resultate Die Anzahl Fallmeldungen von *Campylobacter* hat zwischen 1988 und 2013 zugenommen während diejenige von *Salmonella* zurückgegangen ist. Die höchste Anzahl *Campylobacter*-Fälle wurde im Jahr 2012 mit 8'480 Krankheitsfällen registriert. Mit 7'806 Fällen wurden die höchsten Fallzahlen für *Salmonella* im Jahr 1992 beobachtet. Während diese beiden Pathogene über die Jahre hinweg gegenläufige Trends aufweisen, zeigen sie eine ähnliche Saisonalität mit hohen Fallzahlen während der Sommermonate. Zusätzlich wird bei *Campylobacter* ein kurzer, aber prägnanter Anstieg jeweils um Weihnachten und Neujahr beobachtet. *Campylobacter*-Positivitätsraten nahmen zwischen 2003 und 2012 zu, während sie bei *Salmonella* abnahmen. Die Anzahl durchgeführter Tests stieg für beide Pathogene im Verlauf der Jahre an.
Hepatitis A-Fallmeldungen waren in der Schweiz zwischen 1988 und 2016 rückläufig, ähnlich wie die Salmonellen-Fallzahlen. Der stärkste Rückgang zeigte sich in den frühen 1990er-Jahren, noch bevor die aktive Immunisierung im Jahr 1992 eingeführt wurde. Gleichzeitig veränderten sich die gemeldeten Risikoexpositionen für Hepatitis A im Verlauf der Zeit: zu Beginn des untersuchten Zeitraums wurde intravenöser Drogen-

konsum am häufigsten genannt während in der jüngeren Vergangenheit der Konsum von kontaminierten Speisen und Getränken als mögliche Infektionsquelle dominierte. In diesen 29 Jahren wurden die Meldeformulare und deren Inhalt vielfach überarbeitet.
Experten aus Diagnostik-Laboratorien sind sich einig, dass der beobachtete Anstieg von EHEC-Meldungen durch die Einführung von sogenannten "Multiplex PCR-Panels" für gastrointestinale Erreger begründet ist. Bei diesen Panels ist ein Test auf EHEC mit eingeschlossen, während die traditionelle Diagnostik mittels Stuhlkultur meist nur *Campylobacter* spp., *Salmonella* spp. und *Shigella* spp. berücksichtigte. Neben einem Anstieg der Anzahl durchgeführter Tests stieg jedoch auch die Positivitätsrate von EHEC zwischen 2007 und 2016.
Eine vorläufige Analyse der Anzahl durchgeführter Tests, die seit der Einführung des neuen Epidemiengesetzes im Jahr 2016 gemeldet werden muss, zeigt diverse Probleme in Bezug auf die Datenqualität auf. Die Datenqualität steht mit der komplexen und heterogenen "Labor-Landschaft" in der Schweiz in einem klaren Zusammenhang.
Die Behandlung von Patienten mit akuter Gastroenteritis durch Schweizer Hausärzte ist vielfältig. Dennoch konnten vier Behandlungsstrategien identifiziert werden. Die Mehrheit der Patienten wird mit einem "wait & see"-Ansatz behandelt (frei übersetzt: "Abwarten und Tee trinken"). Dieser Ansatz stützt sich auf das Wissen, dass eine akute Gastroenteritis normalerweise selbst-limitierend verläuft. Zwei der vier Behandlungsstrategien schliessen eine mikrobielle Untersuchung (Stuhltest) mit ein; mit Beginn einer antibiotischen Behandlung bevor oder nachdem die Resultate der Stuhluntersuchung vorliegen. Schweizer Hausärzte sehen sowohl die akute Gastroenteritis als auch die Campylobacteriose als Erkrankungen von geringer Bedeutung im Praxisalltag. Sie räumen jedoch ein, dass sie für den individuellen Patienten unangenehm und beeinträchtigend sein können. Die Überwachung von akuter Gastroenteritis im Rahmen von *Sentinella* zeigte, dass 8.5% der Patienten mit akuter Gastroenteritis ein Antibiotikum verschrieben erhielten, bei 12.3% eine Stuhluntersuchung veranlasst wurde und 86.3% der Berufstätigen nicht arbeiten gehen konnten. Eine Hochrechnung der Fallzahlen ergab, dass akute Gastroenteritis im Jahr 2014 zu 2'146 Erstkonsultationen pro 100'000 Einwohner in der medizinischen Grundversorgung geführt hat.
Im Jahr 2012 führten akute Gastroenteritis und Campylobacteriose in der Schweiz zu geschätzten direkten Gesundheitskosten in Höhe von €29–45 Millionen (36–54 Millionen Schweizer Franken). Davon fielen €8.3 Millionen durch die 8'480 laborbestätigten Campylobacteriose-Fälle an, die im obligatorischen Meldesystem registriert wurden. Schätzungen

ergaben, dass 233'000–629'000 Patienten einen Arzt aufsuchten, ohne dass bei diesen eine Stuhluntersuchung durchgeführt wurde. Dies führte zu Gesundheitskosten von €9.0–24.2 Millionen. Arbeitsausfälle und andere Kosten, die mit akuter Gastroenteritis und Campylobacteriose in Zusammenhang stehen, wurden in dieser Studie nicht berücksichtigt. Diese sozioökonomische Bürde soll aber in einer nächsten Studie zur Krankheitslast von Gastroenteritiden in der Schweiz genauer untersucht werden. Diese sogenannte BUGS-Studie ("**Bu**rden of **g**astroenteritis in **S**witzerland") soll die "wahre" Inzidenz, die Krankheitslast, die Ätiologie und die sozioökonomischen Auswirkungen von akuter Gastroenteritis in der Schweiz näher erforschen, um die "volle" Krankheitsbürde auf Populationsebene sowie die Dunkelziffer – die Krankheitsfälle, die dem Meldesystem verborgen bleiben – aufzuzeigen. Bei dieser geplanten Studie handelt es sich um eine prospektive Kohortenstudie, bei der die Studienteilnehmerinnen und -teilnehmer aus der Allgemeinbevölkerung während eines Jahres wöchentlich befragt werden. Des Weiteren wird die Häufigkeit von vier pathogenen Bakterien (*Campylobacter*, *Salmonella*, *Shigella* und EHEC) und von Bakterien, die gegen bestimmte Antibiotika resistent sind (Fluorchinolon-Resistenz, ESBL, Carbapenemase und mcr-1-Resistenz), unter den Studienteilnehmerinnen und -teilnehmern während einer asymptomatischen Periode erhoben.

Schlussfolgerungen Das schweizerische obligatorische Meldesystem für Infektionskrankheiten ist ein nützliches, von den Akteuren des Gesundheitswesens gut akzeptiertes und stabiles Überwachungssystem. Daten aus dem obligatorischen Meldesystem deuten auf einen steigenden Trend von *Campylobacter* und EHEC und auf einen abnehmenden Trend von *Salmonella* und Hepatitis A hin. Unsere ergänzende Forschungsarbeit kam zum gleichen Schluss, auch wenn die Trends im obligatorischen Meldesystem stärker (EHEC) bzw. schwächer (*Salmonella*) erscheinen könnten als die "wahren" Inzidenzen – dies aufgrund von Änderungen in der Diagnostik. Die verfügbaren Erkenntnisse können den im Meldesystem beobachteten Anstieg nicht vollumfänglich erklären. Eine Veränderung der Inzidenz – der Krankheitshäufigkeit in der Bevölkerung – oder auch eine Ausbruchssituation muss daher aus epidemiologischer Sicht in Betracht gezogen werden. Dies auch in Anbetracht der Tatsache, dass die Dunkelziffer beträchtlich sein dürfte. Die im obligatorischen Meldesystem erfassten Krankheitsfälle zeichnen sich durch einen schweren Verlauf aus, sind häufiger mit Co-Morbiditäten verbunden oder weisen bekannte Risikofaktoren auf. Bedingt durch die Vielzahl an Faktoren, die zur Dunkelziffer beitragen, ist deren routinemässige Erhebung kaum mög-

lich. Deshalb ist ergänzende Forschung wie die geplante BUGS-Studie nötig.
Die Informationen, die im obligatorischen Meldesystem gesammelt werden, sollten auf das nötige Minimum und auf Daten beschränkt werden, die über längere Zeit verlässlich erhoben werden können; dies, um das System so einfach und anpassungsfähig wie möglich zu halten. Ein derartiges System erlaubt eine schnelle Reaktion auf sich verändernde Fallzahlen. Systeme wie *Sentinella* und strategische Forschungspartnerschaften aufrecht zu erhalten bzw. zu fördern ist wichtig, um sofort auf vermutete Ausbrüche und epidemiologische Veränderungen reagieren zu können. Es sollten Strategien erarbeitet werden, wie solide Evidenz für die Gesundheitspolitik generiert und wie Informationen an die relevanten Akteure weitervermittelt werden können.

iv Abbreviations

AG Acute gastroenteritis

AGI Acute gastrointestinal illness

BUGS Burden of gastroenteritis in Switzerland

CDC Centers for Disease Control and Prevention

CI Confidence interval

CJD Creutzfeldt-Jakob disease

CRP C-reactive protein

DALY Disability Adjusted Life Year

EAEC Enteroaggregative *Escherichia coli*

ECDC European Centre for Disease Prevention and Control

EEA European Economic Area

EHEC Enterohaemorrhagic *Escherichia coli*

EIEC Enteroinvasive *Escherichia coli*

EKNZ Ethikkommission Nordwest- und Zentralschweiz (Ethics Committee northwest/central Switzerland)

EPEC Enteropathogenic *Escherichia coli*

ESBL Extended-spectrum β-lactamase

ETEC Enterotoxigenic *Escherichia coli*

EU European Union

FDHA Federal Department of Home Affairs

FERG Foodborne Disease Burden Epidemiology Reference Group

FOPH Federal Office of Public Health

FSO Federal Statistical Office

FSVO Federal Food Safety and Veterinary Office

GBS Guillain-Barré syndrome

GI Gastrointestinal

GP General practitioner

HA Hepatitis A

HAV Hepatitis A virus

HBV Hepatitis B virus

HCV Hepatitis C virus

HEV Hepatitis E virus

HIV Human immunodeficiency virus

HUS Haemolytic-uraemic syndrome

IBD Inflammatory bowel disease

IBS Irritable bowel syndrome

ICD-10 International Statistical Classification of Diseases and Related Health Problems 10$^{\text{th}}$ Revision

IDU Injecting drug user

IHR International Health Regulations

IID Infectious intestinal disease

ILI Influenza-like illness

IQR Interquartile range

mcr-1 Mobilised colistin resistance-1

MSM Men who have sex with men

NENT National Reference Centre for Enteropathogenic Bacteria and Listeria

NGS Next-generation sequencing

NNSID National Notification System for Infectious Diseases

NUTS Nomenclature of Units for Territorial Statistics

OR Odds ratio

PCR Polymerase chain reaction

PPC Physician-patient-contact

PPHS PhD Program Health Sciences

PPI Proton pump inhibitor

PPV Positive predictive value

ReA Reactive arthritis

RKI Robert Koch Institute

SARS Severe acute respiratory syndrome

Sentinella Swiss Sentinel Surveillance Network

SPSU Swiss Pediatric Surveillance Unit

StAR Strategy on Antibiotic Resistance Switzerland

STEC Shiga toxin-producing *Escherichia coli*

Swiss TPH Swiss Tropical and Public Health Institute

TESSy The European Surveillance System

UK United Kingdom

USA United States of America

VFR [Traveller] visiting friends and relatives

VTEC verotoxin-producing *Escherichia coli*

WHO World Health Organization

v Glossary

Acute gastrointestinal illness An illness with gastrointestinal signs and symptoms. In contrast to "acute gastroenteritis", an episode of AGI does not have to fulfil a strict case definition but is rather defined by the individual experiencing the illness.

Acute gastroenteritis "An individual with $\geq$3 loose stools, or any vomiting, in 24h, but excluding those (a) with cancer of the bowel, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibriosis, coeliac disease, or another chronic illness with symptoms of diarrhoea or vomiting, or (b) who report their symptoms were due to drugs, alcohol, or pregnancy." [Majowicz *et al.*, 2008]. Note, however, that Majowicz *et al.* proposed this definition for "gastroenteritis" instead of "acute gastroenteritis".

Epidemic intelligence "All activities related to the early identification of potential health hazards that may represent a risk to health, and their verification, assessment and investigation so that appropriate public health control measures can be recommended. The scope of epidemic intelligence includes risk monitoring and risk assessment and does not include risk management" [Paquet *et al.*, 2006]

Foodborne disease "Any disease of an infectious or toxic nature caused by the consumption of food." [World Health Organization, 2008]

Foodborne intoxication "Illness caused by ingestion of toxins produced in food by bacteria as a naturally occurring by-product of their metabolic processes." [World Health Organization, 2008]. A subset of foodborne diseases.

Illness "[...] a subjective or psychological state of the person who feels aware of not being well; the experience of a person with a disease; a social construct fashioned out of transactions between healers and patients in the context of their common culture." [Porta, 2014]

Laboratory-based surveillance "A form of [...] surveillance of cases that have been confirmed by a laboratory test. The laboratories that perform the testing report the results to the surveillance system, as well as informing the clinicians who requested the tests." [World Health Organization, 2017]

Notification rate The number of newly notified cases per X (usually 100'000) population under surveillance in a given time period. Could be considered the "incidence rate of notified cases".

One Health "Any added value in terms of human and animal health, financial savings or social and environmental benefits from closer cooperation of professionals in the health, animal and environmental sectors at all levels of organisation" [Zinsstag *et al.*, 2012]

Passive surveillance "Regular reporting of disease data by all institutions that see patients (or test specimens) and are part of a reporting network [...]. There is no active search for cases. It involves passive notification by surveillance sites and reports are generated and sent by local staff." [World Health Organization, 2018]

Physician-patient-contact Each consultation in the practice and each domiciliary visit, independent of whether or not the consultation/ visit takes place in the framework of the usual consultation hour or outside consultation hour or during emergency service. This term and definition is used by the Swiss Sentinel Surveillance Network (*Sentinella*).

Sentinel surveillance "Surveillance based on selected population samples chosen to represent the relevant experience of particular groups. [...] In sentinel surveillance, standard case definitions and protocols must be used to ensure validity of comparisons across time and sites despite lack of statistically valid sampling. [...] " [Porta, 2014]

Surveillance "1. Systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so that action can be taken. It is an essential feature of epidemiological and public health practice. The final phase in the surveillance chain is the application of information to

health promotion and to disease prevention and control. A surveillance system includes a functional capacity for data collection, analysis, and dissemination linked to public health programs [...]; 2. Continuous analysis, interpretation, and feedback of systematically collected data, generally using methods distinguished by their practicality, uniformity, and rapidity rather than by accuracy or completeness. [...]" [Porta, 2014]

Syndrome "A complex of signs and symptoms that tend to occur together, often characterizing a disease." [Porta, 2014]

Under-ascertainment "[...] the number of infections occurring in individuals that do not attend healthcare services for every case that attends. There is a symptomatic fraction of all under-ascertained cases that do not attend healthcare due to mild symptoms and/or the knowledge that the illness is self-limiting or for some other reasons, and an asymptomatic fraction that do not seek healthcare as they are not aware of their infection status due to lack of symptoms [1]." [Gibbons *et al.*, 2014]

1. European Centre for Disease Prevention and Control (ECDC): Report: Surveillance and Prevention of Hepatitis B and C in Europe. Stockholm, Sweden: ECDC; 2010

Under-diagnosis Refers to "[...] the cases attending healthcare but whose infection or pathogen is not diagnosed or misdiagnosed [1, 2]". [Gibbons *et al.*, 2014]

1. Hardnett FP, Hoekstra RM, Kennedy M, Charles L, Angulo FJ, for the Emerging Infections Program FoodNet Working Group: Epidemiologic issues in study design and data analysis related to FoodNet activities. *Clin Infect Dis* 2004, 38(Supplement 3):S121–S126
2. MacDougall L, Majowicz S, Dore K, Flint J, Thomas K, Kovacs S, Sockett P: Under-reporting of infectious gastrointestinal illness in British Columbia, Canada: who is counted in provincial communicable disease statistics? *Epidemiol Infect* 2008, 136(02):248–256

Underestimation "[...] the many ways in which surveillance systems fail or are unable to reflect all infections in a given population. [...] UE [underestimation] can be split into two distinct levels [...]; under-ascertainment [...] of infections occurring at the community-level and underreporting [...] of infections occurring at the healthcare-level." [Gibbons *et al.*, 2014]

Under-notification Refers to "[...] the failure to report (using correct International Classification of Diseases (ICD) codes [1, 2]) all positive diagnoses through the notification system [3, 4]." [Gibbons *et al.*, 2014]

1. Khosravi A, Rao C, Naghavi M, Taylor R, Jafari N, Lopez AD: Impact of misclassification on measures of cardiovascular disease mortality in the Islamic Republic of Iran: a cross-sectional study. *Bull World Health Organ* 2008, 86(9):688–696
2. Crowcroft NS, Andrews N, Rooney C, Brisson M, Miller E: Deaths from pertussis are underestimated in England. Arch Dis Child 2002, 86(5):336–338
3. Martin-Ampudia M, Mariscal A, Lopez-Gigosos RM, Mora L, Fernandez-Crehuet J: Under-notification of cryptosporidiosis by routine clinical and laboratory practices among non-hospitalised children with acute diarrhoea in Southern Spain. *Infection* 2012, 40(2):113–119
4. Yuguero O, Serna MC, Real J, Galvan L, Riu P, Godoy P: [Using treatment compliance to determine the under-notification of tuberculosis in a health region for the years 2007–2009]. *Aten Primaria* 2012, 44(12):703–708

Underreporting Refers to infections "[...] in individuals that do seek healthcare, but whose health event is not captured by the surveillance system and not notified through the notification system [1-4]. [...] UR [underreporting] can be due to under-diagnosis [...] and under-notification [...]." [Gibbons *et al.*, 2014]

1. Hardnett FP, Hoekstra RM, Kennedy M, Charles L, Angulo FJ, for the Emerging Infections Program FoodNet Working Group: Epidemiologic issues in study design and data analysis related to FoodNet activities. *Clin Infect Dis* 2004, 38(Supplement 3):S121–S126
2. MacDougall L, Majowicz S, Dore K, Flint J, Thomas K, Kovacs S, Sockett P: Under-reporting of infectious gastrointestinal illness in British Columbia, Canada: who is counted in provincial communicable disease statistics? *Epidemiol Infect* 2008, 136(02):248–256
3. O'Brien S, Rait G, Hunter P, Gray J, Bolton F, Tompkins D, McLauchlin J, Letley L, Adak G, Cowden J, *et al.*: Methods for determining disease burden and calibrating national surveillance data in the United Kingdom: the second study of infectious intestinal disease in the community (IID2 study). BMC Med Res Methodol 2010, 10(1):39
4. Sethi D, Wheeler J, Rodrigues LC, Fox S, Roderick P: Investigation of under-ascertainment in epidemiological studies based in general practice. *Int J Epidemiol* 1999, 28(1):106–112

vi Preamble

Layout and formatting as well as numbering of figures and tables (incl. cross-references) of published articles were adapted. The reference lists of published articles (incl. those submitted or accepted) are provided as in the original published article at the end of the corresponding chapter, with their original numbering. References included in all unpublished chapters (except those submitted or accepted) are summarised in a separate chapter at the end of this thesis.
A monograph of this thesis will be published once final versions of the submitted or accepted articles (chapter 8 and chapter 13) are available (foreseen in 2019). Please contact the author of this thesis or the Swiss Tropical and Public Health Institute (Daniel Mäusezahl; daniel.maeusezahl@swisstph.ch) if you are interested in obtaining a printed or electronic version.
Terms defined in the glossary (chapter v) are marked with an asterisk (*) when used for the first time.

Part I

INTRODUCTION, OBJECTIVES AND METHODOLOGY

1 Introduction

1.1 Surveillance of infectious diseases – the 'burden of illness pyramid'

Infectious diseases are of concern worldwide: globally, 230 million all–age Disability Adjusted Life Years (DALYs) were caused by "diarrhoea, lower respiratory, and other common infectious diseases" in 2016, according to the Global Burden of Diseases Study [GBD 2016 DALYs and HALE Collaborators, 2017]. Thereof, 74.4 million DALYs (95% confidence interval (CI): 63.4–93.4) were attributable to "diarrhoeal diseases", or 10.6 million (95% CI: 6.0–17.3) to "intestinal infectious diseases". Globally, "diarrhoeal diseases" are still ranked fifth in terms of leading causes of total DALYs in 2016 even though the number of DALYs due to communicable diseases decreased while the number of DALYs due to non-communicable diseases increased [GBD 2016 DALYs and HALE Collaborators, 2017].
Surveillance* is defined by Porta as the "1. Systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so that action can be taken. It is an essential feature of epidemiological and public health practice. The final phase in the surveillance chain is the application of information to health promotion and to disease prevention and control. A surveillance system includes a functional capacity for data collection, analysis, and dissemination linked to public health programs [...]; 2. Continuous analysis, interpretation, and feedback of systematically collected data, generally using methods distinguished by their practicality, uniformity, and rapidity rather than by accuracy or completeness. [...]" [Porta, 2014]. Surveillance of infectious diseases is, therefore, key for prevention and control. The disease surveillance and notification required according to the International Health Regulations (IHR) could be considered to constitute the most comprehensive surveillance system for infectious diseases worldwide considering that 196 countries (including all World Health Organization (WHO) member states) are committed to these regulations. However, only "events which may constitute a public health

emergency of international concern within its [the State Party's] territory in accordance with the decision instrument [provided in Annex 2 of the IHR] [...]" should be notified to WHO. Such events include, but are not limited to, a case of smallpox, poliomyelitis due to wild-type poliovirus, human influenza caused by a new subtype, severe acute respiratory syndrome (SARS), and "any event of potential international public health concern, including those of unknown causes or sources [...]". However, at national or regional level, also other infectious diseases or "events" are of concern apart from those potentially representing an international emergency. Therefore, many countries have set up their own infectious disease surveillance system(s). Such surveillance systems can be national, regional or based on sentinel sites; include physicians, hospitals and/or laboratories; and reporting can be compulsory or voluntary. Passive surveillance* systems have in common that they hardly 'measure' disease incidence of the general population. Depending on their set-up, they are subject to different degrees of underestimation*. Therefore, the incidence estimated through surveillance systems does not reflect the incidence of disease (or infection) in the population. To account for this, the term notification rate* is used for the remainder of this thesis when referring to the 'incidence of notified cases'.

The metaphor of a pyramid is frequently used to illustrate underestimation of surveillance systems, especially in the field of foodborne or gastrointestinal (GI) diseases. The different levels of the pyramid, referred to as the "burden of illness pyramid" [Allos *et al.*, 2004], the "disease pyramid" [Lake *et al.*, 2010], the "morbidity surveillance pyramid" [Gibbons *et al.*, 2014], the "surveillance pyramid" [Haagsma *et al.*, 2013; O'Brien *et al.*, 2010], the "reporting pyramid" [Lake *et al.*, 2010; O'Brien *et al.*, 2010; Wheeler *et al.*, 1999], or the "under-reporting pyramid" [MacDougall *et al.*, 2008], depict the various steps involved leading to a case being notified (Figure 1.1). The lowest level of the pyramid reflects the population exposed to a pathogen or the population developing symptoms, depending on the author, while the top level of the pyramid represents the notified cases.

Individuals infected with a foodborne pathogen who either do not develop symptoms and hence, are not aware of their disease or individuals not seeking medical attention (due to mild symptoms or because they are aware of the self-limiting nature of their disease) are referred to as under-ascertained cases [Gibbons *et al.*, 2014]. Individuals not requested to submit a stool sample among those consulting a physician and individuals whose stool sample is tested for the "wrong" pathogens are summarised as under-diagnosed cases [Gibbons *et al.*, 2014]. Finally,

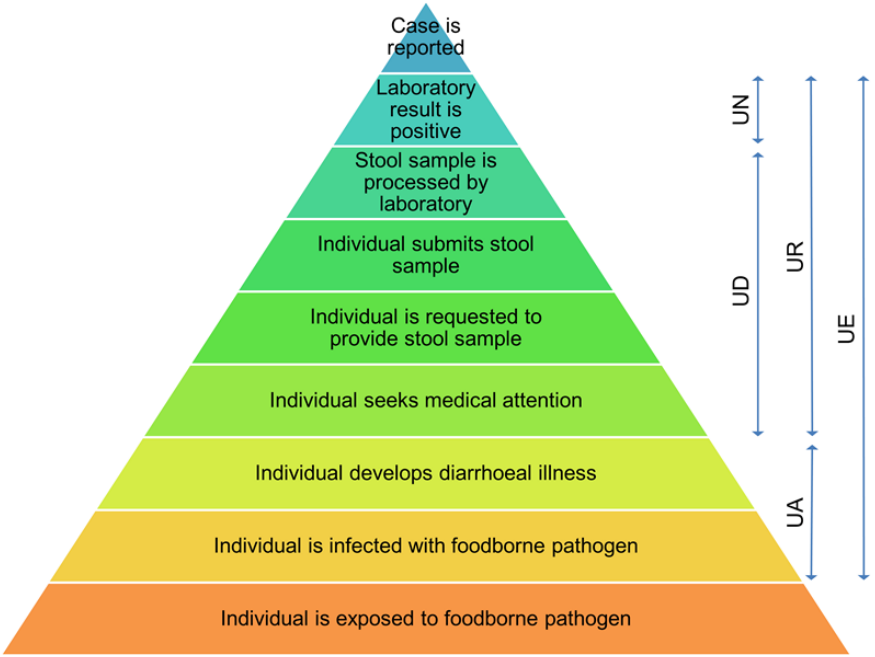

Figure 1.1: The burden of illness pyramid for foodborne pathogens.
UE: underestimation, UA: under-ascertainment, UR: underreporting, UD: under-diagnosis, UN: under-notification. Adapted from Allos *et al.* [2004]; Gibbons *et al.* [2014]; MacDougall *et al.* [2008]

the term of under-notification* is used to refer to cases whose pathogen is identified by the laboratory but not reported to national surveillance. Under-diagnosis* and under-notification are summarised as underreporting*; underestimation is composed of under-ascertainment* and underreporting.

1.2 History of infectious disease surveillance in Switzerland

Already the first federal constitution of Switzerland from 1848 contained an article on infectious diseases:

"**Art. 59.** Die Bundesbehörden sind befugt, bei gemeingefährlichen Seuchen gesundheitspolizeiliche Verfügungen zu erlassen." [Verfassungen der Schweiz. Bundesverfassung der Schweizerischen Eidgenossenschaft vom 12. September 1848, n.d.]

Art. 59. *The federal authorities are entitled to issue decrees for the sanitary police in case of epidemic plagues constituting a public danger.*

With the complete revision of the federal constitution, entering into force in 1874, the corresponding article was rephrased. However, the law still stipulated a reactive rather than a proactive role of the authorities by defining competencies only in case of epidemics (as opposed to preventive measures).

"**Art. 69.** Dem Bunde steht die Gesetzgebung über die gegen gemeingefährliche Epidemien und Viehseuchen zu treffenden gesundheitspolizeilichen Verfügungen zu" [Verfassungen der Schweiz. Bundesverfassung der Schweizerischen Eidgenossenschaft vom 29. Mai 1874, n.d.]

Art. 69. *The federal authorities are responsible to issue decrees for the sanitary police against epidemics and epizootic diseases constituting a public danger.*

On 31st January 1882, the Swiss Federal Council issued the first Epidemics Act which was, however, overruled by the popular vote in July 1882 [Bundesblatt, 1882, 1886a]. Finally, in 1886, the first Epidemics

Act was established in Switzerland and entered into force on 1st January 1887 [Bundesblatt, 1886b]. It targeted "epidemics constituting a public danger" ("gemeingefährliche Epidemien"), namely pox, cholera, epidemic typhus and plague [Bundesblatt, 1886b]. Already this first version of the Epidemics Act stipulated that each case of the aforementioned diseases had to be notified to the local authorities. The draft version from 1882 allowed for an extension of the law to also include "epidemics constituting a public danger temporarily" such as scarlet fever, diphtheria, typhoid fever, dysentery and childbed fever [Bundesblatt, 1882], an earlier version (from 1879) additionally mentioned measles [Bundesblatt, 1911]. This part was, however, discussed controversially and, hence, was not included in the final version [Bundesblatt, 1886a]. In 1887 and 1894, respectively, the Federal Council specified that notification should occur within 12 (cholera) or 24 hours (pox, epidemic typhus and plague), and that reports should include the name and age of the patient, the illness onset and severity, the date of notification, and information about mode of transmission and measures implemented [Bundesblatt, 1887, 1894].
Meanwhile, a division for health ("Schweizerisches Gesundheitsamt"; Swiss Health Authority) was founded in 1893 with three employees, subordinate to the Federal Department of Home Affairs (FDHA) [Bundesblatt, 1893a,b]. The main responsibilities of the Swiss Health Authority, today's Federal Office of Public Health (FOPH), were to coordinate the federal diplomas for physicians, veterinarians and pharmacists, and to control epidemics and food safety [Bundesamt für Gesundheit, 1993].
Concerns were raised that the federal authorities should contribute to the control of diseases other than the four "epidemic diseases constituting a public danger" soon after the implementation of the first Epidemics Act [Bundesblatt, 1911]. Additionally, it was suggested to replace the term "epidemics constituting a public danger" ("gemeingefährliche Epidemien") for two reasons: first, the term "constituting a public danger" is too vague and second, the federal authorities should also be entitled to intervene in case of severe endemic diseases and/or in single cases of epidemic diseases (preventing an epidemic) and hence, the term "epidemic" was considered inappropriate. Therefore, revision of article 69 of the federal constitution from 1874 was suggested to:

"Der Bund ist befugt, gegen übertragbare, stark verbreitete oder bösartige Krankheiten von Menschen und Tieren auf dem Wege	*The federal authorities are entitled to issue decrees for the sanitary police against communicable, widespread or virulent diseases of*

der Gesetzgebung gesundheitspolizeiliche Verfügungen zu treffen." [Bundesblatt, 1911]

humans and animals by means of legislation.

This revision (with slightly different wording) was approved by a popular vote in 1913 [Bundesblatt, 1913]. It provided a basis for revising the Epidemics Act from 1886. Considering that total revision of laws is time-consuming, the Federal Assembly decided on a partial revision of the Epidemics Act in 1921 (based on a communication from the Federal Council from 1920) [Bundesblatt, 1920, 1921]. Among others, Art. 1 (defining the four "epidemic diseases constituting a public danger") was complemented by:

"Der Bundesrat ist indessen ermächtigt, die Bestimmungen dieses Gesetzes auch auf andere besonders gefährliche übertragbare Krankheiten anzuwenden."

The Federal Council is authorised to apply the terms of this law also for other especially dangerous communicable diseases.

The original "Federal Act concerning measures against epidemics constituting a public danger" from 2nd July 1886 was finally replaced by the "Federal Act on combating communicable human diseases" from 18th December 1970 (entering into force on 1st July 1974) [Bundesblatt, 1970b]. Main drivers for this revision were the increasing (awareness of the) importance of viral infections, the change in international traffic (increasing numbers as well as rapidly decreasing duration of a journey), and the outbreak of typhoid fever in Zermatt (Valais, Switzerland) in 1963 with around 400 persons infected [Bundesblatt, 1970a]. Based on this revised Epidemics Act, the Confederation and all cantons were empowered and obliged to implement measures for combating communicable human diseases [Bundesblatt, 1970b]. It defined the obligation for physicians and hospitals to report cases and suspected cases of certain diseases, and persons shedding pathogens to the cantonal authorities who then had to forward the report to the Federal Health Authority. Similarly, it newly obliged diagnostic laboratories to report certain microbiological or serological findings to the cantonal authorities and the Federal Health Authority. The Federal Health Authority, on the other hand, was responsible for publishing weekly, monthly and yearly statistics based on the aforementioned notifications.
The Epidemics Act of 1970 further defined that cantons were responsible for the implementation of measures to control communicable diseases

[Bundesblatt, 1970b]. The Federal Council could, however, mandate the implementation of measures for the whole or parts of the country in case of extraordinary circumstances.
Finally, on 1st January 2016 a newly revised Epidemics Act, the "Federal Act on combating communicable human diseases (Epidemics Act)" of 28th September 2012, entered into force [Die Bundesversammlung der Schweizerischen Eidgenossenschaft, 2012a].
This revised Epidemics Act includes a more refined specification of roles and processes for preparedness and response to crisis situations and lays a basis for establishing national goals and strategies in the context of communicable diseases, strengthening the leading role of the FOPH, representing the federal authorities [Bundesamt für Gesundheit, 2016]. Additionally, adaptations to new, contemporary challenges such as increased mobility and migration, climate change and newly emerging diseases have been made. One of the main triggers for the revision of the Epidemics Act of 1970 was the SARS epidemic of 2003 which showed that coordination between federal and cantonal authorities could be improved.
In conclusion, the inception of the Epidemics Act in Switzerland as well as the two revisions thereof seem mostly triggered by national public health threats in the form of major outbreaks or newly emerging diseases.

1.3 Infectious disease surveillance systems in Switzerland

There are currently four systems for surveillance and early detection in place in Switzerland: a notification system for surveillance of clinical and laboratory findings – the National Notification System for Infectious Diseases (NNSID); a system for surveillance of frequent, communicable diseases – the Swiss Sentinel Surveillance Network (*Sentinella*); a system to survey rare communicable diseases in hospitalised children – the Swiss Pediatric Surveillance Unit (SPSU); and a system for surveillance of therapy-associated infections and resistances of pathogens. Those four systems are all based on the Epidemics Act and its related ordinances [Der Schweizerische Bundesrat, 2015b; Die Bundesversammlung der Schweizerischen Eidgenossenschaft, 2012b]. The purpose and set-up of the two first-mentioned systems is explained in more detail in the following sections.

1.3.1 The National Notification System for Infectious Diseases

The National Notification System for Infectious Diseases (NNSID) is a mandatory surveillance system for infectious diseases in Switzerland. Its legal basis is the current Epidemics Act and more specifically the "Ordinance on the control of human communicable diseases" of 25th April 2015 and the "DHA Ordinance on the reporting of observations on human communicable diseases" of 1st December 2015 [Das Eidgenössische Departement des Innern, 2015a; Der Schweizerische Bundesrat, 2015b; Die Bundesversammlung der Schweizerischen Eidgenossenschaft, 2012b]. In general terms, the Epidemics Act stipulates that it is compulsory to report observations on communicable diseases: a) which can cause epidemics; b) which can have serious consequences; c) which are novel or unexpected; or d) whose surveillance has been internationally agreed. The ordinances explicitly list which clinical and laboratory findings have to be reported, by whom and to whom they have to be reported, as well as within which time limit notification has to occur. Notifiable observations and the content thereof are reviewed for their necessity and purpose as required but at least once a year by the FOPH in collaboration with the cantonal physicians. Currently (as per January 2018), the DHA Ordinance lists 55 notifiable observations. A list of all notifiable observations is provided in appendix A, table A.1. As soon as the criterion for notification is fulfilled, observations have to be reported within 2 hours, 24 hours or 1 week.

The process of notification

Physicians, hospitals and other public or private institutions in the healthcare sector have to report observations on communicable diseases to the cantonal health authorities of the patient's canton of residence and, for selected observations, additionally to the FOPH [Das Eidgenössische Departement des Innern, 2015a; Der Schweizerische Bundesrat, 2015b]. If the patient's canton of residence is not known, the cantonal authorities of the canton in which the observation was made has to be notified. Diagnostic laboratories have to report laboratory findings on communicable diseases both to the cantonal health authorities and to the FOPH. Additionally, cantonal health authorities have to report all observations which could point towards a threat for public health to the FOPH. Similarly, commanders of vessels and airplanes have to report observations indicative of a threat for public health to the operators of harbours and airports.

Cantonal physicians have to check completeness of notifications sent to the cantonal health authorities and request additional information or notifications, if necessary [Der Schweizerische Bundesrat, 2015b]. Furthermore, cantonal physicians forward notifications to the FOPH within the time frame for notification of the concerning observation and inform cantonal chemists, cantonal veterinarians, cantonal pharmacists and/or other cantonal authorities (including cantonal physicians of other cantons) as needed.
Finally, at the FOPH, data from notification forms is manually entered into an electronic database since 1988. The process of disease notification for clinical and laboratory findings is illustrated in appendix B (Figures B.1 and B.2).

The processing of notifications

Cantonal physicians are obliged to conduct epidemiological investigations in their cantons based on notifications, as appropriate [Der Schweizerische Bundesrat, 2015b]. The cantonal authorities may oblige a person who could be infected and/or infectious to undergo medical examination and treatment, or to isolate this person (quarantine) [Die Bundesversammlung der Schweizerischen Eidgenossenschaft, 2012b]. The FOPH is available for consultation and support. The FOPH coordinates epidemiological investigations in case several cantons and/or international authorities or organisations are involved. Additionally, the FOPH itself can initiate epidemiological investigations.
Furthermore, the FOPH has the responsibility to analyse the notifications and to provide anonymised statistics and reports for the general public regularly [Der Schweizerische Bundesrat, 2015b]. Weekly reports on case numbers can be found on the webpage of the FOPH (`https://www.bag.admin.ch/bag/de/home/zahlen-und-statistiken/zahlen-zu-infektionskrankheiten/meldepflichtige-infektionskrankheiten---woechentliche-fallzahlen.html`[1]) and in the "BAG Bulletin" (also available electronically, see `https://www.bag.admin.ch/bag/de/home/das-bag/publikationen/periodika/bag-bulletin.html`[1]). Additionally, analyses of surveillance data are published regularly in the "BAG Bulletin".

[1] last accessed: 24 September 2018

1.3.2 The Swiss Sentinel Surveillance Network

The Swiss Sentinel Surveillance Network (*Sentinella*) is a voluntary sentinel surveillance* system established in 1986 [Bundesamt für Gesundheit, 2018b]. It allows surveying frequent non-notifiable diseases and pathogens and other public health issues as well as researching primary care. Its purpose is to provide important insight into the incidence of contemporary diseases and public health issues in the Swiss population and to highlight the importance of primary care medicine. *Sentinella* is managed by a steering committee consisting of representatives of the participating physicians, of the division of Communicable Diseases at the FOPH, and of academic primary care institutes (of Lausanne, Bern, Basel, Zurich and Geneva) [Sentinella, 2018a]. The network is divided into six regions ("Sentinella-regions"); each region having its representative in the steering committee. The administration of *Sentinella* is at the FOPH. They are responsible for data entry apart from completing other administrative tasks (e.g. organising meetings of the steering committee and managing the database of participating physicians). Finally, physicians working as general practitioners (GPs), internists or paediatricians in a (single or group) private practice are constituting the network (referred to as "Sentinella-physicians" in this thesis).
The steering committee decides which topics are surveyed (usually for at least one year). Between 8 and 14 topics per year were subject to surveillance [Sentinella, 2018b]. Three thereof were included since the implementation of *Sentinella* in 1986: influenza-like illness (ILI), death due to influenza, and mumps.
In contrast to the NNSID, in *Sentinella* also non-communicable diseases or observations can be surveyed. Other differences are that reports within *Sentinella* are anonymous (with respect to the patient; the physician can be identified on the notification form) and that Sentinella-physicians are financially compensated for their work. The network is financed by the FOPH.
In *Sentinella*, physicians also report the number of consultations per day (the so-called "physician-patient-contact (PPC)*" which is defined as "each consultation in the practice and each domiciliary visit, independent of whether or not the consultation/visit takes place in the framework of the usual consultation hour or outside consultation hour or during emergency service"). This allows calculating the incidence per 1'000 consultations and the consultation frequency per 100'000 population. The standard procedure for extrapolation used by *Sentinella* has been described by Altpeter *et al.* [2013].

In conclusion, *Sentinella* provides a platform to investigate a broad range of public health issues at primary care level in Switzerland which may be important but do not qualify for compulsory surveillance in the framework of the NNSID. The topics surveyed within *Sentinella* are set by a steering committee and hence, do not need to fulfil the same strict "requirements" as those surveyed within the NNSID (i.e. potential to cause epidemics, have serious consequences, be novel or unexpected, or be of international importance).

1.4 Foodborne diseases and acute gastroenteritis

1.4.1 The difference between foodborne disease and acute gastroenteritis

Foodborne diseases* are defined as "Any disease of an infectious or toxic nature caused by the consumption of food." [World Health Organization, 2008]. Hence, foodborne diseases include bacterial diseases such as campylobacteriosis, salmonellosis, and listeriosis; viral diseases such as hepatitis A and norovirus; parasitic diseases such as cryptosporidiosis, giardiasis and trichinellosis, but also foodborne intoxications* due to enterotoxins of *Bacillus cereus*, aflatoxins, or toxin of *Clostridium botulinum*. Many foodborne diseases cause GI signs and symptoms; however, they can also manifest differently, for example with neurological symptoms (e.g. botulism).
Illnesses* due to GI signs and symptoms (such as diarrhoea, vomiting, nausea, abdominal pain) are often called "diarrhoeal diseases", "acute diarrhoea", "gastroenteritis", and "acute gastroenteritis". Such illnesses are frequently caused by infectious agents but can also be due to non-infectious conditions (e.g. appendicitis, inflammatory bowel disease (IBD), adverse effects of drugs, pregnancy, cancer) [Frese *et al.*, 2011; Manatsathit *et al.*, 2002; Pfeiffer *et al.*, 2012]. Diarrhoea can further be classified as "acute" (lasting $\leq$14 days), "persistent" (lasting >14 days, or >14 and $\leq$29 days), or "chronic" (lasting >30 days) [DuPont, 2014; Guerrant *et al.*, 2001; Riddle *et al.*, 2016]; and "watery" or "bloody" (in the latter case often referred to as "inflammatory diarrhoea" or "dysentery") [Guerrant *et al.*, 2001; Manatsathit *et al.*, 2002].
This variety of terms used – sometimes with clear definitions, sometimes used interchangeably – for syndromes* associated with GI signs and symptoms and foodborne diseases makes it difficult to compare estim-

ates of the disease incidence and burden from different studies. Using the "correct" terms is further complicated by the fact that not all foodborne diseases result in acute gastroenteritis (AG)*; and conversely, not every person experiencing AG suffers from a foodborne disease.

1.4.2 The burden of foodborne diseases

In 2010, 600 million cases of illness were caused by 31 foodborne hazards, according to estimates of the Foodborne Disease Burden Epidemiology Reference Group (FERG) established by WHO [Havelaar *et al.*, 2015]. An estimated 33 million DALYs were attributable to those 600 million cases of foodborne illnesses including sequelae [Havelaar *et al.*, 2015]. For these calculations, the viral, bacterial and protozoal hazards were classified as "diarrhoeal disease" or "invasive disease" according to their main manifestation; additionally, all hazards were classified as either "entirely foodborne" or "partly foodborne" (Table 1.1; [Havelaar *et al.*, 2015]. It is apparent that none of the pathogens classified as "diarrhoeal disease" (of viral, bacterial and protozoal origin) is entirely foodborne. In contrast, many helminths and chemicals or toxins are considered to be exclusively transmitted through food.

The burden of foodborne disease is not evenly distributed across the world: it was estimated that the 31 foodborne hazards considered by the FERG were causing the least DALYs per 100'000 population (35 DALYs/100'000; 95% uncertainty interval: 23–49) in the "AMR A" region[2] and the most DALYs in the "AFR D" region[3] (1'276 DALYs/100'000; 95% uncertainty interval: 459–2'263) [Havelaar *et al.*, 2015]. The largest burden occurs in children under 5 years of age.

Other estimates of the FERG suggest that 22 diseases (viruses, bacteria and protozoa; 4 of which are distinct manifestations of *Salmonella enterica*) lead to 2 billion illnesses in 2010 worldwide of which 582 million were of foodborne origin [Kirk *et al.*, 2015]. *Campylobacter* spp. and norovirus were the bacterial and viral pathogens causing most illnesses of foodborne origin. Furthermore, it was estimated that the 22 diseases caused 1.1 million deaths in 2010, 32% of which (350'686) were of foodborne origin [Kirk *et al.*, 2015]. The highest number of foodborne deaths

[2]Countries included in "AMR A" region are: Canada, Cuba, United States of America

[3]Countries included in "AFR D" region are: Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo

Table 1.1: Predominant disease manifestation and estimated proportion of foodborne transmission for the "EUR A" region[a] (including Switzerland) of 31 hazards commonly associated with foodborne illness according to Hald *et al.* [2016]; Havelaar *et al.* [2015]

	Predominantly causing	**Entirely foodborne**	**Partly foodborne (estimated % foodborne in "EUR A" region[a])**
Viruses	Acute diarrhoeal disease		Norovirus (26%)
	Invasive infectious disease		Hepatitis A virus (42%)
Bacteria	Acute diarrhoeal disease		*Campylobacter* spp. (76%)
			Enteropathogenic *E. coli* (64%)
			Enterotoxigenic *E. coli* (42%)
			Shiga toxin-producing *E. coli* (60%)
			Non-typhoidal *Salmonella enterica*[b] (76%)
			Shigella spp. (7%)
			Vibrio cholerae (31%)
	Invasive infectious disease	*Listeria monocytogenes*	*Brucella* spp. (66%)
		Mycobacterium bovis	*Salmonella* Paratyphi A (n.a.[c])
			Salmonella Typhi (10%)
Protozoa	Acute diarrhoeal disease		*Cryptosporidium* spp. (10%)
			Entamoeba histolytica (33%)
			Giardia spp. (11%)
	Invasive infectious disease		*Toxoplasma gondii* (61%)

Table 1.1: (continued)

	Predominantly causing	Entirely foodborne	Partly foodborne (estimated % foodborne in "EUR A"[a] region)
Helminths		*Clonorchis sinensis*	*Ascaris* spp. (85%)
		Fasciola spp.	*Echinococcus granulosus* (21%)
		Intestinal flukes[d]	*Echinococcus multilocularis* (52%)
		Opisthorchis spp.	
		Paragonimus spp.	
		Taenia solium	
		Trichinella spp.	
Chemicals and toxins		Aflatoxin	
		Cassava cyanide	
		Dioxins	

[a] "EUR A" region includes: Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom

[b] Diarrhoeal and invasive disease

[c] n.a. = not available

[d] Includes selected species of the families *Echinostomatidae*, *Fasciolidae*, *Gymnophallidae*, *Heterophyidae*, *Nanophyetidae*, *Neodiplostomidae*, and *Plagiorchiidae* (depending on data availability)

was attributed to *Salmonella enterica* Typhi, followed by enteropathogenic *Escherichia coli* (EPEC) and norovirus.
In Europe, *Campylobacter* is the most frequently reported bacterial, foodborne pathogen since 2005 [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. The number of reported confirmed cases was 246'307 in 2016, corresponding to a notification rate of 66.3/100'000 population (based on reports from 27 European Union (EU) member states) [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. Sixteen member states also provided information on the outcome for 178'726 cases. They reported a total of 62 deaths attributable to campylobacteriosis corresponding to a case fatality rate of 0.03%. However, all these figures are subject to underestimation. The "true" incidence of campylobacteriosis in the EU was estimated at 9.2 million cases in 2009 – a year in which 198'252 confirmed cases were reported [Havelaar *et al.*, 2013].
Foodborne disease can also lead to sequelae apart from causing acute illnesses and deaths. Infection with *Campylobacter* can lead, for example, to reactive arthritis (ReA), Guillain-Barré syndrome (GBS), haemolytic-uraemic syndrome (HUS), IBD, and irritable bowel syndrome (IBS) [Keithlin *et al.*, 2014; Mahon and Patrick, 2015; O'Brien, 2017]. Enterohaemorrhagic *Escherichia coli* (EHEC) infection has mostly been associated with HUS, but also thrombotic thrombocytopenic purpura and ReA have been described [Dundas and Todd, 2000; Keithlin *et al.*, 2014]. The best described complications of enteric *Salmonella* infections are ReA and IBS [Keithlin *et al.*, 2015].

1.4.3 The burden of acute gastroenteritis

The Global Burden of Disease Study provided estimates for "diarrhoeal diseases" but not for "acute gastroenteritis" [GBD Diarrhoeal Diseases Collaborators, 2017]. In 2015, "diarrhoeal diseases" were estimated to result in a global burden of 71.6 million DALYs (74.4 million in 2016 [GBD 2016 DALYs and HALE Collaborators, 2017]) and 1.3 million deaths (corresponding to 17.8 deaths per 100'000 population) due to 2.4 billion episodes. The burden of diarrhoeal diseases was estimated at 80'000 episodes, 1'787 DALYs, and 135 deaths (1.6/100'000) for Switzerland [GBD Diarrhoeal Diseases Collaborators, 2017]. Population-based studies investigating the incidence or burden of disease of AG are lacking for Switzerland. However, results of several studies conducted in high-income countries indicate that AG is more frequent than suggested by

the aforementioned Global Burden of Disease Study. For example, a modelling study revealed that, in Australia, there were 16 million cases of "all-cause infectious AG" in 2010, corresponding to around 0.76 episodes per person-year [Gibney *et al.*, 2014]. Around 0.33 cases of AG per person-year were found in a retrospective cross-sectional telephone survey in France in 2009/2010 [Van Cauteren *et al.*, 2012]. A retrospective telephone survey on "intestinal infectious disease" in the UK found 0.53 and 1.53 cases per person-year, depending on the recall period [Viviani *et al.*, 2016]. In the Netherlands, 0.96 episodes of "infectious intestinal disease" were reported per person-year [Doorduyn *et al.*, 2012]. Similarly, the incidence of "acute gastrointestinal illness" was estimated at 0.95 episodes per person-year in Germany [Wilking *et al.*, 2013]. Assuming similar incidence rates for Switzerland of 0.3–1.5 disease episodes per person-year (with a population size of 8.4 million [Bundesamt für Statistik, 2017a]) would result in around 2.5–12.6 million episodes annually. As mentioned above, differences in reported disease incidence cannot only be due to actual differences between countries but could also result from different case definitions and study designs used. To overcome this limitation, Majowicz *et al.* [2008] proposed a standard case definition for AG which is generally used in this thesis: "An individual with $\geq$3 loose stools, or any vomiting, in 24h, but excluding those (a) with cancer of the bowel, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibriosis, coeliac disease, or another chronic illness with symptoms of diarrhoea or vomiting, or (b) who report their symptoms were due to drugs, alcohol, or pregnancy." [Majowicz *et al.*, 2008]. Note, however, that Majowicz *et al.* proposed this definition for "gastroenteritis" instead of "acute gastroenteritis". Still, it has to be noted that this standard case definition is not universally applied and hence, might not always have been used, especially when referring to other literature.
Generally, AG is self-limiting. Therapy should focus on fluid replacement; however in patients with febrile or dysenteric diarrhoea, patients with co-morbidities, and/or in laboratory-confirmed cases of bacterial infection antimicrobial therapy should be considered [DuPont, 2014; Guerrant *et al.*, 2001; Schweiger *et al.*, 2005b].

1.4.4 Foodborne disease or acute gastroenteritis: what is and what should be measured

Laboratory-based surveillance* systems measure the (laboratory-confirmed) incidence of selected pathogens. This incidence will neither reflect the incidence of foodborne disease nor the incidence of AG due to

this pathogen except if the pathogen is entirely foodborne and/or its only manifestation is AG.
Surveillance systems focussing on clinical features of a disease rather than laboratory results could more precisely measure AG. However, this approach would also include cases which are not caused by infectious agents and hence, which require a different approach to control and prevention.
Finally, whether or not a certain pathogen was transmitted via food or through another route of transmission can hardly be determined without detailed investigation. Such detailed investigation could involve identification and molecular characterisation of the pathogen both, in foodstuff and in human samples.
What should be measured largely depends on the purpose of the investigation or the perspective to look at. For characterising the burden of disease in a population, looking at signs and symptoms (hence, AG) rather than the aetiology seems appropriate. However, usefulness of these data is probably limited for defining interventions. Hence, if targeted interventions are the ultimate goal, investigating transmission routes and the frequency of foodborne disease is probably more appropriate.
In summary, most studies and surveillance systems investigate or measure a part or a combination of foodborne disease and AG. Surveillance systems such as the NNSID could be best described as measuring the "incidence of laboratory-confirmed infections caused by pathogens commonly transmitted through food" (apart from many other diseases and pathogens neither associated with foodborne disease nor AG).

1.5 Foodborne disease surveillance in Switzerland

In Switzerland, the following diseases commonly transmitted through food are currently notifiable (as per January 2018): Botulism, brucellosis, campylobacteriosis, cholera, infection with EHEC, hepatitis A, hepatitis E, listeriosis, salmonellosis, shigellosis, trichinellosis, and typhoid fever. Table 1.2 shows the notification criteria for reports on clinical findings (completed by physicians) and on laboratory findings (completed by laboratories) and the time frame for reporting for the aforementioned pathogens. The time frame for reporting most foodborne pathogens has been shortened to 24 hours with the implementation of the new Epidemics Act. For campylobacteriosis, salmonellosis and shigellosis no clinical reports are required; hence, nothing is known about disease manifesta-

Table 1.2: Notifiable pathogens and diseases commonly transmitted through food in Switzerland: notification criteria, process and time frame as per January 2018 [Das Eidgenössische Departement des Innern, 2015a]

	Physician			**Laboratory**	
Disease/pathogen	Notification criterion	Time frame	To whom	Notification criterion	Time frame
Botulism / *Clostridium botulinum*	Clinical suspicion AND administration of antitoxin (not to notify: wound and infant botulism)	2 hours, by phone	CP[a] and FOPH	Positive finding Negative finding (not to notify: wound and infant botulism)	2 hours, by phone
Brucellosis / *Brucella* spp.	Positive laboratory finding	1 week	CP[a]	Positive finding	1 week
Campylobacteriosis / *Campylobacter* spp.				Positive finding Negative finding[b]	Pos: 24 hours Neg: 1 week
Cholera / *Vibrio cholerae*	Positive laboratory finding	24 hours	CP[a]	Positive finding	24 hours
Infection with EHEC / EHEC	Positive laboratory finding	24 hours	CP[a]	Positive finding Negative finding[b]	Pos: 24 hours Neg: 1 week
Hepatitis A / Hepatitis A virus	Positive laboratory finding	24 hours	CP[a]	Positive finding (not to notify: investigation of immune status) Negative finding[b]	Pos: 24 hours Neg: 1 week

Table 1.2: (continued)

Disease/pathogen	Physician			Laboratory	
	Notification criterion	Time frame	To whom	Notification criterion	Time frame
Hepatitis E[c] / Hepatitis E virus[c]	Positive laboratory finding (PCR)	24 hours	CP[a]	Positive finding (PCR only) Negative finding[b]	Pos: 24 hours Neg: 1 week
Listeriosis / *Listeria monocytogenes*	Positive laboratory finding	24 hours	CP[a]	Positive finding Negative finding[b]	Pos: 24 hours Neg: 1 week
Salmonellosis / *Salmonella* spp.				Positive finding Negative finding[b]	Pos: 24 hours Neg: 1 week
Shigellosis / *Shigella* spp.				Positive finding Negative finding[b]	Pos: 24 hours Neg: 1 week
Trichinellosis / *Trichinella spiralis*	Positive laboratory finding	1 week	CP[a]	Positive finding	1 week
Typhoid fever / *Salmonella* Typhi/Paratyphi	Positive laboratory finding	24 hours	CP[a]	Positive finding Negative finding[b]	Pos: 24 hours Neg: 1 week

[a] CP = cantonal physician

[b] Only upon request of the FOPH for epidemiological investigations; since 2018

[c] Notifiable since 2018

Table 1.3: Case numbers and notification rates of notifiable pathogens commonly transmitted through food in Switzerland, 2017.
Source: [Bundesamt für Gesundheit, 2018c]

Pathogen	**Case numbers**	**Notification rate (cases/ 100'000 population)**
Botulism / *Clostridium botulinum*	2	0.02
Brucellosis / *Brucella* spp.	10	0.12
Campylobacteriosis / *Campylobacter* spp.	6'828	80.73
Cholera / *Vibrio cholerae*	0	0
Infection with EHEC / EHEC	698	8.25
Hepatitis A / Hepatitis A virus	114	1.35
Listeriosis / *Listeria monocytogenes*	45	0.53
Salmonellosis / *Salmonella* spp.	1'832	21.66
Shigellosis / *Shigella* spp.	142	1.68
Trichinellosis / *Trichinella spiralis*	1	0.01
Typhoid fever / *Salmonella* Typhi/Paratyphi	22	0.26

tion from surveillance data.
Additionally, in 2016, it was introduced that for *Campylobacter* and *Salmonella* (and selected other non-foodborne pathogens) the total number of tests conducted by month and test method and, thereof, the number of positive results has to be reported once a year. Before this date, no information on the testing volume was available for foodborne infections. Testing volume was only notifiable for human immunodeficiency virus (HIV), influenza and *Legionella* [Das Eidgenössische Departement des Innern, 1999]. Since 2018, the ordinance furthermore stipulates that for selected pathogens (among them are almost all foodborne pathogens) negative findings are notifiable for epidemiological investigations upon request of the FOPH [Das Eidgenössische Departement des Innern, 2015a].
Reports on clinical findings usually include the patient's name and address or the patient's initials and place of residence, date of birth, sex, profession, diagnosis and disease manifestation, information on exposure and risk factors.
Reports on laboratory findings include also the name and address or the initials and place of residence, date of birth and sex of the patient; and

the test result with its interpretation, the sample material, and the diagnostic method used. Additionally, the species, subspecies, serotype or type of toxin (if applicable) have to be reported by laboratories.
Campylobacter spp. is the most frequently reported foodborne pathogen in Switzerland, followed by *Salmonella* spp. and EHEC (Table 1.3). This is in line with surveillance data from the EU [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. However, in the EU, EHEC is relegated to the fourth place by yersiniosis, the latter not being notifiable in Switzerland.

1.6 The epidemiology of selected foodborne pathogens in Switzerland and in the European Union

Campylobacter notifications have been increasing between 2005 and 2012 by about 50% in Switzerland and stabilised at high levels since then [Baumgartner *et al.*, 2012; Bundesamt für Lebensmittelsicherheit und Veterinärwesen and Bundesamt für Gesundheit, 2017]. EHEC case numbers are increasing considerably since 2014 [Bundesamt für Lebensmittelsicherheit und Veterinärwesen and Bundesamt für Gesundheit, 2017]. With almost 700 cases, case numbers in 2017 were the highest ever registered since the beginning of EHEC-reporting in 1999 [Bundesamt für Gesundheit, 2018c; Bundesamt für Lebensmittelsicherheit und Veterinärwesen and Bundesamt für Gesundheit, 2017]. In contrast, *Salmonella* notifications were highest in 1992 with around 7'900 cases and decreased continuously thereafter [Schmid and Baumgartner, 2013]. Since 2009, case numbers stabilised at 1'000–1'500 cases per year [Bundesamt für Lebensmittelsicherheit und Veterinärwesen and Bundesamt für Gesundheit, 2017].
Similarly, in the EU, *Campylobacter* and *Salmonella* showed an increasing and decreasing trend between 2008 and 2016, respectively, which was, however, not statistically significant for the period between 2012 and 2016 [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. Reasons for the increase in campylobacteriosis cases in the EU are manifold: apart from changes in disease epidemiology, some countries have improved their reporting system or changed diagnostic methods leading to an increase in notified cases [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. In a modelling study, Havelaar

et al. [2013] estimated the true incidence of campylobacteriosis and salmonellosis for all EU member states (27 at that time). They came up with factors of underestimation[4] for campylobacteriosis ranging from 0.4 (Finland & Sweden) to 39'400 (Bulgaria) and for salmonellosis ranging from 0.4 (Finland) to 2'080 (Portugal). Additionally, they modelled also the numbers for Switzerland and suggested that reported cases underestimate the true incidence by a factor of 3.3 for campylobacteriosis and 7.1 for salmonellosis. However, there are no other research studies available to support these modelling results for Switzerland. In France, the factor of underestimation was found at 115 (campylobacteriosis) and 20 (salmonellosis) [Van Cauteren *et al.*, 2015a]. Two studies in England / the United Kingdom (UK) revealed multiplication factors of 7.6 and 9.3 for campylobacteriosis, and 3.2 and 4.7 for salmonellosis [Tam *et al.*, 2012; Wheeler *et al.*, 1999].

For EHEC, the epidemiological situation looks different in the EU compared to Switzerland: there was only a slight increase noted in the EU between 2015 and 2016 [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. However, case numbers in the 2012–2016 period are reported to be at higher levels after a large outbreak in 2011 compared to the period before the outbreak [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. The outbreak in Germany in 2011 most likely raised the awareness for EHEC among Swiss physicians, leading to slightly higher case numbers also in Switzerland [Bundesamt für Gesundheit and Nationales Referenzzentrum für enteropathogene Bakterien und Listerien, 2015]. For EHEC, the multiplication factor was estimated at 7.4 in the UK [Tam *et al.*, 2012].

Hepatitis A, the only viral foodborne disease in the Swiss notification system, showed a decreasing trend from 1988 with a notification rate of 10/100'000 population to 2002 (1.9/100'000) [Bundesamt für Gesundheit *et al.*, 2007]. Case numbers remained at a low level until 2016 [Bundesamt für Gesundheit, 2018c]. In early 2017, an increase in cases was noted which may be linked to a European-wide outbreak among men who have sex with men (MSM) [Bundesamt für Gesundheit, 2017b; European Centre for Disease Prevention and Control, 2017]. Underestimation is also an issue in hepatitis A surveillance: in the United States of America (USA) it was estimated that 2 infections occur in the pop-

[4]Havelaar *et al.* [2013] refers to "underreporting", not "underestimation". However, what they compared is the number of reported cases and the "true incidence" which reflects underestimation according to the definition used in this thesis (see chapter v "Glossary")

ulation for every case reported to national surveillance [Klevens *et al.*, 2014]. Furthermore, a systematic review and meta-analysis looking at underreporting of hepatitis A in non-endemic countries revealed that 4 to 97% of hepatitis A cases were reported to public health [Savage *et al.*, 2016].

In conclusion, the huge range of underestimation factors between countries shows that reported case numbers should be compared across countries with caution and that multiplication factors are not interchangeable between countries or health systems not allowing comparing national disease burdens. Similarly, multiplication factors are pathogen-specific. Therefore, exploring the level of underestimation is key in order to understand how surveillance data relate to the incidence in the population. Furthermore, underestimation involves many steps which can change over time; hence, the validity of estimated multiplication factors should be assessed regularly.

2 Rationale, aim and objectives

2.1 Rationale to study the 'burden of illness pyramid'

In Switzerland, notifiable foodborne diseases show both, increasing and decreasing trends in the surveillance data of the NNSID. However, it is largely unknown how these trends observed in national surveillance relate to trends in disease incidence. A variety of factors contributes to the underestimation of the burden of notifiable diseases which depend on characteristics of the pathogen and the health system, both influencing patients' health seeking, physicians' case management and laboratories' testing practices. These steps leading from infection to national disease registration, represented in the burden of illness pyramid, are neither fully understood nor quantified for Switzerland. Underestimation is highly country- and pathogen-specific. Furthermore, the level of underestimation can change over time. Therefore, estimates of underestimation from other countries can only give limited insight into possible multiplication factors for Switzerland.

Knowing the burden of disease at population level is important for priority setting of interventions. However, this burden cannot be quantified in the absence of knowing levels of and factors contributing to underestimation of surveillance data, or of data of population-based studies. Under the assumption that underestimation does not change over time, surveillance data could still be used to assess trends in disease incidence. However, this assumption is daring given the sheer number of factors contributing to underestimation. Hence, decisions based on currently available surveillance data are subject to questionable assumptions.

In summary, understanding the different levels of the burden of illness pyramid and the determinants for advancing from one level to the next is key for correctly interpreting data from the NNSID and for evidence-based decision-making.

2.2 Aim and objectives

The aim of this PhD thesis is to contribute to a better understanding of the burden of illness pyramid for foodborne infections in Switzerland and to apply this knowledge to improve Swiss infectious disease surveillance and control. This will be achieved by characterising data and disease in the surveillance system, researching physicians' and patients' behaviour, determining validity of routine health data bases and assessing the social and economic impacts of foodborne infections. Furthermore, the proportion of individuals advancing from one level to the next in the burden of illness pyramid will be quantified.

Objective 1: To investigate the frequency of cases of foodborne infections as reported to the NNSID and thus, as seen in the top levels of the burden of illness pyramid

a) To describe trends in notification data of foodborne pathogens

b) To calculate positivity rates of foodborne pathogen testing in Switzerland

Objective 2: To investigate the frequency and burden of disease of acute gastroenteritis (AG) at the primary care level in Switzerland

a) To assess trends in the frequency of stool testing for foodborne pathogens

b) To understand and quantitatively characterise physicians' stool testing practices for patients with AG

c) To describe the physicians' perception of AG and foodborne diseases

d) To estimate direct healthcare costs of AG at primary care level in Switzerland

Objective 3: To propose a concept to investigate acute gastrointestinal illness (AGI) at population level in Switzerland

a) To develop a study protocol for a population-based study on the frequency, burden of disease, aetiology and socio-economic impact of AGI in the Swiss population

3 Research concept and methodological overview

The research presented in this PhD thesis is part of a broader research portfolio consisting of several projects and culminating in multiple PhD theses on Swiss health system's research of food- and water-borne infectious diseases. This PhD thesis is the second in the series. The first volume on "Infectious disease surveillance in Switzerland" is entitled "Epidemiology of campylobacteriosis and acute gastroenteritis from a human and health system's perspective in Switzerland" [Bless, 2018].
The research portfolio started by exploring the epidemiology of campylobacteriosis in Switzerland. In this context the importance and lack of understanding of the burden of illness pyramid was noted. Consequently, the scope was broadened to include foodborne diseases in general and strengthened its focus on understanding and quantifying the different levels of the burden of illness pyramid. Furthermore, this research portfolio aims at understanding the validity of data from Swiss infectious disease surveillance and generating a basis for improving national surveillance.

3.1 Overview of research approaches and study designs

The research approach applied for each study is summarised in this section. Figure 3.1 provides an overview of each study undertaken for this thesis studying the various levels of the burden of illness pyramid.

3.1.1 Analysing notification data on *Campylobacter*, *Salmonella*, and hepatitis A

These studies contribute to objective 1a of this thesis.

Notification data of different foodborne pathogens have been analysed in the framework of this thesis to understand the tip of the burden of illness pyramid. For this, data from the NNSID were requested from the FOPH

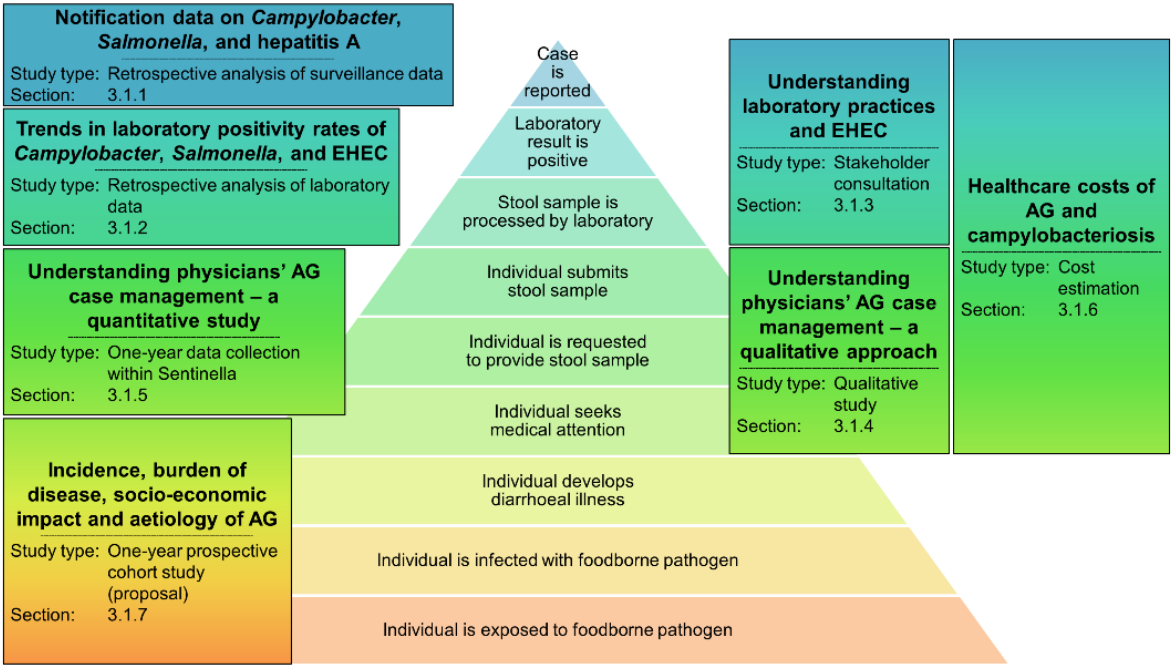

Figure 3.1: Overview of PhD research framework to better understand the burden of illness pyramid for foodborne infections in Switzerland
AG: acute gastroenteritis; EHEC: enterohaemorrhagic *E. coli*; GP: general practitioner

for *Campylobacter* and *Salmonella* (both for the years 1988–2013) and for hepatitis A (years 1988–2016).
Campylobacter and *Salmonella* notification data included only information from reports on laboratory findings. Trends in case numbers and characteristics (age, sex) were analysed and compared for the two pathogens in the light of similar transmission patterns and different public awareness.
For hepatitis A, laboratory reports are complemented by reports on clinical findings providing more detailed information on patient characteristics such as risk factors and suspected exposure sources. Hepatitis A notification data was not only analysed for trends due to changing disease epidemiology and patient characteristics or interventions, but also for trends due to changes in the surveillance system (e.g. changes in notification forms).
Detailed descriptions of the methods applied for these research components are provided in chapter 4 (Schmutz *et al.* [2016]) and chapter 5 (Schmutz *et al.* [2018]).

3.1.2 Studying trends in laboratory positivity rates of *Campylobacter*, *Salmonella*, and EHEC

These studies contribute to objective 1b and objective 2a of this thesis.

The number of tests conducted by diagnostic laboratories is notifiable for selected foodborne pathogens only since the introduction of the new Epidemics Act in 2016. Testing *per se* is a pre-requisite for isolating a pathogen, and hence, the number of tests conducted is strongly influencing the number of case notifications. Therefore, diagnostic laboratories were asked to provide information on all tests conducted for *Campylobacter* spp., *Salmonella* spp. and EHEC over a 10-year period. This data was used to calculate positivity rates, defined as the proportion of positive test results out of all tests conducted for a certain pathogen. Time trends in positivity rates were evaluated together with time trends observed in the NNSID to better understand how notification data translate to the incidence of the disease at population level.
Laboratories reporting highest case numbers for the respective pathogens were selected. Additional laboratories were selected, if necessary, to include all language regions of Switzerland and to represent both hospital and private-sector laboratories.
For *Campylobacter* and *Salmonella*, 11 diagnostic laboratories were se-

lected and asked to provide data for the years 2003–2012. Requested information included case-based data on the patient tested (sex, age, canton of residence, personal identification number assigned by laboratory) and test characteristics (pathogen tested, test result, date of test, test method applied).
For EHEC, the selection included 11 diagnostic laboratories as well. The laboratories were asked for the same information as for *Campylobacter* and *Salmonella* for the years 2007–2016.
Detailed descriptions of the methods applied for these research components are provided in chapter 6 (Bless *et al.* [2017]) and chapter 8.

3.1.3 Understanding laboratory practices and its influence on notification data: the example of EHEC

This study contributes to objective 1a and objective 2a of this thesis.

Usually, stool samples are used for laboratory diagnostics in case of AG, if laboratory diagnostics are considered at all. Physicians as well as laboratory experts influence the selection of pathogens for which the stool sample is tested. Stakeholders from diagnostic laboratories were consulted to understand current practice in laboratory diagnosis of EHEC in Switzerland as well as recent changes therein, potentially influencing surveillance data. Experts working at the laboratories selected for the positivity study on EHEC (see subsection 3.1.2 and chapter 8) were asked to participate. This sampling allowed obtaining background information for interpretation of findings from the positivity study apart from providing important insight into current laboratory practices.
A detailed description of the methods applied for this research component is provided in chapter 7.

3.1.4 Understanding physicians' approaches towards acute gastroenteritis case management – a qualitative approach

This study contributes to objective 2b, objective 2c and objective 2d of this thesis.

Swiss GPs in charge of treating campylobacteriosis patients of a case-control study [Bless *et al.*, 2014] were invited to participate in this qualitative study. GPs were interviewed to get insight into their approaches

to managing patients presenting with AG in general and campylobacteriosis in particular. Understanding case management, and the GPs' decision-making process for or against stool diagnostics in particular, is important for understanding the burden of illness pyramid.
Interviews were additionally used to assess the GPs' perception of the FOPH.
A detailed description of the methods applied for this research component is provided in Bless *et al.* [2016]. A summary of this article including further analyses and additional results on the GPs perception of their role, of the Swiss health system and of the FOPH is provided in chapter 10.

3.1.5 Understanding physicians' approaches towards acute gastroenteritis case management – a quantitative study

This study contributes to objective 2b, objective 2c and objective 2d of this thesis.

In 2014, a study on the frequency of consultations due to AG at the primary care level in Switzerland was conducted within *Sentinella*. All first consultations due to AG were reported by Sentinella-physicians for a full calendar year. Date of birth, sex, hospitalisation status and whether or not the GP requested a stool sample was recorded for all cases. For a subsample of patients, physicians reported additional information including signs and symptoms, medication, absence from work and exposure to selected risk factors. Results from the preceding qualitative study among Swiss GPs (see chapter 10 and Bless *et al.* [2016]) were considered when developing the questionnaire for this study. Apart from providing estimates on the frequency of consultations due to AG at the primary care level, this study provided quantitative insights into GPs' approaches to diagnosis and treatment of AG in Swiss primary care.
A detailed description of the methods applied for this research component is provided in chapter 11 [Schmutz *et al.*, 2017a].

3.1.6 Studying healthcare costs of acute gastroenteritis and campylobacteriosis

This study contributes to objective 2d of this thesis.

This study aimed at estimating healthcare costs of campylobacteriosis in

Switzerland. Given the difficulty to clearly separate campylobacteriosis from AG (without known aetiology), estimates for both conditions were made. Different patient management models were developed based on expert opinions and results from our previous research to account for the heterogeneity in disease presentation and patient characteristics influencing case management. Healthcare costs for consultations, laboratory diagnostics, medication and hospitalisation associated with each patient management model were extracted from official tariff lists. Estimates of the frequency of each model were used to extrapolate individual costs to overall healthcare costs for Switzerland. Estimates were based on costs and case numbers for the year 2012 as this was the year with most available information (health and cost statistics).
A detailed description of the methods applied for this research component is provided in chapter 12 [Schmutz *et al.*, 2017b].

3.1.7 Studying the incidence, burden of disease, socio-economic impact and aetiology of acute gastroenteritis

This study proposal contributes to objective 3a of this thesis.

To understand the lowest levels of the burden of illness pyramid, a population-based study is required. Considering the various studies conducted as part of volume I on "Infectious disease surveillance in Switzerland" [Bless, 2018] and our current understanding of food- and water-borne disease surveillance in Switzerland, a one-year, prospective cohort study is proposed to assess the incidence, burden of disease, socio-economic impact and aetiology of AG in Switzerland. Given our previous research on surveillance data, its generation and limitations, and the awareness of this data situation on the side of the FOPH and the Federal Food Safety and Veterinary Office (FSVO) allowed us to propose such a cohort study to the federal authorities.
A cohort of 3'000 participants, recruited from a random sample of the general population in Switzerland, is followed-up weekly during a one-year period (52 weeks). Occurrence of GI signs and symptoms as well as exposure to transient risk factors are assessed through weekly questionnaires, available electronically and on paper. After reporting an episode of acute gastrointestinal illness (AGI)*, participants receive an additional questionnaire to assess the perceived illness experience, patients' help seeking behaviour and socio-economic consequences of the disease episode (including inability to work). Furthermore, stool samples from a

subsample of symptomatic and asymptomatic participants are obtained to investigate the aetiology of AGI (symptomatic participants) and the prevalence of bacteria harbouring selected antibiotic resistances and of selected bacterial GI pathogens in asymptomatic participants.
As part of this PhD thesis, a detailed proposal for the cohort study was developed and funding was obtained. Operational planning and execution of the study will be conducted in the framework of two upcoming PhD theses.
A detailed description of the proposed cohort study is provided in chapter 13.

3.2 Ethical considerations

Studies involving personal health-related data or human biological material are subject to the Federal Act on Research involving Human Beings (Human Research Act, HRA; SR 810.30) and require ethical clearance except if the data or material is fully anonymised [Die Bundesversammlung der Schweizerischen Eidgenossenschaft, 2011]. Studies conducted or data collected in pursuance of the Epidemics Act are exempted from ethical clearance.
Data from the NNSID was collected under the Epidemics Act and was anonymised. Therefore, the analyses of notification data of *Campylobacter*, *Salmonella* and hepatitis A (chapters 4 and 5) did not require ethical clearance. Similarly, data collection for the study in *Sentinella* (chapter 11) was conducted through the FOPH in pursuance of the Epidemics Act.
For the positivity studies on *Campylobacter* and *Salmonella* (chapter 6), ethical clearance was obtained from the Ethikkommission Nordwest-und Zentralschweiz (EKNZ) (ethics committee northwest/central Switzerland) to work with "already existing, health-related data without individual consent and information" (reference number: EKNZ:2014–164) while the positivity study on EHEC (chapter 8) was mandated by the FOPH and conducted under the Epidemics Act (decree issued by the FOPH).
The stakeholder consultation for understanding laboratory practices of EHEC diagnostics (chapter 7) did neither involve personal health-related data nor biological material and hence, this research was not subject to the Human Research Act.
Similarly, the qualitative study among Swiss GPs (chapter 10) involved their professional experience and opinion rather than personal health-

related information. Furthermore, this project was part of an outbreak investigation [Bless *et al.*, 2014] conducted under the Epidemics Act.
The project estimating healthcare costs of AG and campylobacteriosis (chapter 12) relied on publicly available or aggregated data from previous research and official statistics. Experts were asked about their professional opinion, not about personal- or patient-related information. This part of the project did, hence, not require ethical clearance. However, ethical approval was obtained for using pseudonymised patient invoices to cross-validate cost estimates (reference number: EKNZ:2014–159).
Finally, the cohort study on AG (chapter 13) will require ethical clearance. Submission to the respective ethical committee(s) will occur as soon as the detailed planning of the study is completed and all documents (e.g. questionnaires) are prepared.
Research presented in this thesis was conducted in agreement with the Declaration of Helsinki [World Medical Association, 2013] as well as the Essentials of Good Epidemiological Practice [Altpeter *et al.*, 2005].

3.3 Collaborations

The main external partners for the research presented in this thesis were the FOPH and the FSVO.
The surveillance systems maintained by the FOPH generate data only at the upper level(s) of the burden of illness pyramid. However, the FOPH is well aware of this limitation and has a vested interest in (a) understanding lower parts of the pyramid and (b) generating knowledge to potentially improve current infectious disease surveillance systems. Several projects which are part of this thesis relied on and profited from this openness and interest of the Swiss public health authorities. This PhD research is part of a longstanding research partnership with the FOPH through several mandated research works in foodborne infectious diseases. Specifically, the FOPH provided data for the analyses of trends in *Campylobacter*, *Salmonella* and hepatitis A (chapters 4 and 5), facilitated the initial contact with the diagnostic laboratories involved in the positivity studies (chapters 6 and 8), organised joint visits of laboratory experts (chapter 7), and was instrumental in and funded large parts of these research endeavours. Furthermore, the administrative lead and data management of *Sentinella* is with the FOPH. This enabled us to get access to the data generated through this system (chapter 11). Finally, the FOPH is supporting the upcoming cohort study (chapter 13) both conceptually and financially together with the FSVO.

The FSVO is interested in our research as many GI diseases are zoonoses and/or concern food safety. The two federal offices maintain a close dialogue within this thematic field which is fostered by our research outputs. For example, media communications in response to our research was harmonised between the FOPH and the FSVO as well as between the federal offices and the Swiss Tropical and Public Health Institute (Swiss TPH). Several diagnostic laboratories from all over Switzerland were involved in our research by providing data for the positivity studies and important background information for interpretation of surveillance and laboratory data (chapters 6 and 8).
We collaborated with medical anthropologists from Partners for Applied Social Sciences (PASS) Suisse and with the Centre for Primary Health Care from the University of Basel to investigate the GPs' management and understanding of AG and campylobacteriosis (chapter 10). The latter also supported us in developing the questionnaire for the *Sentinella* study (chapter 11).
Collaboration with the Institute of Pharmaceutical Medicine of the University of Basel and internal collaboration with the Medical Services and Diagnostics department at Swiss TPH was sought for the estimation of healthcare costs of AG and campylobacteriosis (chapter 12).
The cohort study on AG in Switzerland (chapter 13) will involve several partners. Apart from the federal offices, collaboration with the National Reference Centre for Enteropathogenic Bacteria and Listeria (NENT), the German National reference laboratory for *Clostridium difficile* and with the "labormedizinisches zentrum Dr Risch" (a Swiss private-sector diagnostic laboratory) was initiated. Future internal and external collaborators will involve, among others, social scientists and health economists to develop the tools for assessing the social and economic burden and medical personnel to follow-up on patient histories and medical records.

Part II

THE BURDEN OF ILLNESS PYRAMID OF FOODBORNE INFECTIONS: UNDERSTANDING THE TIP OF THE ICEBERG

4 Inverse trends of *Campylobacter* and *Salmonella* in Swiss surveillance data, 1988–2013

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SURVEILLANCE AND OUTBREAK REPORT

Inverse trends of *Campylobacter* and *Salmonella* in Swiss surveillance data, 1988–2013

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Clinical isolates of *Campylobacter* spp. and *Salmonella* spp. are notifiable in Switzerland. In 1995, *Campylobacter* replaced *Salmonella* as the most frequently reported food-borne pathogen. We analysed notification data (1988–2013) for these two bacterial, gastrointestinal pathogens of public health importance in Switzerland. Notification rates were calculated using data for the average resident population. Between 1988 and 2013, notified campylobacteriosis cases doubled from 3,127 to 7,499, while *Salmonella* case notifications decreased, from 4,291 to 1,267. Case notifications for both pathogens peaked during summer months. *Campylobacter* infections showed a distinct winter peak, particularly in the 2011/12, 2012/13 and 2013/14 winter seasons. *Campylobacter* case notifications showed more frequent infection in males than females in all but 20–24 year-olds. Among reported cases, patients' average age increased for campylobacteriosis but not for salmonellosis. The inverse trends observed in case notifications for the two pathogens indicate an increase in campylobacteriosis cases. It appears unlikely that changes in patients' health-seeking or physicians' testing behaviour would affect *Campylobacter* and *Salmonella* case notifications differently. The implementation of legal microbiological criteria for foodstuff was likely an effective means of controlling human salmonellosis. Such criteria should be decreed for *Campylobacter*, creating incentives for producers to lower *Campylobacter* prevalence in poultry.

Introduction

Campylobacter spp. and *Salmonella* spp. are the most frequently reported zoonotic infections in Switzerland. The Federal Office of Public Health (FOPH) monitors communicable diseases in Switzerland. The National Notification System for Infectious Diseases (NNSID) is an integral part of ensuring compliance with this obligation and was implemented nationwide, in a standardised way, in 1987. The regulation on communicable disease notifications determines which diseases have to be reported, by whom and in what timeframe [1]. Among food-borne pathogens, *Campylobacter* spp., *Salmonella* spp., *Listeria* spp., enterohaemorrhagic *Escherichia coli*, *Shigella* spp., and hepatitis A virus are notifiable. Laboratories must report isolates of *Campylobacter* and *Salmonella* within one week of discovery. For patients with suspected bacterial diarrhoea, basic stool culture including *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. is the routine method of laboratory diagnosis [2].

In humans, campylobacteriosis is most frequently caused by *Campylobacter jejuni* and *C. coli* [3]. Signs and symptoms include watery or bloody diarrhoea, fever, abdominal cramps, vomiting and malaise and usually occur after an incubation period of 2–5 days [4]. The disease usually resolves without antibiotic treatment within one week. A recent study on determinants of the disease in Switzerland showed that laboratory-confirmed campylobacteriosis can lead to severe illness in patients [5]. Complications such as Guillain-Barré syndrome can follow *Campylobacter* infections, although this is rare [4,6]. Fatal cases are possible, but the reported case fatality rate of 0.1% is small and four times lower than the fatality rate for salmonellosis [7].

There are more than 2,600 serovars of *Salmonella*, of which *S. enterica* subspecies *enterica* serovars Enteritidis (*S.* Enteritidis) and Typhimurium (*S.* Typhimurium) are the most frequently reported [8]. Signs and symptoms of salmonellosis are similar to those of campylobacteriosis but the incubation period is shorter at 6–72 hours (usually 12–36 hours) [9]. In a group of volunteers, the minimal infectious dose was found to be at least 200 times higher for *Salmonella* than for *Campylobacter* (10^3-10^5 vs 500 organisms) [10]. However, *Salmonella* outbreaks have been reported

Abstract

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In Switzerland, *Campylobacter* replaced *Salmonella* as the most frequent food-borne pathogen isolated from clinical specimens in 1995 [12]. In Europe, predominance of *Campylobacter* has been reported from 2005 onwards [13]. *Campylobacter* notifications were stable in European Union (EU) countries between 2009 and 2013 while *Salmonella* notifications declined. Nonetheless, reported food-borne outbreaks were more often caused by *Salmonella* spp. than by *Campylobacter* spp. (1'168 *vs.* 414 in 2013).
The aim of this study is to describe the epidemiological patterns and trends of *Campylobacter* and *Salmonella* case notifications in Switzerland and to identify factors leading to the inverse trends observed from the NNSID.

Methods

Medical diagnostic laboratories in Switzerland are obliged by law to report positive *Campylobacter* and *Salmonella* test results to the FOPH and to the cantonal chief medical officer in the patient's canton of residence within one week of discovery [1]. Reports must include information

on laboratory diagnosis (test result, interpretation, type of sample, detection method and date), patient data (sex, date of birth and place of residence) and physician- and diagnosing laboratory-related data (name, phone and fax number, and address). The FOPH enters the information into the NNSID database. If the patient's canton of residence is unknown, the canton of the reporting laboratory is entered.
The present study used *Campylobacter* and enteric *Salmonella* case notification data from the present NNSID's first full year of data collection (1988) until the end of 2013. Data on patients residing outside of Switzerland were excluded. If residency was not specified, the record was kept in the analysis. Notification rates, defined as the number of cases per 100'000 resident population, were calculated. The term 'notification rate' was used instead of 'incidence rate' to be consistent with other authors [13] and because the numbers calculated should not be equated with a true population incidence. To calculate notification rates, data on the average permanent resident population, obtained from the Federal Statistical Office's STATTAB database, were used [14]. Data was analysed and graphically represented using the statistical software Stata (Version 13.0).

Results

Campylobacteriosis trends

A 2.5-fold increase in the number of reported campylobacteriosis cases, from 3'127 cases in 1988 to 7'499 cases in 2013, was observed (Figure 4.1). Case numbers increased steadily from 1988 to 2000, until they reached 7'000. Thereafter, *Campylobacter* case notifications dropped and levelled off at 5'000 cases annually and then rose steadily again from 2007, exceeding the peak level reached in 2000. The highest number of cases reported to date was 8'480 cases in 2012. In each year since 1988, a peak was observed during the summer months (June–August) (Figures 4.2 and 4.3).
A second, much shorter peak was noted in December and January in all years. This winter peak has been especially pronounced in the past few years. While the highest weekly case numbers during the summer and winter peaks were comparable in 2009 and 2010, weekly case numbers were much higher during the winter peaks of 2011/12, 2012/13 and 2013/14 compared with the preceding summer peaks (Figure 4.3).
The increase in *Campylobacter* case notification rates differed by age (Figure 4.4). Among younger age groups, the increase in notification

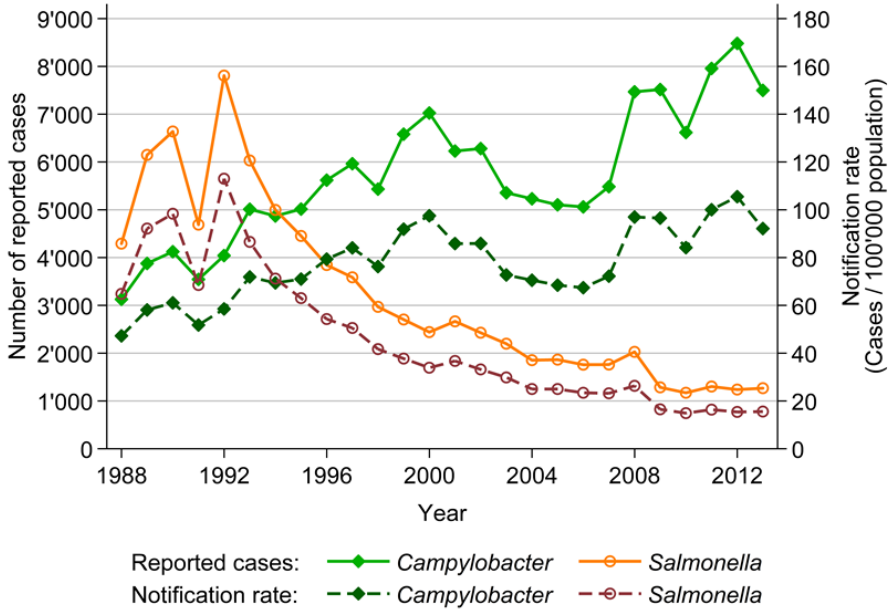

Figure 4.1: Number of *Campylobacter* and *Salmonella* case notifications and notification rates registered at the Federal Office of Public Health, Switzerland, 1988–2013

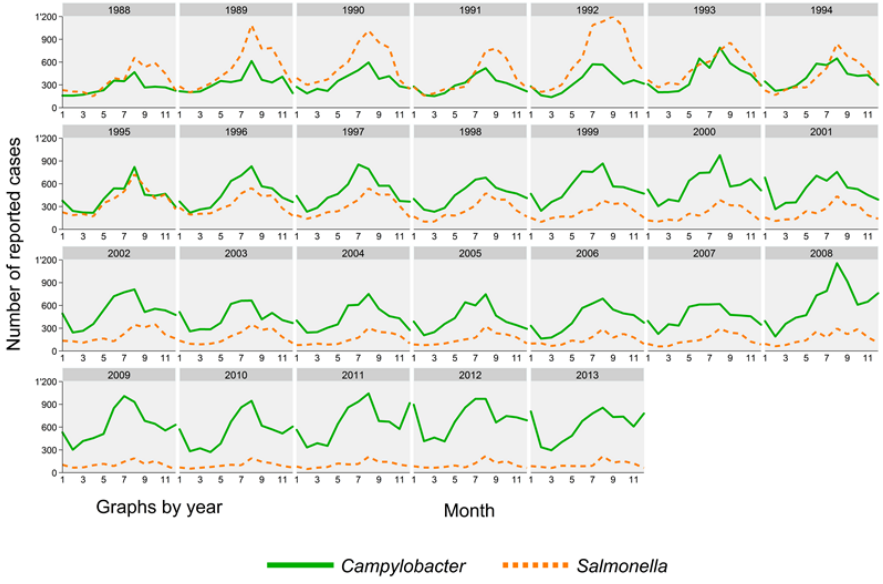

Figure 4.2: Monthly number of notified campylobacteriosis and salmonellosis cases, Switzerland, 1988–2013

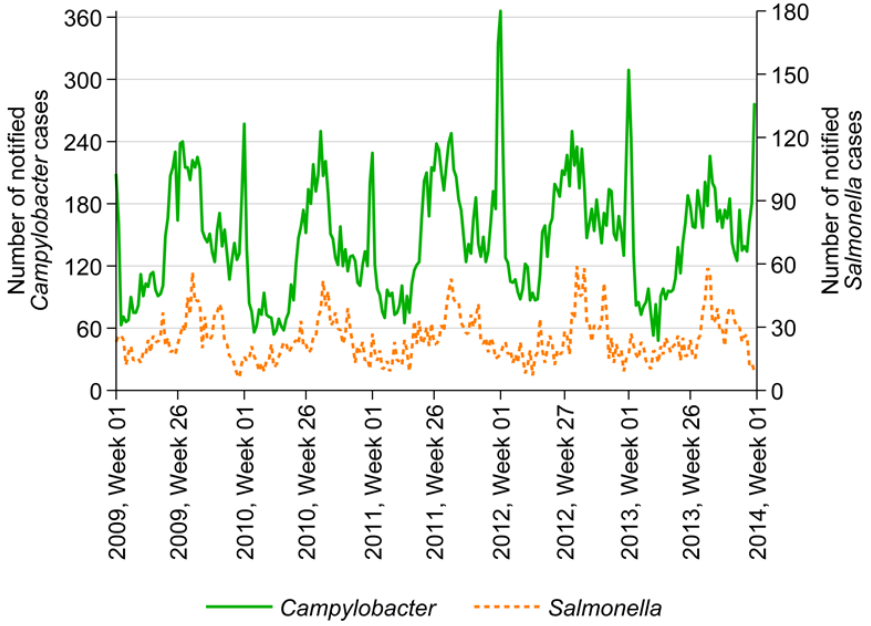

Figure 4.3: Weekly number of notified campylobacteriosis and salmonellosis cases, Switzerland, 2009–2013

Figure 4.4: Trends in *Campylobacter* notification rates between age groups and sexes, Switzerland, 1988–2013

Table 4.1: Comparison of notification rates for *Campylobacter* and *Salmonella* among different age groups, Switzerland, 1988 and 2013

	Campylobacter			*Salmonella*		
Age	Notification rate		%	Notification rate		%
group	1988	2013	increase	1988	2013	increase
<5	105.3	102.3	-3%	216.1	51.5	-76%
5–9	49.9	62.9	+26%	85.1	23.4	-73%
10–14	29.7	58.1	+96%	59.1	15.1	-74%
15–19	54.7	108.1	+98%	63.4	18.1	-71%
20–24	97.4	160.7	+65%	68.1	25.3	-63%
25–44	49.2	91.2	+85%	51.6	10.6	-79%
45–64	24.4	78.3	+221%	41.1	10.9	-73%
65–84	19.2	100.1	+421%	38.6	15.1	-61%
85+	11.7	92.2	+688%	62.7	9.3	-85%

rates over the years was less pronounced than among older age groups. In children younger than five years old, the notification rates decreased from 105.3 to 102.3 cases per 100'000 population between 1988 and 2013 (-3%) (Table 4.1).

This decrease was statistically significant (permutation test for trend, p=0.03). There was no statistically significant (decreasing or increasing) trend in the 5–9 year-olds; in all older age groups, the increasing trend was statistically significant (permutation test for trend, p=0.01 for 20–24 year-olds, p<0.01 for all other age groups). Among those aged 85 years and older, the notification rate increased more than seven-fold, from 11.7 to 92.2 cases per 100'000 population during the same time period. The median age of campylobacteriosis patients increased from 25 years (interquartile range, IQR: 17–38) in 1988 to 39 years (IQR: 23–59) in 2013. In all but the 20–24 year-old age group, notification rates were higher for males than for females (Figure 4.4). Males accounted for 53.4–57.5% of total case notifications each year.

Campylobacter diagnostics identified *C. jejuni* or *C. coli* in the majority of clinical samples (88.5–96.8% every year; data not shown). For most of the remaining cases, the species was not identified or not reported. Reported sample material came from stool (98.8%), blood or serum (0.4%), and other or unspecified materials (0.8%). The majority of cases were tested using culture-based methods directly or confirmatively after PCR (>97%).

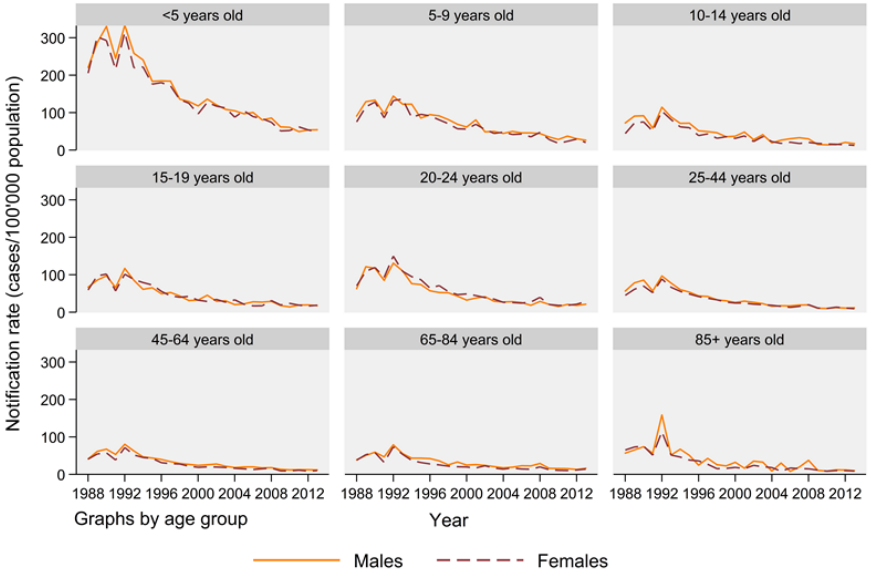

Figure 4.5: Trends in *Salmonella* notification rates between age groups and sexes, Switzerland 1988–2013

Salmonellosis trends

Salmonellosis cases reported to the FOPH increased from 4'291 cases in 1988 to 7'806 cases in 1992 (Figure 4.1). Since 1992, *Salmonella* case notifications steadily decreased until reaching 1'267 cases in 2013. The highest number of *Salmonella* case notifications each year was registered in late summer (July–October), indicating a seasonal pattern (Figures 4.2 and 4.3).
Time trends did not differ between sex and age groups (Table 4.1, figure 4.5).
Each year, 49.6–56.2% of reported cases occurred in males. The median age of salmonellosis patients increased from 25 years (IQR: 7–44) in 1988 to 29 years (IQR: 11–56) in 2013. In terms of notification rates, the highest absolute reduction occurred in the youngest age group (under five years, figure 4.5). The reduction was, however, similar for all age groups when looking at percentage decrease (Table 4.1). The decreasing trend for all age groups from 1988 to 2013 was statistically significant (permutation test for trend, $p<0.01$ for all age groups).
The two most frequently reported serovars were *S.* Enteritidis (54.0%) and *S.* Typhimurium (13.7%). Other reported *S. enterica* serovars included Virchow, Infantis and the monophasic Typhimurium 4,12:i:- (only differentiated in the notification system since 2010).

Discussion

In Switzerland, there has been a marked increase in *Campylobacter* case notifications since 1988, when surveillance began, while case numbers have decreased for salmonellosis. The number of *Campylobacter* infections nowadays is similar to levels of *Salmonella* 20 years ago. Salmonellosis has reduced considerably since then, due to control programmes targeting poultry production. Campylobacteriosis has also increased throughout the EU, though the numbers seem to have stabilised between 2009 and 2013; for salmonellosis, a decreasing trend continues [13]. Time trends for *Campylobacter* in Switzerland differ between age groups, even when looking at age-group-specific notification rates and adjusting for demographic changes in the population.

True increase in campylobacteriosis frequency

One study from the Netherlands showed that stool-testing frequency increased between 1998 and 2008, which might help to explain the in-

crease in campylobacteriosis cases [15]. Along these lines, the decrease in salmonellosis cases would be even larger in the absence of intensified testing.

It is difficult to interpret the changes in the number of positive test results without knowing more about changes in the number of individuals seeking medical consultations, in the proportion of patients being prescribed stool testing and in the total number of tests performed (positive and negative) in Switzerland. Different factors can influence notification data such as changes in risk factors, in patients' health-seeking behaviour, in physician testing practices, in human susceptibility, or in the virulence or pathogenicity of *Campylobacter* spp. and *Salmonella* spp.

When a patient presents with acute gastroenteritis necessitating further laboratory testing, Swiss physicians most commonly request basic stool bacteriology, which includes testing for *Campylobacter*, *Salmonella* and *Shigella* (data not shown). Therefore, a change in testing frequency without a change in disease epidemiology would most likely lead to a similar change in both *Campylobacter* and *Salmonella* case notifications. Some improvements in stool culture methodology have been made in the past 25 years; however, changes cannot explain the inverse trends observed (personal communication, Roger Stephan, 30 July 2015). Furthermore, negative test results are not notifiable and, hence, the total number of tests (denominator) is unknown. Knowing the denominator would help to confirm or reject the hypothesis that a change in testing frequency does not explain the increase in *Campylobacter* case notifications and would allow for a better interpretation of the trends observed in the NNSID. Though stool culture methods did not change significantly, the physicians' awareness towards campylobacteriosis is likely to have increased. It is not known to what extent this might have influenced notification data. Changes in patients' health-seeking behaviour are unlikely to influence *Campylobacter* and *Salmonella* case notifications in different ways. Consequently, we assume that the decrease in *Salmonella* case notifications and the increase in *Campylobacter* case notifications represent real epidemiological trends.

The revised Swiss Epidemics Act effective since January 2016, and its allocated ordinances obligates diagnostic laboratories to report annually the total number of positive and negative *Campylobacter* and *Salmonella* tests performed [16]. This innovation will allow basic routine analysis of trends in testing frequency and positivity rates in the future.

The influence of sex and age on food-borne disease notifications

Salmonella case notifications do not differ between sexes, even when stratified by age groups. In contrast, *Campylobacter* case notifications reveal higher notification rates among males in all age groups, except for those in the 20–24 year-old group. Interestingly, studies from Germany and England and Wales also show that females in their twenties are more frequently affected by campylobacteriosis than males, while male cases dominate in all other age groups [17, 18]. Schielke *et al.* [17] suggested that women in this age group are more frequently involved in childcare activities, which might lead to increased human-to-human transmission. They also suggest that women in this age group are more often exposed to potentially contaminated chicken because they prepare and eat chicken more frequently than men of the same age. They may also be in closer contact with pets, which often harbour the same strains as their owners [19]. Different help-seeking behaviour of patients in this age group or different testing practices of physicians could also explain variations. Moreover, it seems likely that genetic or hormonal factors lead to differences by sex, as notification rates in males and females differ already in the youngest age group (under five years) (Figure 4.4) [20]. We assume that in the youngest age group, health-seeking behaviour and eating habits are not yet dependent on sex and are rather driven by parents or other persons engaged in childcare.

Available information from England and Wales also shows that adults, including the elderly, increasingly test positive for *Campylobacter* [18]. It has been suggested that the increasing use of proton pump inhibitors (PPIs) might explain a part of this phenomenon, especially among the elderly. Several studies have found that the use of PPIs is a risk factor for infection with *Campylobacter* and other enteric pathogens [21]. However, one study revealed that patients prescribed PPIs were already at increased risk of gastrointestinal infection, even before prescription of these drugs [22]. In any case, conditions leading to PPI use or prescription are likely associated with acute infectious gastroenteritis. Why the aforementioned risk factor would only influence the frequency of *Campylobacter* but not *Salmonella* case notifications remains unknown. One possible explanation is that the infective dose of *Campylobacter* is generally lower than that of enteric *Salmonellae*. A recent study of poultry consumers' behaviour, risk perception and knowledge related to campylobacteriosis and domestic food safety showed that unsafe cooks were more likely to be male and of younger age [23]. Even though this finding

is consistent with high *Campylobacter* notification rates observed among young adults, it does not explain the increasing rates among the elderly.

Food safety regulations

Campylobacter and *Salmonella* infections are assumed to be mainly food-borne. Genotyping and epidemiological studies in Switzerland have shown that chicken meat is the most likely source of infection in the majority of human campylobacteriosis cases [5, 24-26]. In concert with these findings, a recent time-series analysis showed a significant association between *Campylobacter* prevalence in broiler chickens and human illness [27]. In Switzerland, poultry consumption has increased in the past 25 years. While the average per capita consumption was 7.8kg in 1988, it was 11.4kg in 2013 [28, 29].

Eggs and egg-containing products were shown to be risk factors for salmonellosis in Switzerland in 1993 [30]. The legislating authorities addressed the risk of these food-borne pathogens by setting and enforcing microbiological criteria.

As early as 1969, an official method to detect enteritic *Salmonella* in foods was published in the Swiss Food Manual [31]. Also, guidance levels for *Salmonella* in different food categories were given.

In 1981, legal microbiological criteria for foods were decreed for the first time in a Federal Ordinance [32]. Criteria for *Salmonella* were as follows. For baby foods and diet products: not detectable (nd) in 50g; drinking water: nd in 5l; other products: nd in 20g. For 'other products', authorities could refrain from measures if the product in question had to undergo treatment (e.g. cooking) prior to consumption. In 1995, after a revision of the ordinance, criteria for *Salmonella* were set at as follows. For baby foods: nd in 50g; drinking water: nd in 5l; ready-to-eat foods: nd in 25 g; and spices: nd in 25g [33]. In 2005, Swiss food legislation adopted the European Union's microbiological criteria for *Salmonella* in food [34].

Salmonella limits for some categories of raw meat were issued as the national law adapted to EU hygiene regulations in 2006 [35]. To combat the epidemic with *S.* Enteritidis in eggs, mandatory screening of layer hens and measures to eradicate positive flocks were decreed by the Ordinance for the Control and Eradication of Epizoonotic Diseases as early as 1993 [36]. Apart from a ban on battery-caged chicken rearing (in effect since 1992 [37]), no further measures (such as vaccinations of layer hens against *S.* Enteritidis) are implemented in Switzerland.

As early as 1987, a limit for *Campylobacter* was decreed in the Ordinance

on Hygiene, which was 'not detectable in 10g of ready-to-eat foods' (later, not detectable in 25g) after enrichment. This microbiological criterion was abrogated in 2006. To address the risk of *Campylobacter* in connection with poultry liver, since 2014 the Ordinance has stipulated that poultry liver must be sold frozen if it cannot be shown that the product comes from a *Campylobacter*-free flock [35]. Furthermore, a process hygiene criterion to minimise *Campylobacter* in poultry slaughterhouses is underway and should enter into force in 2016. However, criteria for *Campylobacter* on raw poultry meat are not currently being considered.

Relevant epidemiological studies in Switzerland

In 2013, 37.7% (169/448) of broiler flocks and 65% (226/348) of rectum-anal swab samples taken from pigs at slaughter tested positive for *Campylobacter* [38]. In the same year, only 1% of 3'636 samples of fresh poultry meat, poultry meat preparations and poultry meat products at different stages of processing tested positive for *Salmonella*. Twenty-three years prior, *Salmonella* contamination levels in Switzerland were much higher. In a 1990 study, 19.2% of chicken neck skin lobs and 47.7% of broiler flocks were found to be *Salmonella*-positive [39]. As a consequence, *Salmonella* control measures as described above were implemented in the 1990s and led to a significant reduction in the number of human cases reported.

In Switzerland, salmonellosis and campylobacteriosis case curves crossed in 1995; in Austria, it was in 2006 [40]. The reason for this striking difference might be that Switzerland addressed the epidemic of *S.* Enteritidis in eggs at a very early stage.

The reduction of domestic salmonellosis cases resulted in a higher prominence of travel-associated transmission risks in relative terms, which was shown by Schmid and Baumgartner: the (relative) proportion of travel-associated *S.* Enteritidis cases increased substantially from 20% in 1993 to 45% in 2011/12 [41]. Two case-control studies on campylobacteriosis [5, 26] and a case-control study on salmonellosis [30] conducted in Switzerland identified travel abroad as a risk factor for the diseases. However, this finding has to be interpreted with care, as patients with travel history are more likely to be tested (data not shown) and all studies recruited laboratory-confirmed cases.

The observed winter peak in *Campylobacter* infections can be attributed partly to the traditional consumption of meat fondue over Christmas and New Year [5]. However, it is not known why this winter peak has been more pronounced in the past few years. Given the increasing per

capita consumption of poultry meat [28, 29], one could hypothesise that poultry has become more popular in meat fondues.
Outbreaks due to *Campylobacter* or *Salmonella* also occurred in Switzerland. However, the number of foodborne outbreaks decreased significantly between 1993 and 2010, mainly due to the reduction of salmonellosis [12]. The number of registered *Salmonella* outbreaks dropped from 27 in 1993 to one in 2010 while the number of *Campylobacter* outbreaks varied between none and five throughout this time period. In relation to the number of cases, *Salmonella* is causing more outbreaks than *Campylobacter* both in Europe and in Switzerland.

Public awareness and knowledge about the diseases

Public awareness and people's knowledge of *Campylobacter* and *Salmonella* in Switzerland are as different as the trends observed in the two pathogens in the NNSID. In 2011, a consumer survey showed that 76% of participants were 'very concerned' or 'somewhat concerned' about *Salmonella* in foods [42]. Only 1% of respondents stated that they had not heard of the *Salmonella* bacterium. In contrast, only 33% were 'very concerned' or 'somewhat concerned' about *Campylobacter* and more than half (52%) had not heard of the pathogen. Unpublished data from a recent case-control study in Switzerland [5] confirm those figures: 55% of people infected with campylobacteriosis (cases) and 68% of healthy people (population-based controls) had never heard of *Campylobacter*, while only 2% of cases and 3% of controls had never heard of *Salmonella*. The lack of knowledge about safe food handling and avoidance of cross-contamination, and low personal risk perception are the main reasons for unsafe food handling [23, 43]. The high prevalence of *Campylobacter* in chicken products, the low infective dose of *Campylobacter* and the increasing consumption of chicken meat combined with the apparent lack of knowledge about the *Campylobacter*-pathogen are all factors facilitating infection.

Conclusions

Campylobacter spp. infections are a serious and increasing public health concern in Switzerland. For *Salmonella* spp. infections, an epidemiological turnaround has been achieved through concerted efforts and legal regulations of the poultry- and food-production industries, but little has been done to date to prevent *Campylobacter* infections on a large scale. Food safety interventions before the sale of poultry meat are urgently

required to reduce *Campylobacter* contamination frequencies. Since the number of control options is limited, the hygienic treatment of chicken carcasses with chemicals, for example peracetic acid, should not be excluded from discussion [44]. However, the population's limited awareness of *Campylobacter* must also be addressed. It seems reasonable to believe that the same type of behaviour changes that reduced *Salmonella* infections can be applied to prevent *Campylobacter* infections and that caution can be extended from eggs to raw poultry meat, cutting boards and knives.

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Conflict of interests

The authors declare that they have no conflict of interest.

Authors' contributions

DM and MM conceived the idea of and designed the study with CS; MJ provided the data; CS and DM analysed the data and CS wrote the first draft; MJ, AB, MM and DM contributed to the interpretation of the data, writing and reviewing of the manuscript.

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5 Hepatitis A in Switzerland: An analysis of 29 years of surveillance data and contemporary challenges

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Hepatitis A in Switzerland: An analysis of 29 years of surveillance data and contemporary challenges

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ABSTRACT

Background: Hepatitis A (HA) incidence declined in most European countries in the past decades. We analysed HA notification data for Switzerland of 29 years looking for disease- and notification system-related factors possibly contributing to observed trends.

Method: Notification data were descriptively analysed using five time intervals (1988–1993, 1994–1999, 2000–2005, 2006–2011, 2012–2016); and notification rates were calculated.

Results: From 1988 to 2016, the HA notification rate decreased from 9.5 to 0.5 per 100'000 population in Switzerland. Median age and the proportion of hospitalised cases increased over time. In the 1988–1993-time period, intravenous drug use was the most frequently mentioned risk exposure while consumption of contaminated food/beverages was most frequently mentioned in the 2012–2016-time period.

Conclusions: Notification data does not allow reliably identifying current risk groups (e.g. travellers) due to low case numbers, limited availability and reliability of information. It is important to document changes in the surveillance system for later analyses and interpretation of long-term trends. Population susceptibility likely increases underlining the importance of continued and continuous surveillance and prevention efforts despite decreasing case numbers. Operational research is recommended to further investigate observed trends of HA and to enhance the abilities for decision making from Swiss HA surveillance data.

1. Introduction

In most European countries, incidence and endemicity of hepatitis A virus (HAV) infection are classified as low or very low[1] [2–5]. However, this does not mean that the disease can be ignored. It rather implies that the characteristics of HAV infections differ from those countries with high or intermediate HAV endemicity features.

HAV infection is usually asymptomatic or mild in young children [6]. HAV infection is more often symptomatic with increasing age, and may present with fever, malaise, anorexia, nausea, abdominal discomfort, diarrhoea, vomiting, fatigue and jaundice after an incubation period of 15–50 days [1,6]. Signs and symptoms of acute hepatitis A (HA) are indistinguishable from acute hepatitis B (HBV) and C virus (HCV) infections [6]. However, in contrast to HBV and HCV, HAV does not lead to chronic infection even though relapse of symptoms and fulminant hepatitis can occur [6].

Safe and effective vaccines against HAV exist. HAV vaccination rather than passive immunisation is recommended for pre- and post-exposure prophylaxis and can be considered to contain outbreaks [1]. In areas of high endemicity, most people get infected at very young age. Hence, asymptomatic infection is likely and the burden of disease of HA is low in these countries. With decreasing level of endemicity, average age at infection and disease severity increase. Therefore, it is assumed that countries with intermediate endemicity levels benefit the most from universal vaccination against HAV [1]. The World Health Organization (WHO) recommends large-scale vaccination in areas with intermediate HAV endemicity and targeted vaccination of people at high risk in areas of low and very low endemicity [1].

HAV is transmitted via the faecal-oral route from person-to-person or through contaminated food and water [6]. Young children are an important reservoir and source of transmission considering that the majority of young children infected with HAV are asymptomatic [6,7].

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[1] Levels of endemicity have been defined by WHO on the basis of seroprevalence as follows: "high (≥90% by age 10 years); intermediate (≥50% by age 15 years, with < 90% by age 10 years); low (≥50% by age 30 years, with < 50% by age 15); and very low (< 50% by age 30 years)" [1].

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Abstract

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Introduction

In most European countries, incidence and endemicity of hepatitis A virus (HAV) infection are classified as low or very low[1] [2-5]. However, this does not mean that the disease can be ignored. It rather implies that the characteristics of HAV infections differ from those countries with high or intermediate HAV endemicity features.
HAV infection is usually asymptomatic or mild in young children [6]. HAV infection is more often symptomatic with increasing age, and may present with fever, malaise, anorexia, nausea, abdominal discomfort, diarrhoea, vomiting, fatigue and jaundice after an incubation period of 15–50 days [1,6]. Signs and symptoms of acute hepatitis A (HA)

[1] Levels of endemicity have been defined by WHO on the basis of seroprevalence as follows: "high (≥90% by age 10 years); intermediate (≥50% by age 15 years, with<90% by age 10 years); low (≥50% by age 30 years, with<50% by age 15); and very low (<50% by age 30 years)" [1].

are indistinguishable from acute hepatitis B (HBV) and C virus (HCV) infections [6]. However, in contrast to HBV and HCV, HAV does not lead to chronic infection even though relapse of symptoms and fulminant hepatitis can occur [6].

Safe and effective vaccines against HAV exist. HAV vaccination rather than passive immunisation is recommended for pre- and post-exposure prophylaxis and can be considered to contain outbreaks [1]. In areas of high endemicity, most people get infected at very young age. Hence, asymptomatic infection is likely and the burden of disease of HA is low in these countries. With decreasing level of endemicity, average age at infection and disease severity increase. Therefore, it is assumed that countries with intermediate endemicity levels benefit the most from universal vaccination against HAV [1]. The World Health Organization (WHO) recommends large-scale vaccination in areas with intermediate HAV endemicity and targeted vaccination of people at high risk in areas of low and very low endemicity [1].

HAV is transmitted via the faecal-oral route from person-to-person or through contaminated food and water [6]. Young children are an important reservoir and source of transmission considering that the majority of young children infected with HAV are asymptomatic [6,7]. Infectivity of HA is highest during the second half of the incubation period up until a few days after onset of jaundice [6]. Most people are no longer infectious one week after onset of jaundice [6]. High-risk groups for HAV infection include unimmunised travellers to areas of high endemicity, men who have sex with men (MSM), and injecting drug users (IDUs) [1].

Case fatality of HA ranges from 0.1 to 0.3%, but increases strongly with age with rates of sometimes >10% observed in hospitalised adults ≥40 year old or older age groups [6,8,9]. Globally, 14'900 deaths were attributable to HAV infection in 2013 compared to 22'600 in 1990 [10].

In 2016, WHO published a guide for viral hepatitis surveillance [11]. One of the three mentioned purposes of viral hepatitis surveillance is relevant for HA: "detect outbreaks, monitor trends in incidence and identify risk factors for new, incident infections". Syndromic surveillance is recommended to detect outbreaks while enhanced case reporting is recommended to "describe trends in type-specific acute hepatitis and identify risk factors". Case definitions suggested by WHO and case definitions used by the European Centre for Disease Prevention and Control (ECDC) and by the Federal Office of Public Health (FOPH) for Switzerland are presented in table 5.1. In Switzerland, there is currently no syndromic surveillance for hepatitis but reporting of laboratory-confirmed cases of hepatitis A (and B and C; and hepatitis E as per 01.01.2018) is mandat-

Table 5.1: World Health Organization (WHO), European Centre for Disease Prevention and Control (ECDC) and Federal Office of Public Health (FOPH) case definitions for hepatitis A surveillance

Acute hepatitis / hepatitis A case definition according to WHO [11]		
Presumptive case / case definition for syndromic surveillance ("acute hepatitis"):	Any person meeting the • **Clinical criteria**	
Confirmed case (type-specific surveillance; hepatitis A):	Any person meeting the • **Clinical criteria** AND • **biomarker or epidemiological criteria**	
	Clinical criteria:	"Discrete onset of an acute illness with signs/symptoms of (i) acute viral illness (e.g. fever, malaise, fatigue) and (ii) liver damage, which can be clinical (e.g. anorexia, nausea, jaundice, dark urine, right upper quadrant tenderness), and/or biochemical (alanine aminotransferase [ALT] levels more than 10 times the upper limit of normal.[a]" [11] [a] Ten times the upper limit of normal (400 IU/L) is the threshold used by the State and Territorial Epidemiologists (CSTE). Countries may also select lower thresholds that could be more sensitive or higher thresholds that could be more specific
	Biomarker criteria:	IgM anti-HAV positive

Table 5.1: (continued)

	Epidemiological criteria:	Epidemiological link[b] with a confirmed case [11]
		[b] Contact with a confirmed case-patient during the referent exposure period or context of an etiologically confirmed outbreak
Hepatitis A case definition according to ECDC [70]		
Confirmed case	Any person meeting the • **Clinical criteria AND** • **Laboratory criteria**	
Probable case	Any person meeting the • **Clinical criteria AND** • **Epidemiological criteria**	
	Clinical criteria:	"Any person with a discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting) AND at least one of the following three: fever, jaundice, elevated serum aminotransferase levels" [70]
	Laboratory criteria:	"At least one of the following three: detection of hepatitis A virus nucleic acid in serum or stool, hepatitis A virus specific antibody response, detection of hepatitis A virus antigen in stool" [70]
	Epidemiological criteria:	"At least one of the following four: human to human transmission, exposure to a common source, exposure to contaminated food/drinking water, environmental exposure" [70]

Table 5.1: (continued)

Hepatitis A case definition according to FOPH	
Confirmed case	Any person meeting the • **Laboratory criteria** AND • **Clinical criteria or epidemiological link** In absence of information on laboratory criteria: • Both **clinical criteria** (icterus and increased transaminase) present AND **contact with laboratory-confirmed case**
Probable case	Any person meeting the • **Clinical criteria** but **without any information on laboratory criteria** (with indication of name of laboratory and/or reason for testing on clinical notification form)
Possible case	Any person meeting the • **Laboratory criteria** but **without any information on clinical and epidemiological criteria** OR • **Clinical criteria** but **without any information on laboratory criteria** (without indication of name of laboratory and/or reason for testing on clinical notification form)
No case	• **Neither laboratory nor clinical criteria** met OR • **Laboratory criteria** met, but **neither clinical criteria** met **nor epidemiological link** present (but information from clinical notification form is available) • **Neither laboratory criteria** met **nor epidemiological link** present (independent of presence or absence of clinical criteria)

Table 5.1: (continued)

Laboratory criteria:	anti-HAV IgM positive
Clinical criteria:	Icterus and/or increased transaminase
Epidemiological link:	Stay in an endemic region (high or moderate risk according to WHO, p. 95 [71]) or contact to a laboratory-confirmed case

ory [12].
HAV seroprevalence and incidence vary substantially across countries of the European Union (EU) and the European Economic Area (EEA), but decreased in all countries between 1975 and 2014 [2,5]. However, the notification rate of HAV, 3.0 cases per 100'000 population in 2014, has been slightly increasing again since 2011 [13]. There is a high variability across EU/EEA countries also in terms of notification rates: Iceland reported zero cases per 100'000 population, while Romania reported 33.3 cases per 100'000 population in 2014. In Switzerland, the notification rate decreased from 10/100'000 population in 1988 to 2.6/100'000 population in 2004 [14].
Most EU/EEA countries recommend vaccination against HAV for selected risk groups while only few recommend universal vaccination (included in national immunisation programme: Greece; universal childhood vaccination for parts of the country: Italy, Spain; recommended, but not included in national immunisation schedule: Bulgaria, Cyprus, Czech Republic, Estonia) [2]. In Switzerland, the first HAV vaccine was available in 1992 [15]. Before, only passive immunisation was available for travellers at risk [15]. Risk groups, for which vaccination against HAV is recommended, are presented in table 5.2. The costs of HAV vaccination have been covered by the compulsory health insurance for risk groups since 2008 except for travel-related and occupational indications [17]. For the latter, the employer usually covers the costs for vaccination.
This study describes the notification data of HA for Switzerland. It identifies factors potentially contributing to observed trends, including changes in the notification system. We investigated the epidemiology of HA in Switzerland in relation to the current Swiss vaccination recommendations and trends observed in other European countries.

Material and methods

The National Notification System for Infectious Diseases

HA has been a notifiable disease in Switzerland since 1984 [14]. Mandatory notification of HA includes a "report on laboratory findings" and a "report on clinical findings". Current reporting forms can be accessed at `www.bag.admin.ch/infreporting` (available in German, French and Italian).
Reports on laboratory findings are completed by those responsible at the diagnosing laboratory, upon confirmation of a HAV infection. Reports

Table 5.2: Overview of Swiss recommendations for vaccination against hepatitis A virus (HAV)

1992	**2005**	**2007**	**Summary of current (2007) vaccination recommendations as published in yearly vaccination schedule (2017)**
Source: [15]	Source: [16]	Source: [14]	Source: [17]
Primary prevention			
Non-immune travellers to countries with high risk of HAV infection (mainly "third world countries" and selected countries in Eastern Europe)	[travellers][a]	Travellers to countries with medium or high endemicity (according to `www.who.int/ith` or `www.safetravel.ch`). In case of adoption of a child from a country of high endemicity, all family members (not only those travelling) should be vaccinated.	Travellers to countries with medium and high endemicity
Illegal drug users	Drug users	People injecting drugs	People injecting drugs
Partly recommended: Children >12 months of age visiting relatives in "third world countries" or in Eastern Europe and attending day care in Switzerland		Children from countries of medium and high endemicity living in Switzerland and temporarily returning to their country of origin	Children from countries of medium and high endemicity living in Switzerland and temporarily returning to their country of origin

Table 5.2: (continued)

1992	2005	2007	Summary of current (2007) vaccination recommendations as published in yearly vaccination schedule (2017)
Partly recommended: Selected staff of day care facilities and children hospitals			
Partly recommended: Persons in close occupational contact with refugees, asylum seekers or drug users		Persons in close occupational contact to people injecting drugs (including prison staff); and to persons from countries of medium and high endemicity (asylum seekers, refugees)	Persons in close occupational contact to drug users; and to persons from countries of high endemicity
	Persons with chronic hepatopathies	Persons with chronic liver disease (Hepatitis B, C or other chronic hepatopathies, especially candidates of liver transplantation	Persons with chronic liver disease
	Persons in close contact to people with HAV infection		

Table 5.2: (continued)

1992	2005	2007	Summary of current (2007) vaccination recommendations as published in yearly vaccination schedule (2017)
	Staff of microbiological laboratories	Laboratory personnel working with HAV or with primates infected with HAV, or investigating stool samples	Laboratory personnel working with HAV
	Men who have sex with men (MSM)	Men who have sex with men (MSM) (outside of stable relationship)	Men who have sex with men (MSM)
		Drainers and employees of sewage plants	Drainers and employees of sewage plants
Secondary prevention			
		After close contact with a person with acute hepatitis A, or after exposure to a potential source within 7 days after exposure (or after development of symptoms of the primary case)	Within 7 days after exposure

Table 5.2: (continued)

1992	2005	2007	Summary of current (2007) vaccination recommendations as published in yearly vaccination schedule (2017)
		Staff and persons in institutions, in which there was a case of HAV (e.g. day-care centres, home for persons with disabilities, retirement homes, casern), and their families, if appropriate In case of an epidemic (social environment of cases)	

[a] Travel-related vaccination recommendations / indications were not considered in this document

are sent within 24 h to the FOPH and to the cantonal physician of the patient's canton of residence. The current laboratory notification form includes date of diagnosis, type of sample, laboratory method, patient's name, address, date of birth, and sex.
Physicians are to complete the "report on clinical findings" upon receipt of a positive laboratory result for HAV, and send it to the cantonal physician of the patient's canton of residence, within 24 h. The cantonal physician forwards this information to the FOPH and takes appropriate disease control and prevention measures, if indicated. The FOPH takes on and/or coordinates prevention and control measures if several cantons and/or other countries are involved, or if requested by the cantonal physician. The notification form on clinical findings contains information on the patient (name, date of birth, sex, address, nationality), and the course of disease (date of disease onset and diagnosis, signs and symptoms, reason for laboratory testing, hospitalisation, sequelae, death). The patient's vaccination status and exposure within 2 months before disease onset are also recorded. Information from both notification forms (laboratory and clinical findings) is then entered into an electronic database at the FOPH. Reports on the same patient are linked, whenever possible.

Data sources and analysis

Surveillance data on HA was extracted from the National Notification System for Infectious Diseases' (NNSID) database for the years 1988–2016 (data as of 12 April 2017). Data before 1988 were not available. Cases residing outside Switzerland and the Principality of Liechtenstein, and cases finally classified as "no case" (see table 5.1 for case classification) were excluded.
Data were analysed descriptively in terms of case numbers and case characteristics (incl. possible transmission routes). For description of case characteristics, notification years were grouped into four 6-year and one 5-year-period. Notification rates, defined as the number of notified cases per 100'000 resident population, were calculated using population statistics from the Federal Statistical Office (FSO). Population statistics were not yet available for 2016 at the time of data extraction; therefore, we used 2015 population statistics to calculate notification rates for 2016. We compared the number of hospitalised cases and deaths as reported on notification forms with the number of hospitalisations and deaths due to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes B15.0 ("hepatitis

A with hepatic coma") or B15.9 ("hepatitis A without hepatic coma") according to official hospital and mortality statistics (data obtained from the FSO). Main and secondary diagnoses/deaths were considered for extraction of hospitalisations/deaths due to ICD-10 codes B15.0 and B15.9 from hospital and mortality statistics, respectively. Data were analysed using the statistical software Stata (Version 13.1 [18]).
Notification data were collected under the Swiss Epidemics Act and hence, no ethical approval was required.

Results

Trends in hepatitis A case numbers and demographic characteristics

The notification rate of HA decreased from 9.5/100'000 population (628 cases) in 1988 to 0.5/100'000 population (43 cases) in 2016 in Switzerland (Figure 5.1). The highest notification rate was observed in 1990 (14.2/100'000).
Median age of cases increased from 25 years (1988–1993) to 43 years (2012–2016). In the most recent years, no age group predominated while in the early 1990s there was a clear predominance of young adults for both sexes (highest notification rate in 15–24 year age group, followed by 25–44 year age group; figure 5.2). In the two youngest and in the oldest age groups (0–4, 5–14 and 65+ age groups) there was no clear sex-pattern observed. In the 15–24, 25–44 and 45–65 year age groups, males had a higher notification rate. However, this male predominance decreased over the years. In 2015 and 2016, the overall female notification rate was even slightly higher than the male notification rate.
The proportion of cases of Swiss or Liechtensteiner nationality decreased during the observation period: 83.9% were Swiss/Liechtensteiner (excluding those with nationality not specified) during the 1988–1993-period, while in the 2012–2016-period 70.1% were reported to be Swiss/Liechtensteiner (Table 5.3). A similar trend was observed in the proportion of Swiss among the permanent resident population of Switzerland: in the 1988–1993-period, between 81.7 and 84.6% were of Swiss nationality while in the 2012–2015-period (2016 data not yet available) between 75.6 and 77.0% were Swiss [19].
In all notification periods, between 2.4 and 4.9% of cases were reported to be vaccinated against HAV. For 45 of 285 cases with reported vaccination prior to HA infection, at least the year of the first and/or last vaccination was reported. Of those, 3 were reported to be vaccinated before 1992,

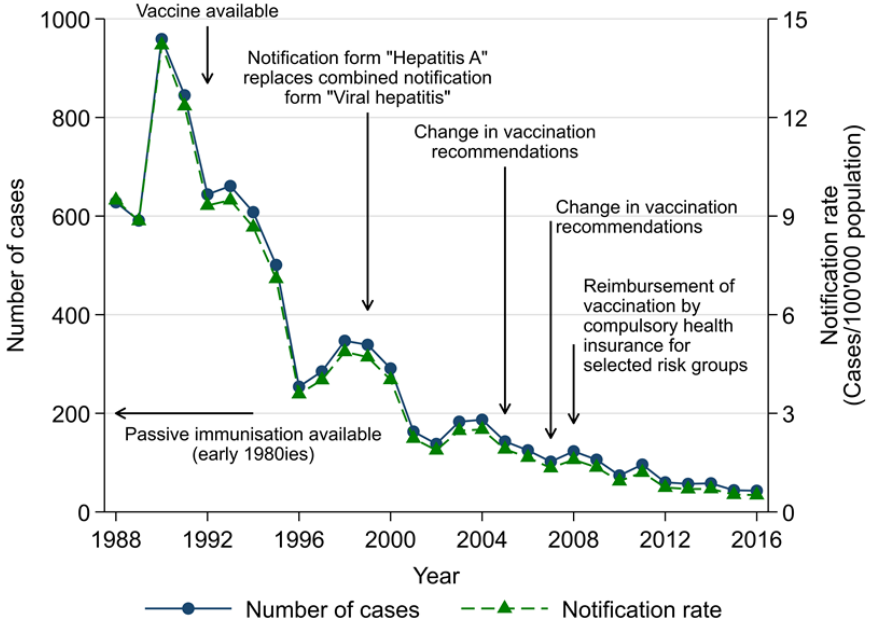

Figure 5.1: Trend in number of reported hepatitis A cases and notification rate from 1988–2016 with major "events" (e.g. concerning vaccination) labelled, Switzerland.

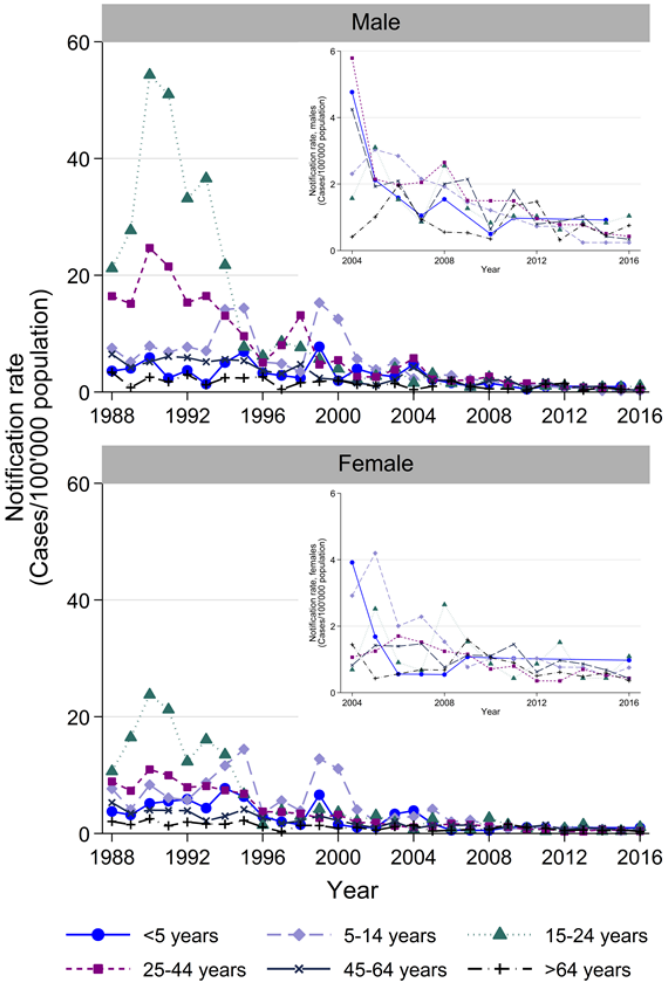

Figure 5.2: Male and female hepatitis A notification rate by age group and year, 1988–2016, Switzerland.

Table 5.3: Characteristics of notified hepatitis A cases, 1988–2016, Switzerland

	1988–1993 % (N)		1994–1999 % (N)		2000–2005 % (N)		2006–2011 % (N)		2012–2016 % (N)		All cases 1988–2016 % (N)	
Total cases		**(4'328)**		**(2'334)**		**(1'105)**		**(626)**		**(262)**		**(8'655)**
Possible case	-	(0)	-	(0)	-	(0)	7.0	(44)	8.4	(22)	0.8	(66)
Probable case	0.3	(14)	1.1	(25)	0.2	(2)	4.5	(28)	4.2	(11)	0.9	(80)
Confirmed case	0.6	(27)	11.0	(256)	89.8	(992)	78.4	(491)	87.4	(229)	23.1	(1'995)
Case not classified	99.1	(4'287)	88.0	(2'053)	10.0	(111)	10.1	(63)	-	(0)	75.3	(6'514)
Sex												
Male	64.2	(2'779)	60.5	(1'412)	60.1	(664)	56.1	(351)	51.7	(136)	61.7	(5'342)
Female	34.5	(1'494)	38.9	(908)	39.4	(435)	43.6	(273)	48.3	(126)	37.4	(3'237)
Not specified	1.3	(55)	0.6	(14)	0.5	(6)	0.3	(2)	-	(0)	0.9	(77)
Age group, years												
<5	2.4	(103)	5.1	(120)	5.6	(62)	3.2	(20)	1.5	(4)	3.6	(309)
5–14	7.6	(330)	19.8	(462)	23.1	(255)	12.8	(80)	9.2	(24)	13.3	(1'151)
15–24	35.1	(1'517)	16.4	(382)	12.3	(136)	11.2	(70)	15.6	(41)	24.8	(2'146)
25–44	40.4	(1'750)	39.1	(912)	33.6	(371)	32.9	(206)	25.6	(67)	38.2	(3'306)
45–64	10.2	(441)	15.2	(355)	18.8	(208)	28.4	(178)	30.9	(81)	14.6	(1'263)
>64	2.7	(116)	4.2	(99)	6.6	(73)	11.5	(72)	17.2	(45)	4.7	(405)
Not specified	1.6	(71)	0.2	(4)	-	(0)	-	(0)	-	(0)	0.9	(75)

Table 5.3: (continued)

	1988–1993 % (N)		1994–1999 % (N)		2000–2005 % (N)		2006–2011 % (N)		2012–2016 % (N)		All cases 1988–2016 % (N)	
Total cases with notification on clinical findings	**80.9**	**(3'503)**	**89.5**	**(2'088)**	**93.0**	**(1'028)**	**91.4**	**(572)**	**93.9**	**(246)**	**85.9**	**(7'437)**
Nationality												
Swiss/ Liechtensteiner	70.2	(2'458)	62.2	(1'299)	63.4	(652)	62.6	(358)	60.2	(148)	66.1	(4'915)
Foreign	13.5	(472)	21.1	(441)	22.4	(230)	21.2	(121)	25.6	(63)	17.8	(1'327)
Not specified	16.4	(573)	16.7	(348)	14.2	(146)	16.3	(93)	14.2	(35)	16.1	(1'195)
Reported location of exposure												
Switzerland	<0.1	(1)	3.2	(66)	33.4	(343)	27.3	(156)	25.6	(63)	8.5	(629)
Switzerland and abroad	-	(0)	<0.1	(1)	1.7	(17)	4.7	(27)	2.4	(6)	0.7	(51)
Abroad[a]	39.3	(1'375)	46.5	(971)	42.2	(434)	51.9	(297)	55.7	(137)	43.2	(3'214)
Europe[b]	38.3	(527)	49.0	(476)	38.6	(174)	34.9	(113)	25.2	(36)	40.6	(1'326)
Africa[b]	24.0	(330)	17.6	(171)	22.0	(99)	34.0	(110)	37.1	(53)	23.4	(763)
America[b]	18.0	(247)	17.4	(169)	18.8	(85)	11.1	(36)	17.5	(25)	17.2	(562)
Asia[b]	17.3	(238)	12.7	(123)	14.4	(65)	16.0	(52)	19.6	(28)	15.5	(506)
Australia[b]	0.4	(6)	1.2	(12)	0.7	(3)	0.3	(1)	1.4	(2)	0.7	(24)
Not specified[b]	3.6	(49)	3.3	(32)	6.4	(29)	4.9	(16)	0.7	(1)	3.9	(127)

Table 5.3: (continued)

	1988–1993 % (N)		1994–1999 % (N)		2000–2005 % (N)		2006–2011 % (N)		2012–2016 % (N)		All cases 1988–2016 % (N)	
Unknown or not specified	60.7	(2'127)	50.3	(1'050)	22.8	(234)	16.1	(92)	16.3	(40)	47.6	(3'543)
Reported exposure risk[a]												
Food/beverages	2.2	(76)	8.7	(181)	22.0	(226)	25.3	(145)	28.5	(70)	9.4	(698)
Contact with infected person	18.2	(639)	21.6	(451)	17.6	(181)	11.2	(64)	12.6	(31)	18.4	(1'366)
Sexual contact with infected person	3.5	(124)	5.5	(115)	2.9	(30)	4.0	(23)	4.1	(10)	4.1	(302)
Intravenous drug user	33.4	(1'171)	10.0	(208)	1.7	(17)	0.3	(2)	-	(0)	18.8	(1'398)
Other	3.3	(117)	5.0	(105)	2.8	(29)	3.7	(21)	3.7	(9)	3.8	(281)
Unknown or not specified	50.5	(1'768)	57.3	(1'197)	56.0	(576)	58.9	(337)	58.9	(145)	54.1	(4'023)
Immunisation status												
Vaccinated[c]	4.5	(158)	3.1	(64)	2.4	(25)	4.5	(26)	4.9	(12)	3.8	(285)
Vaccinated with 1 dose[d]	0.6	(1)	6.3	(4)	48.0	(12)	57.7	(15)	66.7	(8)	14.0	(40)
Vaccinated with ≥2 doses[d]	-	(0)	-	(0)	16.0	(4)	30.8	(8)	8.3	(1)	4.6	(13)

Table 5.3: (continued)

	1988–1993 % (N)		1994–1999 % (N)		2000–2005 % (N)		2006–2011 % (N)		2012–2016 % (N)		All cases 1988–2016 % (N)	
Not specified[d]	99.4	(157)	93.8	(60)	36.0	(9)	11.5	(3)	25.0	(3)	81.4	(232)
Not vaccinated or not specified	95.5	(3'345)	96.9	(2'024)	97.6	(1'003)	95.5	(546)	95.1	(234)	96.2	(7'152)
Manifestation[a]												
Jaundice	74.1	(2'596)	75.9	(1'585)	76.7	(788)	70.1	(401)	65.0	(160)	74.4	(5'530)
Transaminase increased ≥2.5fold	70.1	(2'457)	57.1	(1'192)	76.8	(790)	83.4	(477)	86.6	(213)	69.0	(5'129)
Other	-	(0)	0.4	(10)	4.7	(52)	19.2	(120)	39.3	(103)	3.8	(285)
None	1.2	(41)	1.6	(33)	3.0	(31)	1.6	(9)	1.2	(3)	1.6	(117)
Unknown or not specified	12.9	(451)	9.5	(199)	5.3	(54)	2.8	(16)	2.8	(7)	9.8	(727)
Hospitalisation												
Yes	21.4	(750)	20.0	(418)	24.8	(255)	30.6	(175)	44.7	(110)	23.0	(1'708)
Due to hepatitis A[e]	-	(0)	-	(0)	0.4	(1)	56.6	(99)	63.6	(70)	10.0	(170)
Other reason[e]	-	(0)	-	(0)	-	(0)	21.1	(37)	18.2	(20)	3.3	(57)
Due to hepatitis A and other reason[e]	-	(0)	-	(0)	-	(0)	-	(0)	0.9	(1)	0.1	(1)
Unknown or not specified[e]	100	(750)	100	(418)	99.6	(254)	22.3	(39)	17.3	(19)	86.7	(1'480)
No or not specified	78.6	(2'753)	80.0	(1'670)	75.2	(773)	69.4	(397)	55.3	(136)	77.0	(5'729)

Table 5.3: (continued)

	1988–1993 % (N)		1994–1999 % (N)		2000–2005 % (N)		2006–2011 % (N)		2012–2016 % (N)		All cases 1988–2016 % (N)	
Complications												
Yes	-	(0)	-	(0)	-	(0)	3.7	(21)	4.5	(11)	0.4	(32)
No or not specified	100	(3'503)	100	(2'088)	100	(1'028)	96.3	(551)	95.5	(235)	99.6	(7'405)
Death												
Yes	0.5	(19)	0.4	(8)	0.1	(1)	0.9	(5)	1.2	(3)	0.5	(36)
Due to hepatitis A[f]	15.8	(3)	12.5	(1)	-	(0)	-	(0)	-	(0)	11.1	(4)
Other reason[f]	10.5	(2)	50.0	(4)	100	(1)	100	(5)	100	(3)	41.7	(15)
Unknown or not specified[f]	73.7	(14)	37.5	(3)	-	(0)	-	(0)	-	(0)	47.2	(17)
No or not specified	99.5	(3'484)	99.6	(2'080)	99.9	(1'027)	99.1	(567)	98.8	(243)	99.5	(7'401)

[a] Multiple answers possible

[b] % among cases with exposure "Switzerland and abroad" or "abroad"

[c] Occasionally reported for cases already before 1992 when hepatitis A virus (HAV) vaccination was introduced. It cannot be determined whether these cases received passive immunisation against HAV (which was available already before 1992) or whether the information on the notification form was incorrect. It is suspected that physicians may not be able to easily differentiate active from passive immunisation based on information from vaccination cards and – in the absence of vaccination cards – patients may confuse HAV and hepatitis B virus vaccination

[d] % among all vaccinated cases

[e] % among hospitalised cases

[f] % among deceased cases

13 received vaccination ≤14 days before disease onset and 7 received vaccination between 14 and 28 days before disease onset. For one case, the date of last vaccination was after disease onset. However, it was reported that this case received 3 doses of HA vaccine, the first one in the year prior to disease onset in mid-January. For the remaining 21 cases, disease onset was reported between 31 days and 14 years after their last (or only) vaccination.

Clinical characteristics

Jaundice was reported for 65.0–76.7% and increased transaminases for 57.1–86.6% of cases over all notification periods (Table 5.3). Other reported signs and symptoms included fever, gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhoea), reduced general state, weakness, myalgia, arthralgia, dark urine and pale stools. Fever, listed on the notification form since 2015, was specified for 39.3% of cases since 2015 but only for 2.9% of cases between 1999 and 2014 (no option to list "other symptoms" before 1999).

The proportion of hospitalised cases increased from 21.4% in 1988–1993 to 44.7% in 2012–2016 (Table 5.3, figure 5.3a). The number of cases with hospitalisation indicated as "yes" on the report on clinical findings is much lower than the number of hospitalisations due to ICD-10 codes B15.0 and B15.9 according to Swiss hospital statistics from 1998 to 2015 (the years for which hospital statistics were available; figure 5.3b). However, when considering only main diagnoses (as opposed to main and secondary diagnoses), numbers from the two statistics are comparable. The reason for hospitalisation (due to HA and/or for other reason) has been included in the reporting form since 2006. In three quarters of cases (171/228) with this information available, HA was indicated as the reason for hospitalisation (including one case hospitalised due to HA and another reason).

Complications, recorded since 2006, were reported for 3.9% (32/818) of cases and included coagulopathy, acute or imminent liver failure, cholecystitis, and general malaise.

Official mortality statistics, coded according to ICD-10, were available for 1995–2014. During this time period, 46 HA-related deaths were recorded (ICD-10 codes B15.0 and B15.9 as main or secondary cause). In the notification data, only 14 deaths among HA cases were captured during this time period (36 deaths from 1988–2016).

Reported location of exposure and exposure risks

Exposure abroad (or both, in Switzerland and abroad) increased from 39.3% in 1988–1993 to 58.1% in 2012–2016 while the proportion of "unknown or not specified" location of exposure decreased (Table 5.3).
European followed by African countries were most frequently mentioned as countries of exposure in the past. In the most recent years, exposure in African countries was more frequently reported (Table 5.3). The proportion of cases exposed in the Americas, Asia and Australia remained stable over the entire time period. Italy, Turkey and Germany were the three most frequently mentioned European countries between 2012 and 2016 while from 1988–1993 Italy, Spain and former Yugoslavia were lead exposure countries. Morocco, Tunisia, Egypt and Kenya were most frequently mentioned African countries from 1988–1993 and Morocco, Egypt, Togo, Ethiopia and Cap Verde from 2012–2016.
For the majority of cases (50.5%–58.9% for all notification periods), the source of exposure was reported to be unknown or was not specified. Intravenous drug use was the most frequently reported exposure risk in the 1988–1993 notification period while this exposure risk was not mentioned in the 2012–2016 period (Table 5.3). In contrast, the proportion of cases for which contaminated food or beverages was indicated as exposure risk increased over the years (2.2% of cases in 1988–1993; 28.5% of cases in 2012–2016). The mentioning of "contact with an infected person" as exposure risk decreased over the observation period (18.2% in 1988–1993; 12.6% in 2012–2016) while "sexual contact with an infected person" remained stable at around 4%. Exposure risks mentioned in the "other" category included occupational exposures, exposure to blood or blood products (including transfusions), or (previous and/or current) residency abroad.

Discussion

Our analysis of Swiss hepatitis A notification data from 1988–2016 revealed temporal trends in case numbers and case characteristics which may be caused by changes in disease epidemiology but also are likely to reflect changes in disease reporting and notification.

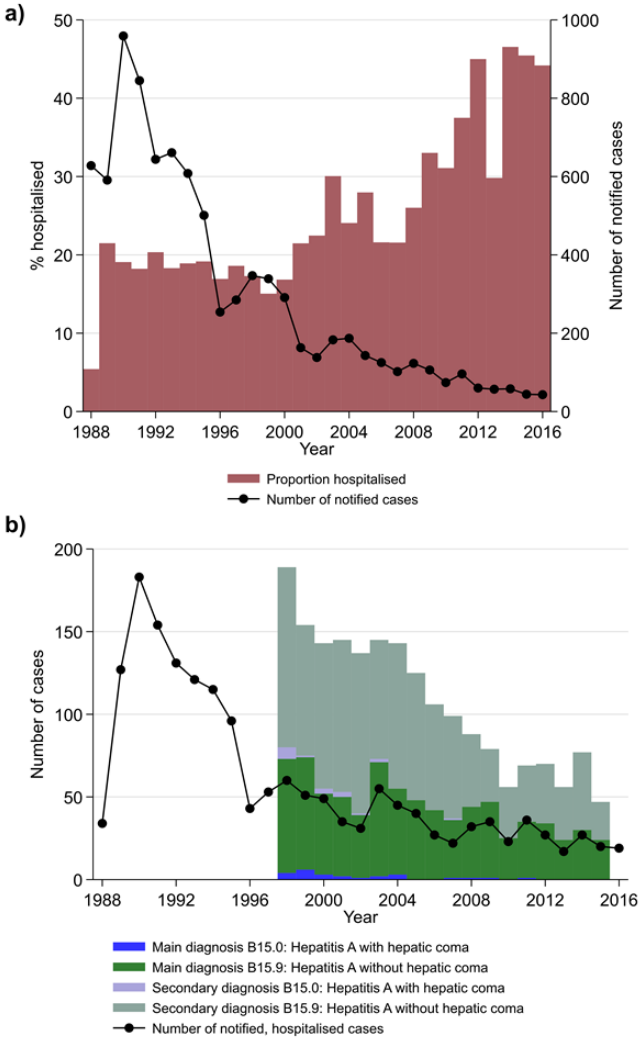

Figure 5.3: (a) Proportion of hospitalised hepatitis A cases according to notification data (bars, left axis) and number of notified cases (line, right axis), and (b) hospitalisations due to hepatitis A according to notification forms (solid black line) and hospital statistics (bars; data for 1998–2015 only), 1988–2016, Switzerland.
Source of hospital statistics: Federal Statistical Office, Neuchâtel, Switzerland.

No unexpected risk group for HAV infection according to Swiss notification data

Recently published analyses of HA notification data in Switzerland included data until 2004 apart from a recent article of the FOPH reporting on an increase in case numbers in early 2017 [14,20,21]. All analyses except of the latter documented decreasing trends regarding HA notification rates that continue into contemporary times. Today, the notification rate in Switzerland is comparable for all age groups and for males and females, though fluctuating quite substantially in the setting of low case numbers. In contrast, the notification rate of 2014 in 30 EU/EEA countries was still highest for the 5–14 year age group, followed by the 0–4 and the 15–24 year age groups, and slightly higher in males compared to females [13].

The strongest decline in HAV notifications started in 1990, even before the introduction of HAV vaccination in Switzerland (Figure 5.1). However, passive immunisation was already available since the early 1980ies [22]. Additionally, campaigns among IDUs could have contributed to the observed decline: The most frequently mentioned risk exposure in the early 1990s, intravenous/injecting drug use, has infrequently been reported in the last 10 years. It has been hypothesised that transmission of HA among IDUs could occur through sharing equipment or due to contaminated drugs or generally poor hygienic conditions [23,24]. Decreasing case numbers were also observed for hepatitis B together with a strong decline in IDU as reported risk exposure [25]. The decreasing case numbers were attributed to preventive measures introduced to control human immunodeficiency virus (HIV). The HIV/AIDS epidemic in the late 1980s and peak levels of drug consumption in the early 1990s resulted in the establishment of needle exchange facilities providing a "safe" environment for drug consumption [26]. A study among persons entering heroin-assisted treatment found that the proportion of HAV-infected persons decreased from 2003 to 2013 while the proportion of people vaccinated against HAV increased [27]. Nevertheless, the prevalence of HA is still higher in persons entering heroin-assisted treatment in Switzerland than among the general population [27]. Reports on IDU as a risk exposure among notified cases of HA from other countries are scarce. In Eastern Sydney, Australia, one third of notified cases was associated with IDU between September 1994 and June 1995 while this proportion dropped to 9% between July 1995 and December 1996 [28]. In New South Wales, Australia, recreational drug use decreased among reported HA cases between 2000 and 2009 [29]. In contrast, in Italy,

the frequency of IDUs among cases of viral hepatitis (slightly more than half of which were HA cases) remained at constant but low levels (<5%) between 1991 and 2006 [30]. Similarly, IDU was a reported risk factor for 2% of HA cases in 1994–1995 as well as in 2006–2007 in Arizona, United States [31].

HA vaccination failure and clinical cases of HA among vaccinated individuals reported in the literature are very rare [32-42]. Nevertheless, 3.8% of notified cases (285/7437) were reported to be vaccinated against HAV in Switzerland between 1988 and 2016. There are several explanations for this notably high proportion: (i) "vaccinated" cases might include persons having received passive immunisation (see also footnote in table 5.2) which has only a short-term protective effect [1,43]; (ii) vaccination may have occurred only shortly before travel or in the framework of post-exposure prophylaxis – potentially too late to prevent disease onset (even though the notification form asked for vaccination status prior to infection); and (iii) HAV vaccination may be confused with other vaccinations, e.g. HBV vaccination, especially if information provided by physicians is obtained from patients rather than from vaccination cards (as it has been shown that travellers could frequently not recall their vaccination history [44]). Nevertheless, vaccination failure cannot be ruled out, especially in immunocompromised patients. A recent study among Swedish travellers under immunosuppressive medication due to reactive arthritis has shown that similar protection after two months can be achieved by administering a 3-dose regimen (1 + 1 + 1 or 2 + 1) at 0, (1) and 6 months compared to a 2-dose regimen at 0 and 6 months among healthy individuals [45].

The decline in the HA incidence led to an increase in the population susceptible to HAV in the EU/EEA which was not compensated by increased vaccination rates, as highlighted by Gossner *et al.* [3]. This is assumed to be the case also in Switzerland in the absence of universal vaccination recommendation. However, data on population susceptibility are not available. Vaccination coverage was assessed in Switzerland for 2-, 8- and 16-year old children and adolescents and was 4% [95% confidence interval (CI): 3.2–4.6], 11% [95% CI: 9.5–11.7], and 28% [95% CI: 24.8–30.6] for two doses, and slightly higher for one dose, in 2014–16 [46]. Between 2002 and 2012, 53.1% of travellers seeking pre-travel health advice in one Swiss travel clinic received HAV vaccination (in part combined with HBV vaccination) [47]. On the other hand, a survey among travellers to tropical and subtropical countries at a Swiss airport in 2002 revealed that only 26% of travellers were protected against HAV and an additional 12% were potentially protected [48]. It has to be considered

that surveys conducted at the airport might be biased (over-representing frequent travellers, and considering only one mode of transport) as highlighted by Pedersini *et al.* (2016) [44]. They showed that the frequency of international travel and endemicity at destination are both associated with HA vaccination among travellers in five European countries. In 2014, 62.6% of MSM reported to be vaccinated against HAV in a Swiss online survey among MSM [49]. Further insights into vaccination rates and knowledge about HA among Swiss MSM are expected once the data from the European MSM Internet Survey (EMIS-2017) becomes available [50].

Recently, HAV outbreaks among MSM have been reported in several European countries [51] including England [52], the Netherlands [53] and Germany [54]. Our analysis did not suggest any similar outbreak among MSM in Switzerland: in 2016 sexual contact with an infected person was specified as a risk exposure only for one case and the male-to-female ratio did not change compared to 2015. However, case notifications for HAV more than doubled in the first 22 weeks of 2017 compared to the same time period in 2016 (41 *vs.* 17 cases) [21]. A link to the European outbreaks among MSM seems likely considering that the increase in case numbers mainly affects males.

"Exposure abroad" was indicated for more than half of recently notified cases, suggesting that travelling is still a main risk factor for acquiring HA. Previous analyses of Swiss HAV notification data identified risk groups or different exposure patterns among subgroups of notified cases (e.g. among cases below 20 years of age, those with Swiss nationality tended to be exposed in Switzerland while those with foreign nationality tended to be exposed abroad [14]). We did not conduct such subgroup analyses considering the low case numbers in recent years.

Relative increase in hospitalisations

Data on hospitalisations revealed two interesting trends: (i) the proportion of hospitalised patients increased among reported cases, and (ii) hospital statistics suggest substantial underreporting of hospitalisations due to HA in the NNSID. An increasing proportion of hospitalisations has also been reported in the United States [55]. Ly and Klevens hypothesised that this observation is explained by a shift of the susceptible population towards older adults together with the fact that HA leads to more severe disease with increasing patient age. This is likely also the case for Switzerland: while the median age of reported cases was 26 and 25 years in non-hospitalised (incl. hospitalisation status not spe-

cified) and hospitalised patients, respectively, in 1988–1993, median age for those two groups increased to 36.5 and 47 years in 2012–2016. An alternative explanation links the decreasing frequency of HAV infection in Switzerland (or at least the decreasing notification rate) to physicians' decreasing awareness for the disease, especially in patients with mild manifestations.

The number of hospitalisations according to hospital statistics is comparable with the number of hospitalised cases according to notification data when considering the main diagnosis in hospital statistics. When also considering secondary diagnoses, hospital statistics suggest more than double the number of HA cases compared to notification data (Figure 5.3b). It should be considered that re-admission of the same patient is counted as a new case in Swiss hospital statistics except if readmission occurs within 18 days and in the same hospital (personal communication, FSO, 11 July 2017). Still, we believe that the striking difference between hospital statistics and notification data is not fully explained by re-admissions alone. We also speculate that the observed difference, apart from under-notification, could arrive from GPs completing notification forms before the patient is hospitalised. If the hospital physician then does not complete another notification form (assuming or knowing that the case was already reported by the GP), the patient's hospitalisation is not captured by the NNSID. The same probably applies to mortality data.

System changes influence trends in notification data

The notification form is provided by and submitted to the FOPH. The notification form was changed several times between 1988 and 2016, as were case definitions, classifications and data entry procedures. All these changes are difficult to document *post-hoc* for the purpose of this study and to separate from each other; they make interpretation of long-term trends difficult. In the following we discuss such issues using examples from Swiss HA notification given that these experiences likely also apply for other diseases and surveillance systems.

Introducing a new variable on the notification form is a change which is relatively easy to track as it leads to a rather abrupt change in the data. The location of exposure to HAV could be recorded as "abroad" before 1999 and as "abroad" and/or "in Switzerland" thereafter. In the notification data, this is reflected in a sudden increase in the proportion of cases exposed in Switzerland and a parallel drop in the "unknown or not specified" category.

Similarly, the "reason for hospitalisation" and "complications" were included on the form probably only since 2006 (notification forms for 2002–2005 were not available to check). Such changes can potentially be noticed even if old notification forms are not available, but their impact is difficult to quantify. In contrast, more subtle changes, e.g. in wording can also influence answers given, but might not be easily recognisable in the absence of actual notification forms or stringent documentation of changes on the reporting forms. For example, main features of HA (increased transaminases and jaundice), were recorded from 1988 until 2016. Nevertheless, changes occurred repeatedly: from 1988–1990, they were listed under the heading "clinic". From 1991–1998, they were listed under the heading "reason for laboratory test" while since 1999 they are part of the section on "manifestation". Also, in 1999 the wording changed from "increased transaminases" to "transaminase(s) $\geq 2.5\times \uparrow$". While asking for symptoms under the headings "clinic" and "manifestation" are likely to result in the same responses, the heading "reason for laboratory test" might not: a symptom might be present but not be considered the reason for laboratory testing and hence, not checked on the form.

Another, potentially important, change: up until 1998, all cases of viral hepatitis were captured using the same notification form entitled "Viral hepatitis". Only since 1999, separate notification forms exist for hepatitis A, B, and C (other types of viral hepatitis are not reportable as per 2017). At the same time, the notification form was revised substantially. Revisions of notification forms are complex processes involving a number of people and perspectives; we exemplify the Swiss experience: the expert analysing the notification data for a given disease tries to get the most relevant information needed for appropriate interpretation of the epidemiology. Managers of the overall notification system (including data entry and management), and hence, with a view on all notifiable diseases, try to avoid long notification forms, frequent changes and heterogeneous forms – e.g. once asking for nationality, once for country of origin, and once for country of birth. Furthermore, information should not be too difficult to obtain/know by laboratory personnel or physicians (those requested to complete the forms), otherwise compliance will be low. Finally, the legal department will critically review the forms aiming at reducing the personal information obtained to the essentials for fulfilling the mandate of the FOPH for early detection, monitoring, prevention and containment of communicable diseases.

In summary, changes in notification forms and procedures may be needed at times, but should be kept to a minimum in order to allow analysis

and interpretation of long-term trends. This in turn is only possible if changes made are meticulously documented.

System-inherent limitations

Patients' information is provided by physicians in charge of HA patients. However, it is not known how complete and systematically they assess e.g. exposure history. Assessing exposure risks in a systematic fashion is likely not a priority of physicians given that the source of infection does not matter for treatment. This is reflected in the high proportion of cases (>50%) for which exposure risk is indicated as "unknown" or not specified at all. We hypothesise that "traditional" (well-known) risk factors are often overestimated compared to less known risk exposures in surveillance systems. This could also be a reason for the observed increase in "contaminated food and/or water" mentioned as risk exposure: in the absence of "specific" risk factors such as IDU and travel, physicians may be choice-biased being tempted to indicate "contaminated food and/or water" instead of ticking "unknown" or not indicating any risk factor(s).

Probably almost every person has consumed a food item which could have been contaminated with HAV during the relevant time window of 15–50 days before symptom onset. At the same time, reports of food-borne outbreaks of HA – recently frequently associated with fresh and frozen berries and fruits [56-61] – could also have increased awareness that HAV can be transmitted through contaminated food. The rather long incubation period, together with a wide range, and more or less non-specific or ubiquitous risk exposures could also explain the high proportion of unknown or unspecified exposure risks. Suspected sources of infection are usually not followed-up, unless there is evidence of an outbreak. Therefore, location of exposure remains speculative as long as no mandated research studies are conducted.

Furthermore, the surveillance system is likely to capture mainly severe and/or "typical" cases as these are most likely to undergo laboratory testing. Gastroenteritis patients reporting recent travel were found to have a 3.6 times increased odds for stool testing compared to patients not reporting travel in the 7 days preceding symptom onset [62]. Similarly, we suspect that travel-related HA cases (or patients with a history of recent travel) are more likely to be captured by the NNSID. This may not compromise validity of the surveillance system, but should be born in mind when interpreting surveillance data.

In contrast, we have anecdotal evidence from notification forms that

physicians suspect transmission from a (symptomatic or asymptomatic) contact person who had been travelling recently, but the patient him" / herself (the suspected secondary case) stayed in Switzerland. These HA cases would no longer be considered an imported/travel-related case as the reported patient did not travel and was indeed exposed in Switzerland. Hence, the distinction between imported and autochthonous cases might be flawed.
Similarly, the importance of migrants and travellers visiting friends and relatives (VFR) is difficult to evaluate: on the one hand, those born in high-endemicity countries could already be immune and hence, increase population seroprevalence in Switzerland. On the other hand, young children having visited their home country (or the home country of their parents) could be asymptomatically infected and spread the disease once back in Switzerland. Generally it is known that VFR are at increased risk of infectious diseases during travel [63-65], they are less likely to seek pre-travel health advice [65-67] and are less adherent to pre-travel health advice [68,69].
Furthermore, it is not known how often contact persons of HA cases are tested and how this may influence notification data. Testing may be considered unnecessary for both, secondary cases showing clear and typical signs and symptoms, and (potential) secondary cases not showing any signs and symptoms of HAV infection.

Conclusions

Hepatitis A incidence is declining globally including in Switzerland, apart from outbreaks (such as the recent European outbreak among MSM). Case numbers have been low in recent years. However, considering that the population is becoming increasingly susceptible to HAV infection and hence, the probability of outbreaks is increasing, it is important to strengthen surveillance and prevention efforts as shown by the recent outbreak among MSM in Europe.
Current Swiss notification data on HAV do not allow reliably identifying existing (IDU, MSM, travellers) and potential new risk groups as information on exposure to HAV available to and provided by physicians is limited and case numbers are low. Patient information on exposure is often poorly filled in on the notification forms. Thus, changes in NNSID data or outbreaks need to be followed up with indepth investigations to understand contemporary transmission patterns.
Thorough understanding of physicians' approaches to diagnose a patient with HAV infection, changes in notification forms, case definition, case

classification, and data entry is required for correct interpretation of notification data. Additionally, research studies are needed to complement information from routine surveillance to answer specific questions such as estimating levels of under-ascertainment, under-diagnosis and under-notification, or evaluating best practices to collect data on exposure. Such complementary information is especially important for interpretation of long-term trends of hepatitis A in particular and of highly dynamic diseases and surveillance systems in general.

Authors' contributions

DM, CS and MJ conceptualised the study. MJ extracted the data. CS developed and carried out the statistical analysis. CS, DM and MJ interpreted the results. CS wrote the first draft of the manuscript. DM and MJ contributed to the writing and revision of the manuscript. All authors approved the final version.

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Conflict of interest

MJ is working at the Federal Office of Public Health and contributed to this project/article in her capacity as public health specialist and her function as scientific collaborator within the organisation.

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6 Time trends of positivity rates from foodborne pathogen testing in Switzerland, 2003 to 2012

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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.

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

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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

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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 (2'832 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.

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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.

Materials and methods

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 1'000 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.

Analysis of positivity rates

Datasets from individual laboratories were transformed uniformly, merged and analysed with STATA^{TM} 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 calculating positivity rates from laboratory data from the whole observation period pooled by month or calendar week.

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.

Ethics 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).

Results

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 (4'163 positive) between 2003 and 2012. Excluding data from the three laboratories with incomplete data led to the exclusion of 43'530 (3'345 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 (1'245 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 (2'832 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 (Tables 6.1 and 6.2).

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 asso-

Table 6.1: Comparison of campylobacteriosis cases from laboratory data with cases registered in the National Notification System for Infectious Diseases 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 with cases registered in the National Notification System for Infectious Diseases 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

ciated with the geographical location of the laboratory that performed the test.

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). 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.

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 the age group 20–24 years, for which the rate remained rather stable. The largest relative decrease of positivity rates

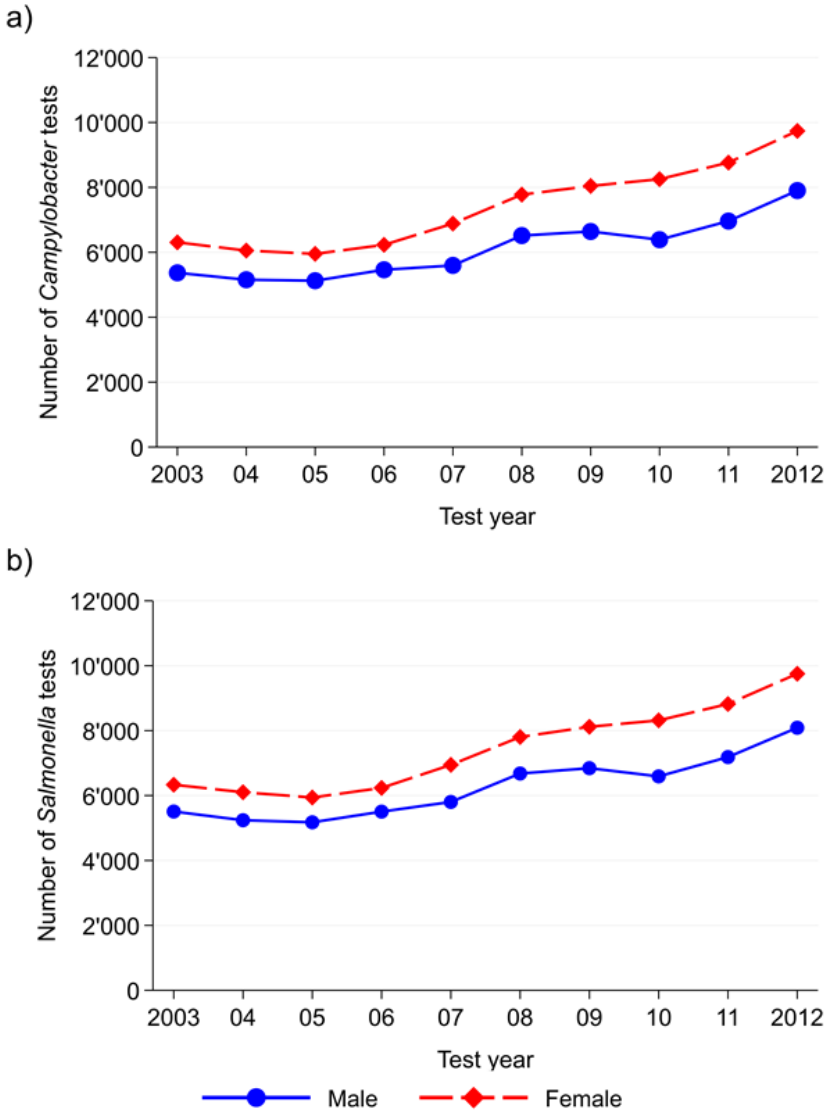

Figure 6.1: Number of stool tests for *Campylobacter* (a) and *Salmonella* (b) by sex in five diagnostic laboratories, Switzerland, 2003–2012.

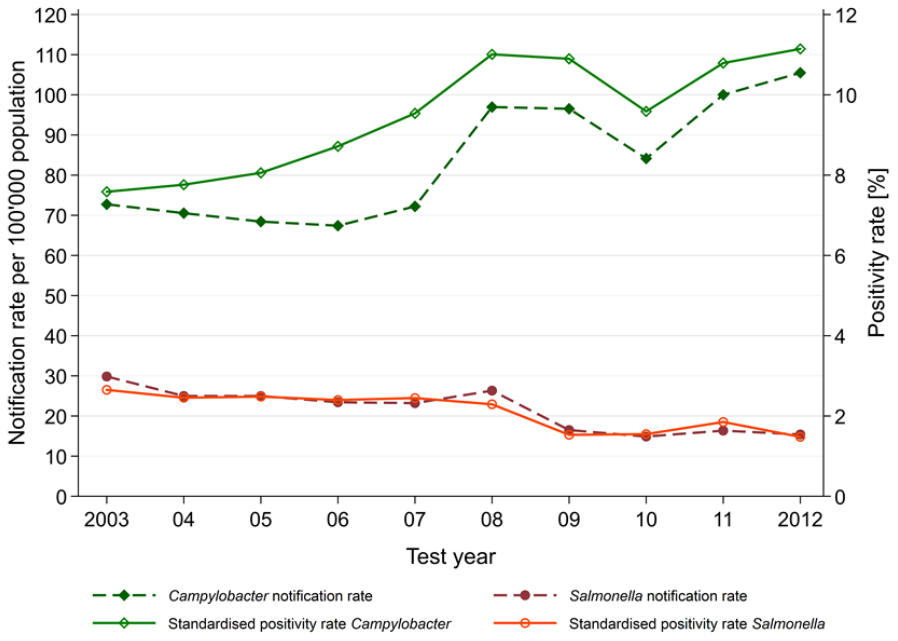

Figure 6.2: National Notification System for Infectious Diseases (NNSID) notification rates and positivity rates (standardised for age and sex) of *Campylobacter* and *Salmonella*, Switzerland, 2003–2012. NNSID data provided by the Federal Office of Public Health, Bern, Switzerland

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).

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. 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.

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, appendix 1). Patients in the age groups 15–19 years and 20–24 years had

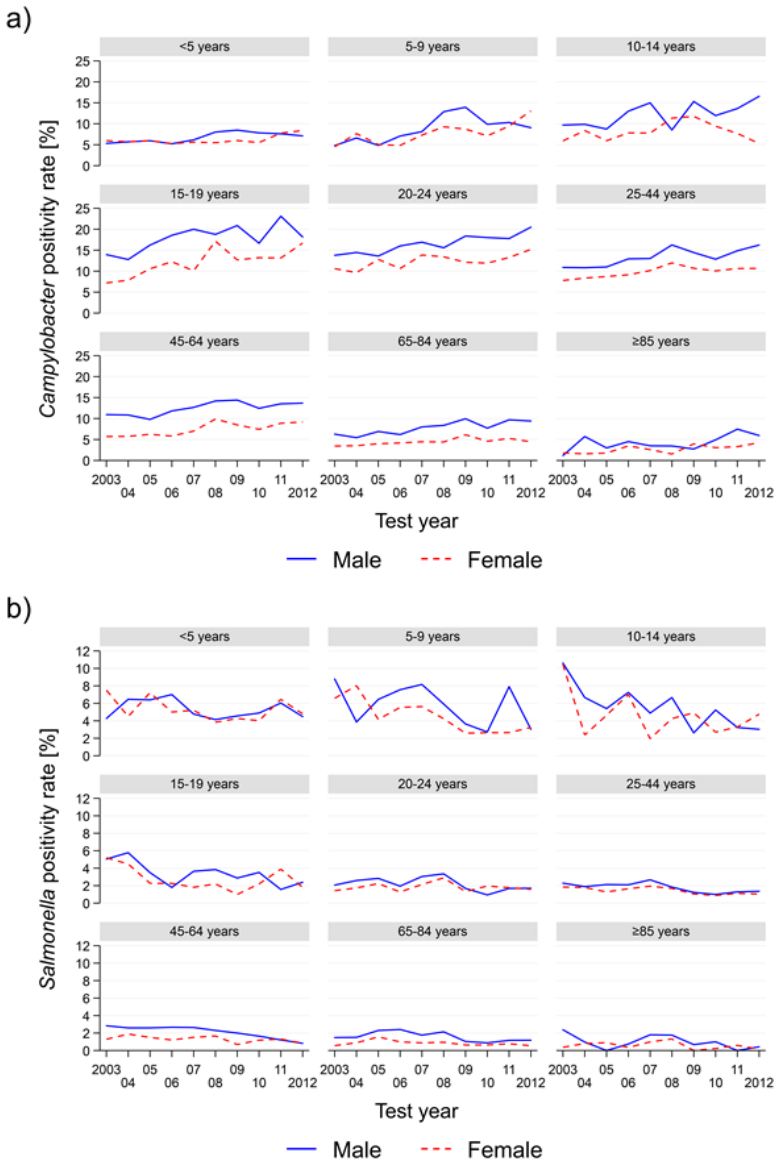

Figure 6.3: Annual positivity rates of *Campylobacter* (a) and *Salmonella* (b) by age group and sex, Switzerland, 2003–2012

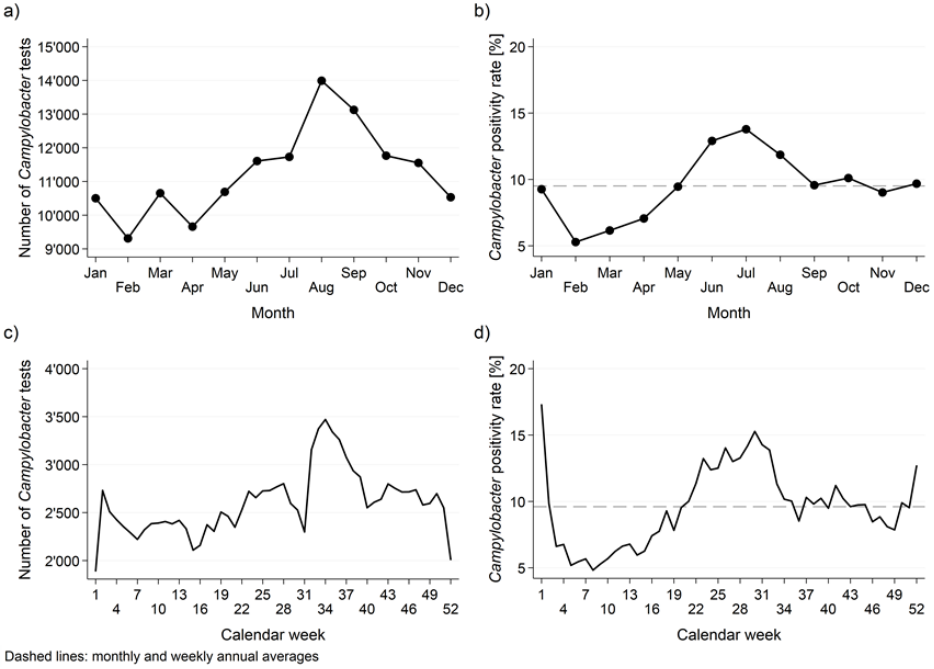

Figure 6.4: Seasonality of *Campylobacter* tests and positivity rates (pooled over study period) per month and calendar week, Switzerland, 2003–2012.

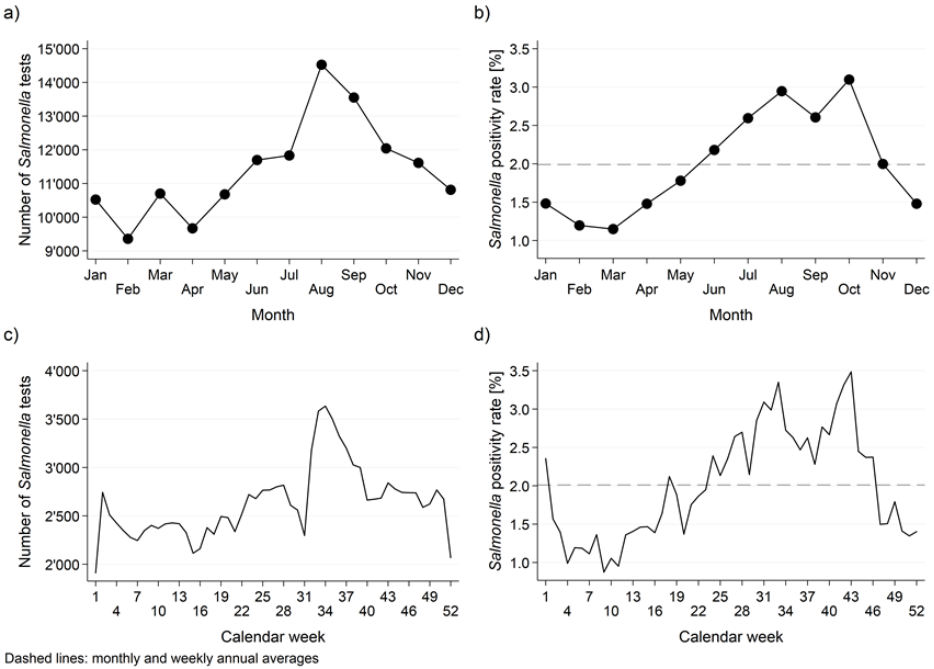

Figure 6.5: Seasonality of *Salmonella* tests and positivity rates (pooled over study period) per month and calendar week, Switzerland, 2003–2012.

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 continuously 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). 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). 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). 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).

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].

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, appendix 1).

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 frequency. 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.

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.

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.

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 pretest 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.

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.

Supplementary data

For supplementary data accompanying this paper visit `https://doi.org/10.4414/smw.2017.14569`.

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Competing interests

The authors declare that they have no conflicts of interest.

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7 Enterohaemorrhagic *E. coli* (EHEC) in Switzerland: epidemic pattern due to changing laboratory methods?!

Parts of this chapter are extracted/adapted from an unpublished report prepared for the FOPH:

> Schmutz C, Mäusezahl D. Abklärung der steigenden EHEC-Meldezahlen bei den Laboratorien. Report of laboratory visits. 27 Oct 2016; Basel: Swiss Tropical and Public Health Institute.

7.1 Introduction

The Federal Office of Public Health (FOPH) noticed a strong increase in enterohaemorrhagic *Escherichia coli* (EHEC) case notifications in 2015 without obvious geographical clusters (Figure 7.1) [Bundesamt für Gesundheit and Nationales Referenzzentrum für enteropathogene Bakterien und Listerien, 2015]. It was suspected that new laboratory techniques, namely multiplex polymerase chain reaction (PCR) panels, could have contributed to this increase. Such panels allow testing a sample for multiple pathogens in one single run. Different multiplex PCR panels for gastrointestinal (GI) pathogens are commercially available, among those the BD MAX™ Enteric Bacterial Panel [Becton, Dickinson and Company, 2016], the xTAG® Gastrointestinal Pathogen Panel (GPP) [Luminex, 2012], and the FilmArray® Gastrointestinal (GI) Panel [BioFire Diagnostics, 2016]. An overview of pathogens included in those three panels is provided in table 7.1.

Traditionally, routine testing of stool samples for bacterial pathogens included only *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. [Schweiger *et al.*, 2005a], using culture-based techniques. It is conceivable that EHEC – which is included in all three of the above-mentioned panels – is tested more frequently if traditional stool culture is replaced by multiplex PCR. However, it was not known if this was indeed the case. Therefore, the FOPH initiated several studies to investigate if the increase seen in EHEC notification data is due to an underlying out-

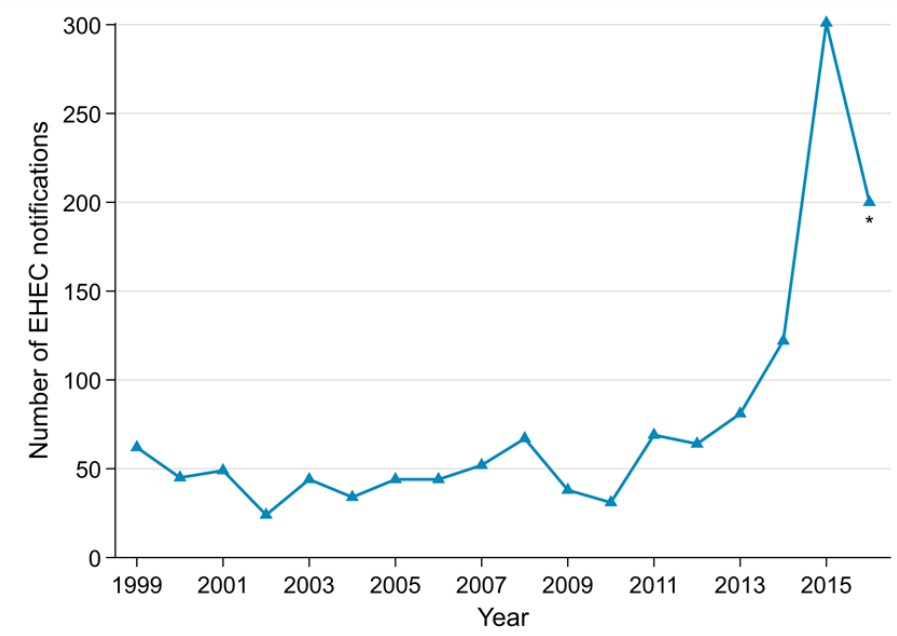

Figure 7.1: Annual number of probable and confirmed enterohaemorrhagic *Escherichia coli* (EHEC) cases reported to the Federal Office of Public Health between 1999 and 2016 (* Data as per 20 July 2016). Cases residing outside Switzerland were excluded

Table 7.1: Overview of pathogens included in four commercially available multiplex PCR panels for gastrointestinal pathogens

	BD MAX™ Enteric Bacterial Panel	**xTAG® Gastrointestinal Pathogen Panel (GPP)**	**FilmArray® Gastrointestinal (GI) Panel**
Bacteria	*Campylobacter* spp. (*jejuni* and *coli*)	*Campylobacter*	*Campylobacter* (*C. jejuni/C. coli/C. upsaliensis*)
	Salmonella spp.	*Salmonella*	*Salmonella*
	Shigella spp./EIEC	*Shigella*	*Shigella*/EIEC
	Shiga toxin-producing organisms (STEC, *Shigella dysenteriae*)	Shiga-like Toxin producing *E. coli* (STEC) *stx1/stx2*	Shiga-like toxin producing *E. coli* (STEC) *stx1/stx2*
		Escherichia coli O157	*E. coli* O157
		Clostridium difficile toxin A/B	*Clostridium difficile* (toxin A/B)
		ETEC LT/ST	ETEC *lt/st*
			Vibrio (*V. parahaemolyticus/ V. vulnificus/V. cholerae*)
		Vibrio cholerae	*Vibrio cholerae*
		Yersinia enterocolitica	*Yersinia enterocolitica*
			Plesiomonas shigelloides
			EAEC
			EPEC

Table 7.1: (continued)

	BD MAX™ Enteric Bacterial Panel	xTAG® Gastrointestinal Pathogen Panel (GPP)	FilmArray® Gastrointestinal (GI) Panel
Viruses		Adenovirus 40/41	Adenovirus F 40/41
		Norovirus GI/GII	Norovirus GI/GII
		Rotavirus A	Rotavirus A
			Astrovirus
			Sapovirus (Genogroups I, II, IV, and V)
Parasites		*Cryptosporidium*	*Cryptosporidium*
		Entamoeba histolytica	*Entamoeba histolytica*
		Giardia	*Giardia lamblia*
			Cyclospora cayetanensis

break situation or whether it reflects a change in laboratory methods. One of these studies aimed to get a better understanding of the current diagnostic algorithms and methods used by Swiss diagnostic laboratories and of their reporting procedures. Therefore, visits to Swiss diagnostic laboratories reporting many EHEC cases were scheduled with the objectives to:

- assess the laboratory techniques currently used by Swiss diagnostic laboratories to test for EHEC with special emphasis on the importance of multiplex PCR panels
- network to personalise the institution "FOPH" and to foster the relationship between the FOPH and the laboratories
- enhance the mutual understanding of the Swiss notification system and associated challenges
- prepare for a subsequent study, a so-called "positivity study", by explaining its aims and objectives, its significance, and the data requirements, and enquiring about data availability and willingness to participate

7.2 Methods

The 10 laboratories reporting most EHEC cases in 2015 were selected. Two of those 10 laboratories were closely collaborating; the same person was responsible for EHEC testing in those two laboratories. Therefore, an additional laboratory was selected. Furthermore, the sample of 10 laboratories included only one hospital laboratory. Hence, a second hospital laboratory was selected to increase the variety of possible approaches to EHEC diagnostics.
The visit was kept as informal as possible in order to establish (in parts for the first time) a personal relationship with laboratory staff. The laboratory staff should not feel controlled or intimidated despite being visited by an authority. In contrary, the visit was supposed to facilitate interaction and enhance mutual understanding of everyday activities and challenges. Therefore, the term "conversation" is used instead of "interview" for the remainder of this chapter. Nevertheless, conversations were prepared similar to preparing interviews for a qualitative research study. A question guide with leading questions was developed jointly between the Swiss Tropical and Public Health Institute (Swiss TPH) and the FOPH to help structure the conversation. The FOPH sent letters explaining the current epidemic increase of EHEC in Switzerland and the

need to understand underlying reasons to the selected laboratories. Afterwards, FOPH staff contacted the laboratories by phone and fixed an appointment with the person responsible for microbiology and/or EHEC diagnostics, if they agreed to participate. One or two employees of the FOPH and one Swiss TPH staff (two in one case) attended the conversations. The employee of the FOPH lead the conversation; Swiss TPH staff was responsible for note taking and for explaining the planned positivity study. Conversations were not recorded as this would defy the intended informal character.

7.3 Results

All 11 laboratories were visited between 08 June and 13 July 2016. Four laboratories were in the French-speaking part of Switzerland with conversations conducted in French while seven were in the German-speaking part of Switzerland with conversations in German.

7.3.1 Use and characteristics of multiplex PCR panels

Laboratory experts unanimously agreed that the increasing use of multiplex PCR panels is responsible for the increase in EHEC case numbers seen in the National Notification System for Infectious Diseases (NNSID). Some spontaneously noted "Wer sucht, der findet" ("seek and you shall find"). All except two laboratories had at least one multiplex PCR system in use for GI pathogens at the time of the visit. One of the two laboratories not currently using a multiplex PCR panel, however, evaluated different panels in 2013/14. The majority of laboratories visited uses GI multiplex PCR panels since 2014 or 2015.
The number of EHEC notifications by participating laboratory and the time of introduction of the multiplex PCR panel is displayed in figure 7.2. In some laboratories, routine testing of stool samples has been changed from using traditional culture-based techniques to using the "small" multiplex PCR panel (BD MAX^{TM} Enteric Bacterial Panel). Hence, in these laboratories, all stool samples which were previously tested for *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. are now (additionally) tested for EHEC.
Laboratory experts stated that multiplex PCR panels give more frequently positive results than culture-based methods. Their estimates on what proportion of additional cases is identified with PCR compared to culture differed: for *Campylobacter* estimates ranged from "20% more" to "40% more" with multiplex PCR than with culture. Others stated

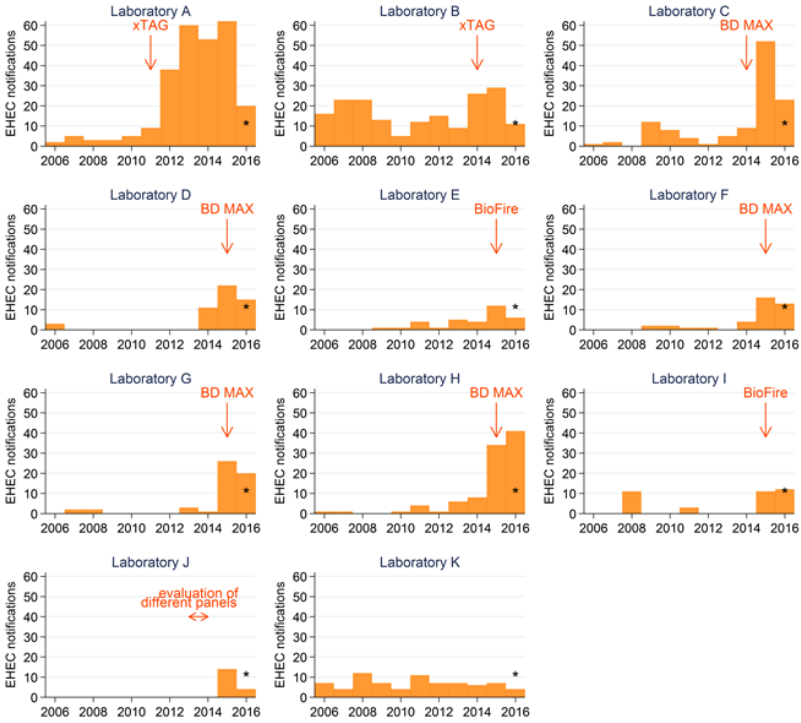

Figure 7.2: Number of enterohaemorrhagic *Escherichia coli* (EHEC) notifications registered at the Federal Office of Public Health (FOPH) per year between 2006 and 2016 (data as per 20 July 2016) and time point of introduction of multiplex PCR panels, among laboratories visited by the FOPH and the Swiss Tropical and Public Health Institute in June/July 2016

that "5–10%" or "up to 40%" of PCR-positive results cannot be confirmed by culture.
Opinions differed also when asked if a positive PCR result for EHEC is considered clinically relevant or rather an accidental finding. Even though most laboratory experts consider EHEC an accidental finding – physicians hardly ask specifically for EHEC testing – some seemed more confident in relying on multiplex PCR panel results than others. Some laboratory experts assess the clinical relevance together with the physician, on a case-by-case level. An expert mentioned that BD MAX™ Enteric Bacterial Panel only detects *vtx1* and *vtx2* (cytotoxins expressed by EHEC) but that the clinical relevance also depends on other pathogen characteristics. Similarly, it was mentioned that all serotypes (harbouring at least one of the cytotoxins) are detected by the test and reported to the FOPH but one single serotype (O157) is responsible for 80% of cases of haemolytic-uraemic syndrome (HUS).
On the other hand, it is assumed that patients are sick (do show signs and symptoms) when stool samples are sent in for diagnostics. Hence, if a pathogen is detected this is considered the likely cause. In this context, interpretation of multiple positive PCR results was discussed. Again, expert opinions differed. Some stated that multiple infections are rarely found in patients without travel history; hence, in cases without travel history, the identified pathogen is considered causing the symptoms. In contrast, in patients with travel history, multiple positive findings are more frequent. In those cases it is difficult to evaluate which of the organisms is causing disease. One respondent stated that identifying 2–3 pathogens is plausible in a returning traveller depending on the travel destination. He also referred to the manual of the testing kit stating that results have to be questioned or re-checked only in case of 4 or more positive test results. Other experts seemed more sceptical towards multiple positive results. It has to be noted, however, that some experts may have referred to the "small" panel (BD MAX™ Enteric Bacterial Panel) while others may have thought of the "large" panel (FilmArray® Gastrointestinal (GI) Panel) when talking about multiple infections. Furthermore, the "large" panel might more frequently be used in returning travellers than in persons without travel history (see also next section).

7.3.2 Diagnostic algorithm in case of diarrhoea

Laboratory experts were also asked about the diagnostic procedures that are applied in case of receiving a stool sample from a patient with diarrhoea. Responses to this question were heterogeneous: in some

laboratories the pathogens tested for and the diagnostic methods applied are exclusively defined by the ordering physician; others apply their own diagnostic algorithms. For example, several experts mentioned that they would test using BD MAX™ Enteric Bacterial Panel if "general bacteriology" was requested for a patient without travel history and they would use the FilmArray® Gastrointestinal (GI) Panel in a patient with travel history. Others use a "single PCR" if only one pathogen is requested by the physician but a multiplex PCR panel if testing for two or more pathogens is requested. Such decisions can also be based on economic reasons (cost- and time-effectiveness).
Many laboratories confirmed relying on PCR in the first instance for stool diagnostics but most still conduct a culture-based confirmation test in case a PCR-test generated a positive result. Reasons mentioned for using culture-based diagnostics after PCR-positive results were: for knowing the antibiotic resistance profile, for obtaining the isolate, for typing, for billing purposes, and for distinguishing species which are not distinguished by PCR (e.g. *Arcobacter* spp. from *Campylobacter* spp. or *Shigella* spp. from enteroinvasive *Escherichia coli* (EIEC)).

7.4 Discussion

7.4.1 "Seek and you shall find (EHEC)"

The conversations with the laboratory experts revealed that the laboratories in Switzerland operate independently and apply heterogeneous algorithms for stool diagnostic testing. However, one issue was undisputed among the experts: the increase in EHEC notifications is due to the change from conventional stool culture to multiplex PCR panels. Looking at the date of implementation of the multiplex PCR panels as reported by laboratory representatives and the number of reported EHEC cases by laboratory supports this finding (Figure 7.2). Apart from confirming the switch from culture-based to multiplex PCR methods, laboratory representatives also highlighted that testing specifically for EHEC is rarely asked for by physicians.
The potentially large impact of laboratory practices was already described by a Swiss diagnostic laboratory for *Aeromonas* spp.: They excluded *Aeromonas* spp. from routine testing ("basic stool culture") due to a change in the official tariff structure in 2006 [Tritten *et al.*, 2014]. After that change, this pathogen was rarely isolated until its reintroduction in routine testing in this laboratory in 2011. This change was not noted by the FOPH as it did not concern a notifiable disease/pathogen.

However, it shows the importance of understanding laboratory practices for interpreting laboratory data including notifications.

7.4.2 Implications of laboratory practices for surveillance and outbreak detection

Interestingly, the number of confirmed EHEC cases remained rather stable in the European Union (EU) between 2012 and 2015 with a slight increase in 2016 [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. In 2016, the notification rate in the EU was 1.82 confirmed cases per 100'000 population. For comparison, the Swiss notification rate was at 5.5 per 100'000 population which is the highest notification rate since 1999, the year in which EHEC became notifiable [Bundesamt für Lebensmittelsicherheit und Veterinärwesen and Bundesamt für Gesundheit, 2017; European Food Safety Authority and European Centre for Disease Prevention and Control, 2017]. It has to be noted, however, that the notification rate in the EU differed quite substantially by country with two countries (Ireland and Sweden) reporting higher rates than Switzerland [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017].
Even though the "EU summary report on zoonoses, zoonotic agents and food-borne outbreaks 2016" [European Food Safety Authority and European Centre for Disease Prevention and Control, 2017] mentions that "diagnosis by direct detection of the toxin or toxin genes by PCR without strain isolation is increasing", it also states that diagnosis is "generally performed by culture from stool samples and indirect diagnosis by detection of antibodies [...]". Hence, the fact that EHEC notifications are not (yet) increasing in the EU could be linked to differences in laboratory techniques.
In the US, testing of all stool samples from patients with acute, community-acquired diarrhoea for EHEC was recommended already in 2009, before PCR methods were widely used for EHEC diagnosis and before multiplex PCR panels were available [Gould *et al.*, 2009]. Nevertheless, also in the US an increase in EHEC infections was noticed in 2016 compared to 2013–2015 both in culture-confirmed and 'culture-independent diagnostic test positive-only' cases [Marder *et al.*, 2017].
In Switzerland, the number of HUS cases among notified EHEC cases remained stable in absolute terms despite the strong increase in the number of EHEC cases, hence, reflecting a relative decrease [Bundesamt für Lebensmittelsicherheit und Veterinärwesen and Bundesamt für Gesundheit, 2017]. This observation additionally supports the hypothesis of

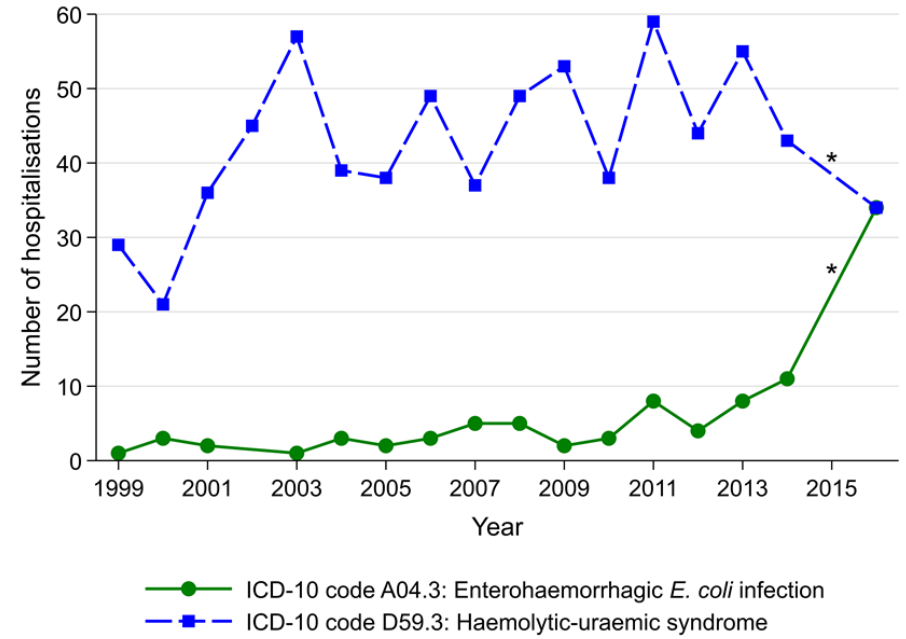

Figure 7.3: Number of hospitalisations due to enterohaemorrhagic *Escherichia coli* (ICD-10 code A04.3) and haemolytic-uraemic syndrome (ICD-10 code D59.3) according to Swiss hospital statistics, 1999–2016.
* Data from 2015 were not available online. Source: Bundesamt für Statistik [n.d.]

increased testing rather than dealing with an outbreak: with the new methods, also patients in which there was no direct suspicion of EHEC are tested. Those patients are unlikely to show severe symptoms or even serious complications of this disease.
Considering that laboratory results are available faster with PCR than with culture, one could argue that notification forms are completed at an earlier time point during the course of disease by physicians. This could result in a lower proportion of sequelae reported given that HUS usually occurs 5–13 days after onset of diarrhoea [Karch *et al.*, 2005]. However, HUS cases (whether or not caused by EHEC) are also not increasing according to Swiss hospital statistics (Figure 7.3).
Finally, in other countries, several EHEC outbreaks have been detected by an increase in HUS cases in the first instance [Germinario *et al.*, 2016; Vygen-Bonnet *et al.*, 2017; Werber *et al.*, 2008]. In summary, there is no evidence of an EHEC outbreak in Switzerland despite increasing case numbers.

7.4.3 Importance of good relations among national surveillance actors

The visits of health authority personnel also aimed at enhancing the relationship between diagnostic laboratories and the FOPH. Different statements and observations suggest that this was both necessary and successful to foster a sense of community. The rather formal reception of the FOPH and Swiss TPH employees in some laboratories showed the partly existing reserved attitude towards the FOPH. It was mentioned repeatedly that getting into contact with the FOPH by phone or identifying the person in charge at the FOPH for questions (e.g. concerning notification forms) was always difficult. It is also perceived that the obligation to report creates a lot of work at the laboratories with no "return" (i.e. feedback). Similarly, it was stated that "knowing the faces behind" (from this visit) tremendously facilitates future contacts and interactions.
On the web page of the German Robert Koch Institute (RKI), for example, each department and unit is presented, naming the leader and the substitute and providing contact details (e.g. Surveillance unit: `https://www.rki.de/EN/Content/Institute/DepartmentsUnits/InfDiseaseEpidem/Div32/div32_node.html` [accessed: 27 July 2018]). Providing such information also on the web page of the FOPH could be appreciated by the laboratories and facilitate closer contact given the results of the laboratory visits. Furthermore, the RKI

publishes an annual report with data analyses of all notifiable observations[1]. Developing something similar for Switzerland could address the perceived lack of feedback on notifications by laboratory staff. The importance of close collaboration and communication among stakeholders in the framework of disease surveillance has also been stressed, especially in the context of outbreak investigations [Henao *et al.*, 2015; Knoblauch *et al.*, 2015; Schjørring *et al.*, 2017]. Therefore, those laboratory visits initiated by the FOPH were important. The positive effects resulting from the visits should be maintained and strengthened, e.g. by repeating those visits regularly, inviting laboratories for a return visit at the FOPH, or organising regular (e.g. annual) meetings between all stakeholders involved in the NNSID (laboratory experts, physicians, cantonal and national public health authorities). Furthermore, laboratory experts mentioned that actively informing their clients (i.e. physicians) about new technologies and changes in their laboratory practices is key and can prevent fears and a negative attitude towards those changes. This common practice of actively informing clients, partners or collaborators about changes in a personal manner, e.g. by letters instead of through official communication channels only (e.g. BAG Bulletin) should be adopted by the FOPH.

7.5 Conclusions

The example of EHEC suggests that changes in diagnostic methods must not only be considered for long-term trends but can also be a reason for rather rapid changes in case numbers. Such factors should be considered before or in parallel to initiating outbreak investigations.
Apart from being an important resource for interpretation of notification data, talking to the experts from diagnostic laboratories also proved important to enhance mutual trust and understanding. It is important for institutions such as the FOPH to "step out of anonymity". Good networks with experts "in the field" could even prevent unnecessary outbreak investigations if they can provide convincing arguments for changes in case numbers which are not linked to disease incidence.

[1] Available online at `https://www.rki.de/DE/Content/Infekt/Jahrbuch/jahrbuch_node.html` (accessed: 27 July 2018)

8 Do changes in EHEC diagnostics mislead interpretation of disease surveillance data in Switzerland? Time trends in positivity from 2007 to 2016

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Abstract

Laboratory-confirmed cases of enterohaemorrhagic *Escherichia coli* (EHEC) are notifiable to the National Notification System for Infectious Diseases in Switzerland since 1999. Since 2015 a large increase in case numbers has been observed. Around the same time, syndromic multiplex PCR started to replace other diagnostic methods in standard laboratory practice for gastrointestinal pathogen testing in Swiss diagnostic laboratories, suggesting that the increase in notified cases is due to a change in test practices and numbers.

We analysed laboratory data from 11 laboratories across Switzerland from 2007 to 2016 to calculate the positivity – i.e. the rate of the number of positive test results for EHEC divided by the total number of tests performed.

The age- and sex-standardised positivity of EHEC testing increased from 0.8% in 2007 to 1.7% in 2016. This increasing positivity suggests that the increase in case notifications cannot uniquely be attributed to an increase in test numbers alone.

Therefore, we find no evidence to exclude a real epidemiological trend for the observed raise in EHEC-related disease frequency. The apparent epidemic seems restricted to Switzerland as notification data of other European countries do not show comparably strong increasing trends.

Introduction

Enterohaemorrhagic *Escherichia coli* (EHEC) is a subtype of *E. coli* characterized by the potential of causing human illness, belonging to the group of Shiga toxin-producing *Escherichia coli* (STEC). EHEC infection is sometimes asymptomatic and generally self-limiting but it can also lead to severe gastroenteritis with haemorrhagic diarrhoea, and potential subsequent life-threatening conditions, such as haemolytic-uraemic syndrome (HUS) [1, 2].

EHEC transmission can occur through consumption of contaminated food and drinks or by direct contact with infected individuals or animal shedders [1, 3-5]. EHEC is endemic in Europe and Switzerland. Cases appear sporadically or as clusters in outbreaks. A large outbreak occurred in 2011 in Germany and was attributed to contaminated sprouts [6]. Smaller outbreaks were reported from, e.g. Italy in 2013 due to contaminated milk and Romania in 2016 due to fresh cheese [7].

It is estimated that STEC leads to 2.8 million of illness cases annually, including over 3'800 cases of HUS [8]. However, those estimates may be

conservative.
In Switzerland, the Federal Office of Public Health (FOPH) refers to this group of notifiable pathogens as "*Escherichia coli*, enterohämorrhagische (EHEC, VTEC or STEC)" [9]. The Swiss National Notification System for Infectious Diseases (NNSID), managed by the FOPH, gathers all notifications on laboratory-confirmed EHEC infections since 1999. Case numbers were stable until 2010, with only a few laboratories reporting EHEC in Switzerland. A slight rise in cases was observed in 2011 after intensified testing following the outbreak in Germany and numbers of EHEC notifications strongly increase since 2015 [10]. It is hypothesised that this recent increase in case notifications is due to the introduction of multiplex polymerase chain reaction (PCR) panels for the analysis of stool samples. Gastrointestinal multiplex PCR panels are able to detect multiple gastrointestinal pathogens in one single test [10, 11]. Traditionally, routine testing of stool samples for bacterial pathogens involved only *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. using culture-based techniques. With multiplex PCR panels, stool samples can be tested for up to 22 pathogens including EHEC in one single run.
Previously, EHEC was rarely tested and only on demand by the physician alerted by clinical signs. The increase in testing rate for EHEC, likely occurring when PCR panels are introduced, could lead to identification and notification of cases that were simply not discovered beforehand [10].
This study aims to assess the development of the EHEC positivity in the Swiss population between 2007 and 2016 and to give more insight into the epidemiology and notification numbers of EHEC infections in Switzerland in recent years.

Methods

Individual-based testing data were requested from 11 Swiss diagnostic laboratories. Laboratories were selected based on providing most EHEC notifications in 2015, to include all regions of Switzerland and to include both, hospital and private diagnostic laboratories.
Data collected comprised all tests performed for EHEC between January 2007 and December 2016, including positive and negative test outcomes. Information requested included date of test, test result, test method, patient identification number, and patients' date of birth, sex and canton of residence.
Test records indicating patients' residence outside Switzerland and those

without a (conclusive) test result were omitted. Duplicate entries, defined as identical values for all variables, and "repeated tests" were excluded from the analyses. Repeated tests were defined as more than one test performed for the same patient during a single disease episode. The analysis was planned *a priori* and was performed using STATA 14 (StataCorp., USA).

We use the term positivity as the rate of number of positive tests in relation to the total number of tests performed for EHEC [12, 13]. The positivity was calculated for different demographic groups, test methods, spatial (based on the patients' canton of residence) and temporal (annual and seasonal) trends. The main outcome, the annual positivity, was age- and sex-adjusted using direct standardisation with the sample population (2007–2016) as reference population.

Univariable logistic regression was used to test the association between test result and test year, season, time trend, sex, age group, laboratory, test method and greater region. Season was modelled using a sine and cosine function with an annual period. The time trend was a continuous variable combining test month and test year. The greater regions correspond to the Nomenclature of Units for Territorial Statistics (NUTS)-2-level. Categories with most observations were chosen as reference categories, except for the seasonality (first month of the year).

A multivariable mixed effect logistic regression model was defined *a priori*, independent of the outcome of the univariable regressions. The model's explanatory variables included sex, age group, seasonality, time trend, greater region and diagnostic test method. The model included an interaction term for sex and age group. The variable "laboratory" was included as a random effect to account for clustering. The clustering effect of the same patient (same identification number) was omitted.

Finally, the multivariable model was compared to a reduced model without adjustment for test method in order to validate the results and ensure the consistency of the time trend, independently from the diagnostic method.

Based on multivariable regression results, predicted probabilities for a positive test result were computed and plotted for direct visualisation and comparison of categories and models.

Ethical statement

This study was funded by the Swiss FOPH. The authors declare that they have no conflict of interest. The study was conducted under the Epidemics Act (SR 818.101). The data, provided by laboratories, were

anonymised for the analysis. Other data (e.g. notification data, population statistics) is publicly available from the FOPH or the Swiss Federal Statistical Office.

Results

Data received

The participating 11 laboratories provided in total 91'685 records of EHEC tests (thereof 1'366 positives). Only five laboratories provided data for the entire study period (2007–2016, N=61'916). Three of the remainder six laboratories did not perform EHEC tests for the entire study period, two laboratories could not extract all data requested due to changes in the information technology and data storage system; one laboratory did not specify a reason for missing years of data.
Following our exclusion criteria, 1'407 records (22 positives) were excluded. After initial cleaning of the dataset, further 71 observations (3 positives) with either missing sex or age were excluded. Finally, 1'110 duplicated entries (31 positives) and 3'054 repeated tests (96 positives) were excluded. In total, 6.2% (N=5'642) of the original dataset were excluded. The final dataset comprised 86'043 observations (1'149 positives).
Figure 8.1 shows the number of EHEC cases in the NNSID, and in our dataset as obtained by the laboratories. Data from the NNSID show that the laboratories selected for this study reported 61.9% of all cases registered in the NNSID between 2007 and 2016 (range 39.4% in 2011 to 73.2% in 2009).

Characteristics of the patient population

The proportion of males to females tested remained constant between 2007 and 2016 with 44.3% males and 55.7% females across all study years. The median age of the tested population increased from 30 years to 44 years old (Kruskal-Wallis test: $p<0.01$). Median age of patients differed significantly between laboratories (median by laboratory ranging from 27–55, overall median: 40 years old) and greater regions (median by greater region ranging from 37–44) (Kruskal-Wallis test: $p<0.01$).

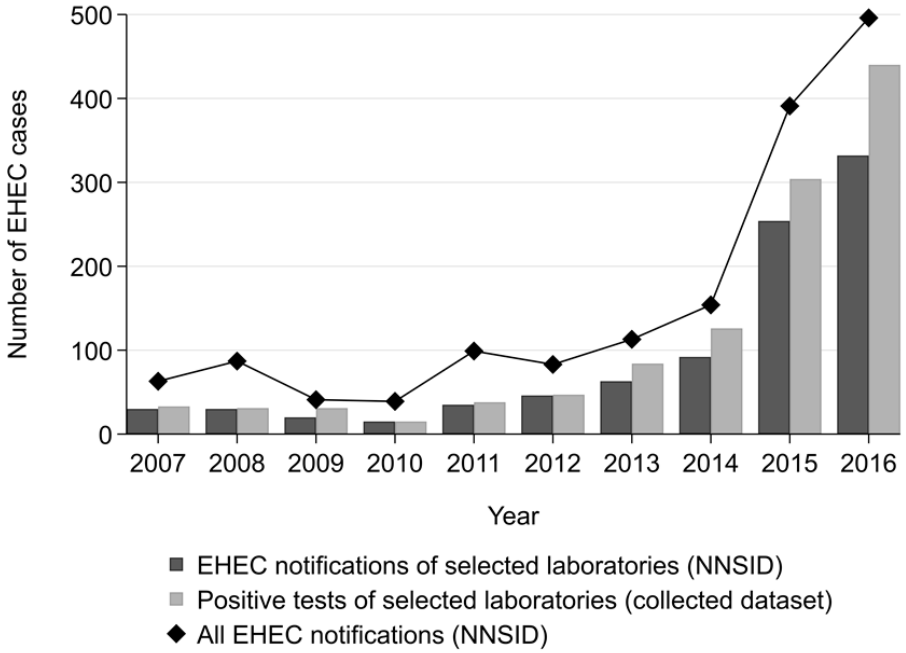
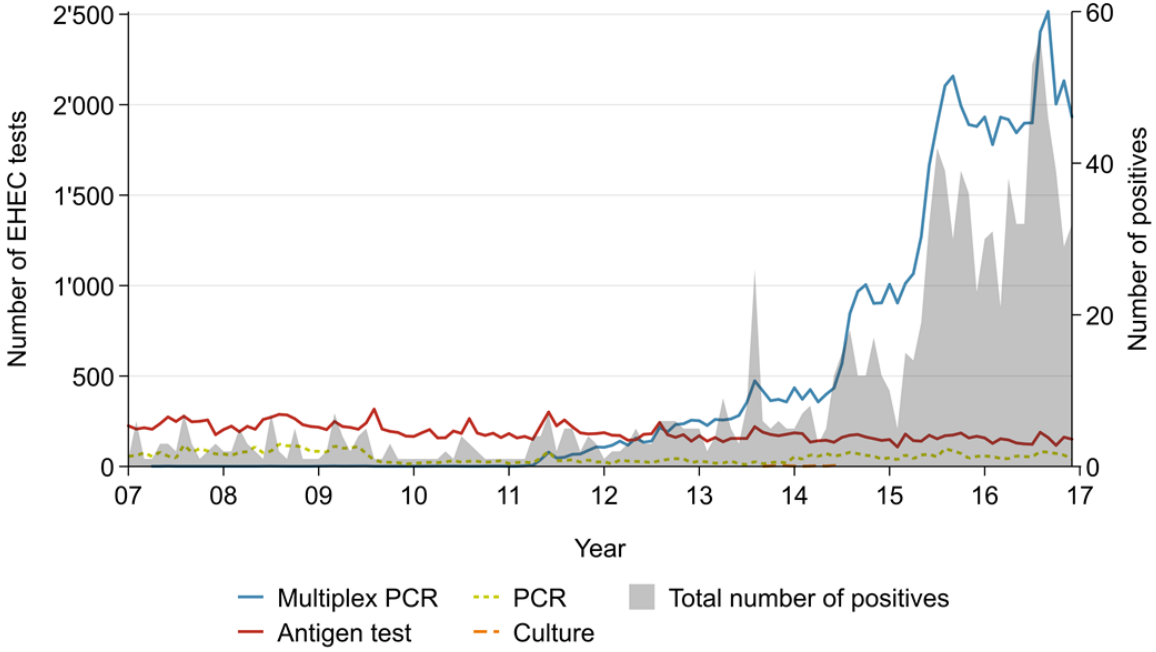
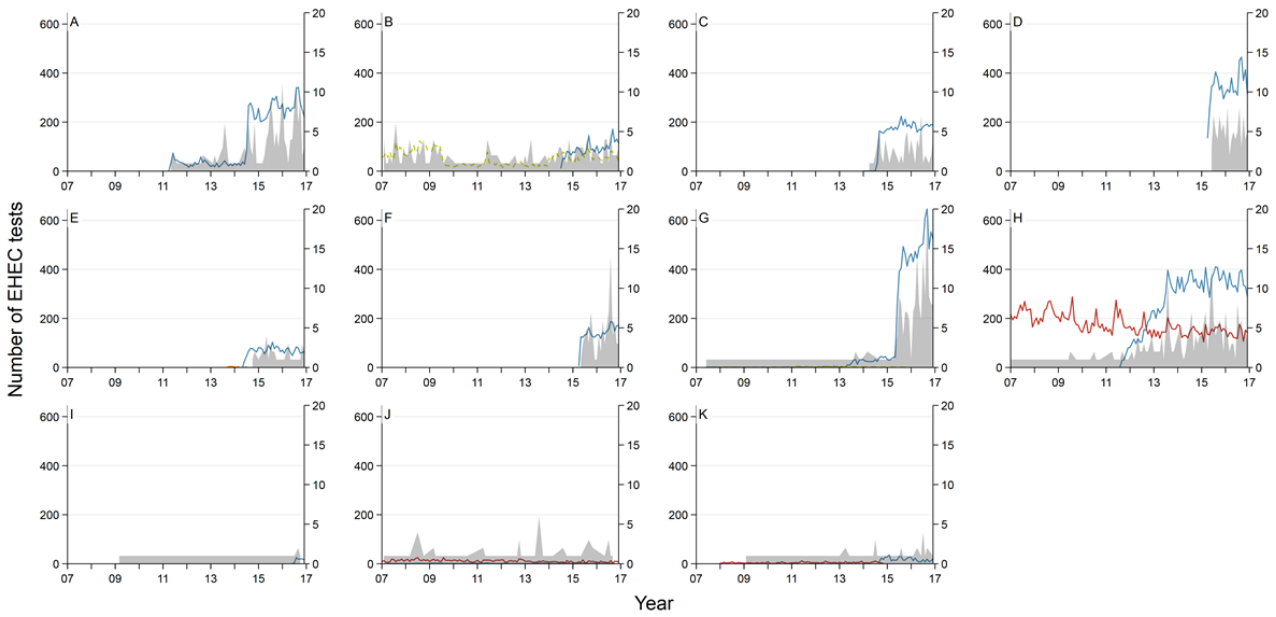


Figure 8.1: Number of enterohaemorrhagic *Escherichia coli* (EHEC) notifications of 11 Swiss diagnostic laboratories as reported in the National Notification System for Infectious Diseases (NNSID), the number of positive tests of the laboratories in their own datasets, and the total number of EHEC notifications reported in the NNSID per year, 2007–2016, Switzerland



(a) Data of 11 Swiss diagnostic laboratories

Figure 8.2: Total number of enterohaemorrhagic *Escherichia coli* tests performed by test method and number of positive tests for the entire study period (2007–2016)



(b) By laboratory

Laboratories, diagnostic methods and greater regions

The variables "laboratory", "greater region" and "diagnostic test used" strongly correlated (Fisher's exact test: $p<0.01$ for all three tests).
The diagnostic methods performed included multiplex PCR (66.5%, N=57'168), antigen test (26.3%, N=22'588), PCR (7.3%, N= 6'247) and culture-based diagnostics (<0.1%, N=24). Multiplex PCR panels able to detect different pathogens were distinguished from PCR panels targeting EHEC/*E. coli* only (thereafter referred to as "single PCR"). Multiplex PCR panels used were mainly BD MAX™ (Extended) Enteric Bacterial Panel (52%), Luminex xTAG® Gastrointestinal Pathogen Panel (36%), BioFire FilmArray™ Gastrointestinal Panel (5.9%), and Seegene (not specified whether Allplex™ Gastrointestinal Panel or Seeplex® Diarrhea ACE Detection, 4.6%).
The number of tests performed using the antigen test, single PCR or culture remained stable between 2007 and 2016, while the number of multiplex PCR panels performed increased by 42% (Figure 8.2a). The five laboratories providing data for the entire study period were using single PCR or antigen tests before the introduction of multiplex PCR (Figure 8.2b). Only one of these five laboratories kept using primarily antigen tests for the entire study period.
From the six laboratories that could not provide data for the entire study period, three started to perform EHEC testing only between 2014 and 2015, once multiplex PCR panels were available.

Positivity

The number of tests for EHEC increased sevenfold from 2007 to 2016 (3'711 to 26'639) while the number of positive test results increased 13-fold in the same time period (33 to 440). The age- and sex-standardised positivity of EHEC testing increased from 0.8% in 2007 to 1.7% in 2016 (Figure 8.3).
Positivity increased for all age categories. The positivity calculated over the entire study period is highest for children 1–4 years old (2.2%) and increased from 1.4% in 2007 to 2.9% in 2016. The largest relative increase was seen in the elderly aged "80+", from zero (no positive case in 2007) to 1.8%.
The overall positivity is similar for men (1.4%) and women (1.3%) and increased from 0.7% and 1.1% to 1.7% and 1.6%, respectively.
The positivity and trend in positivity differed across laboratories (Figure 8.4). The overall positivity ranged from 0.6% to 5.8%. Three laboratories showed a large fluctuation in the annual positivity, due to the small

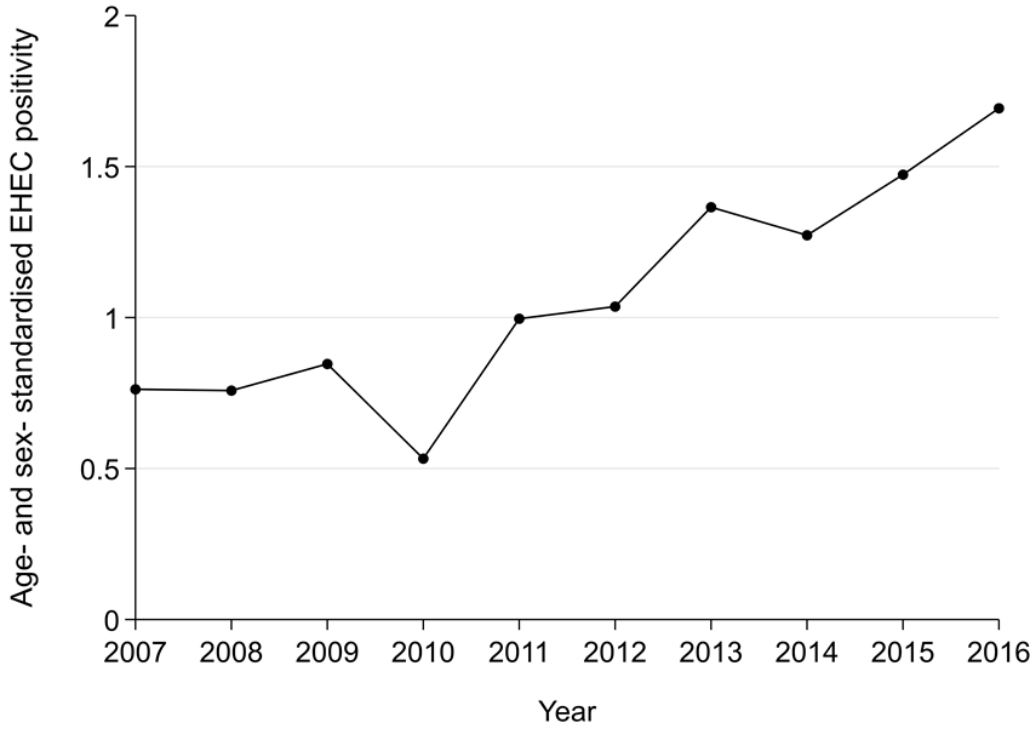
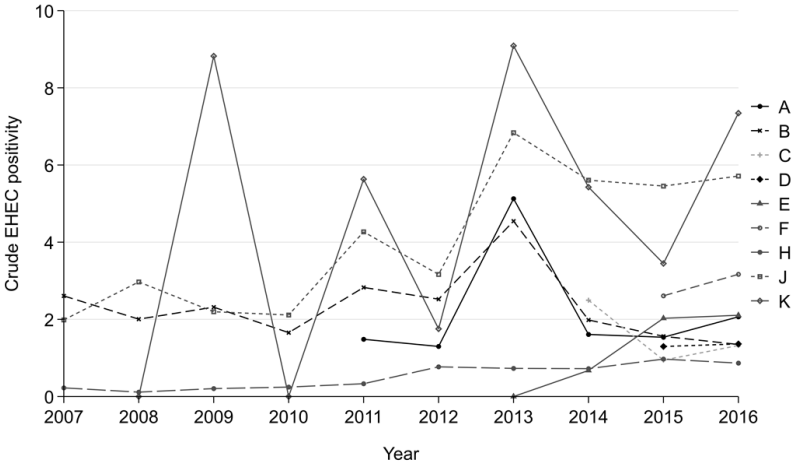


Figure 8.3: Age- and sex-standardised positivity of enterohaemorrhagic *E. coli* testing, Switzerland, 2007–2016

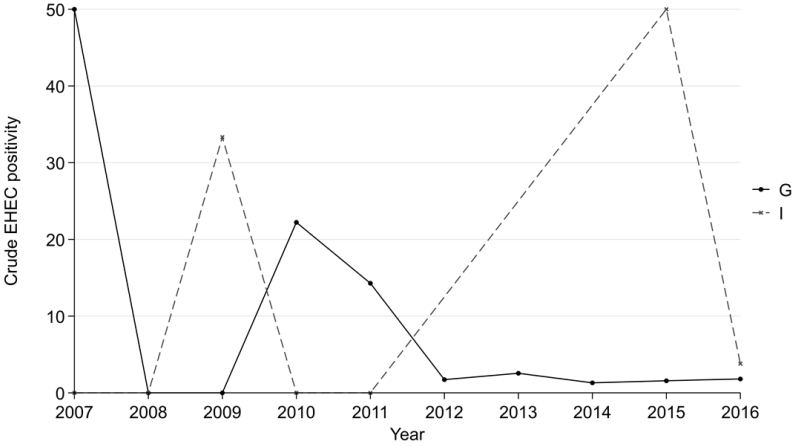
number of tests performed. The largest relative increase in positivity was 2.8-fold from 2% to 5.7%. After 2014 the positivity of most laboratories stabilised, though at different levels.
The positivity further differed by test method. The positivity of culture-based tests was not calculated due to (i) the small number of observations and (ii) the exclusion process for "repeated tests". Most culture-based tests performed were confirmation tests; therefore, they were often classified as "repeated tests" and excluded. The positivity across all test years was highest for tests using single PCR (2.4%) and lowest for the antigen test (0.6%), positivity of multiplex PCR panels was at 1.5%. The positivity of multiplex PCR increased from 1.1% in 2014 to 1.7% in 2016. In contrast, the positivity for single PCR and antigen tests started to decrease in 2013 and 2014 respectively, just after peaking at 4.3% (PCR; 2013) and 1.4% (antigen test; 2014).

Determinants of a positive diagnostic test result

The univariable regressions showed a marginal but significant trend for the time trend variable (Odds ratio [OR] 1.003, $p<0.01$) as shown in Table 8.1. Almost all test years, except 2013 showed decreased odds for a positive test outcome compared to the reference year 2016. All calendar months except July have smaller odds for a positive test outcome than the reference month of August.
The age groups "1–4" and "5–9" years old were almost twice as likely to have a positive test outcome (OR 1.88, $p<0.01$ and OR 1.80, $p<0.01$) than the reference category of "20–39" years old. No difference was seen between sexes.
Compared to multiplex PCR panels, the use of the antigen test had a 63% lower probability to generate a positive test outcome, while the use of single PCR showed 56% higher chance for a positive test outcome. The odds of culture-based tests could not be evaluated due to the small sample size.
The ORs and significance levels from the fully-adjusted multivariable model varied only marginally from the univariable models and do not alter the interpretation, therefore, they will not be detailed, but are presented in Table 8.1.
Predicted probabilities based on the multivariable model showed an increasing time trend for all test methods and regions.
Comparison of the fully adjusted model to a model excluding the adjustment for test method showed increasing predicted probabilities for both models, but with a lower slope for the fully adjusted model (Figure 8.5).



(a) Data of nine Swiss diagnostic laboratories, scale y-axis: 0–10%



(b) Data of two laboratories, using a different scale for the y-axis: 0–50%

Figure 8.4: Enterohaemorrhagic *E. coli* positivity by Swiss laboratory for the entire study period (2007–2016)

Table 8.1: Odds ratios for a positive test result for enterohaemorrhagic *Escherichia coli* of the uni- and multivariable logistic regression models, 2007–2016, Switzerland

	N	OR	95% CI	aOR[a]	95% CI
Age group (year)					
Under 1	2'915	0.97	(0.67–1.40)	1.28	(0.72–2.28)
1–4	8'855	1.88 ***	(1.56–2.27)	3.38 ***	(2.56–4.45)
5–9	2'593	1.80 ***	(1.34–2.43)	1.66 *	(1.07–2.58)
10–19	5'898	1.03	(0.79–1.35)	1.03	(0.71–1.49)
20–39	21'971	1		1	
40–59	19'404	1.00	(0.84–1.20)	1.03	(0.81–1.31)
60–79	17'685	1.10	(0.92–1.32)	1.05	(0.82–1.34)
Over 79	6'722	1.14	(0.89–1.45)	1.11	(0.81–1.52)
Sex					
Male	38'209	1.03	(0.91–1.16)	0.93	(0.72–1.20)
Female	47'834	1		1	
Male, age group (year)					
Under 1	1'582			1.14	(0.52–2.47)
1–4	4'962			0.92	(0.62–1.36)
5–9	1'325			1.23	(0.67–2.27)
10–19	2'827			1.14	(0.66–1.95)
20–39	9'080			1	
40–59	8'833			1.02	(0.70–1.47)
60–79	7'408			1.27	(0.88–1.84)
Over 79	2'192			1.17	(0.69–1.95)
Greater region					
Lake Geneva region	15'526	0.79 **	(0.66–0.93)	1.20	(0.89–1.60)

Table 8.1: (continued)

	N	OR	95% CI	aOR[a]	95% CI
'Espace Mittelland'	20'000	1		1	
Northwestern Switzerland	15'273	0.39 ***	(0.32–0.49)	0.69 **	(0.53–0.89)
Zurich	14'439	0.79 **	(0.66–0.94)	0.75 *	(0.58–0.98)
Eastern Switzerland	6'474	0.70 **	(0.55–0.90)	0.88	(0.67–1.16)
Central Switzerland	10'015	0.90	(0.74–1.09)	0.92	(0.70–1.21)
Ticino	1'008	0.74	(0.43–1.30)	1.30	(0.73–2.32)
Test method					
Multiplex PCR	57'168	1		1	
Antigentest	22'588	0.37 ***	(0.31–0.45)	0.34 ***	(0.26–0.44)
PCR	6'247	1.56 ***	(1.31–1.86)	2.31 ***	(1.55–3.45)
Culture	24	-		-	
Time trend	86'043	1.00 ***	(1.00–1.01)	1.00 *	(1.00–1.01)
Test month					
January	6'040	0.50 ***	(0.37–0.68)		
February	5'529	0.59 **	(0.44–0.80)		
March	6'137	0.58 ***	(0.43–0.77)		
April	5'872	0.76 *	(0.58–0.99)		
May	6'357	0.69 **	(0.53–0.90)		
June	7'084	0.77 *	(0.60–0.99)		
July	7'321	1.08	(0.86–1.35)		
August	9'154	1			
September	8'919	0.68 **	(0.54–0.87)		
October	8'098	0.78 *	(0.61–0.99)		
November	8'000	0.71 **	(0.55–0.91)		

Table 8.1: (continued)

	N	OR	95% CI	aOR[a]	95% CI
December	7'532	0.62 ***	(0.47–0.81)		
Seasonality					
$\sin(d * 2 * \pi/T)$		0.84 ***	(0.77–0.91)	0.89 ***	(0.82–0.98)
$\cos(d * 2 * \pi/T)$		0.83 ***	(0.76–0.90)	0.81 *	(0.75–0.89)
Test year					
2007	3'711	0.53 **	(0.37–0.76)		
2008	3'978	0.47 ***	(0.32–0.67)		
2009	3'421	0.54	(0.38–0.79)		
2010	2'536	0.35 ***	(0.21–0.59)		
2011	3'393	0.67 *	(0.48–0.94)		
2012	4'483	0.63 **	(0.47–0.85)		
2013	6'152	0.82	(0.65–1.04)		
2014	10'246	0.74 **	(0.61–0.90)		
2015	21'484	0.85 *	(0.74–0.99)		
2016	26'639	1			
Laboratory					
A	8'712	2.98 ***	(2.44–3.64)		
B	8'861	3.15 ***	(2.59–3.83)		
C	5'102	2.09 ***	(1.60–2.75)		
D	7'181	2.13 ***	(1.68–2.70)		
E	2'197	2.84 ***	(2.02–4.00)		
F	2'904	4.80 ***	(3.75–6.16)		
G	9'852	2.86 ***	(2.36–3.48)		
H	38'796	1			

Table 8.1: (continued)

	N	OR	95% CI	aOR[a]	95% CI
I	121	9.66 ***	(4.46–20.95)		
J	1'438	6.14 ***	(4.55–8.28)		
K	879	8.09 ***	(5.81–11.27)		

N, number of observations; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio

[a] Adjusted for sex, age group, method, temporal trend, seasonality (refer to supplementary material for details). Interaction between age and sex. Random effect of laboratory

* p<0.05; ** p<0.01; *** p<0.001

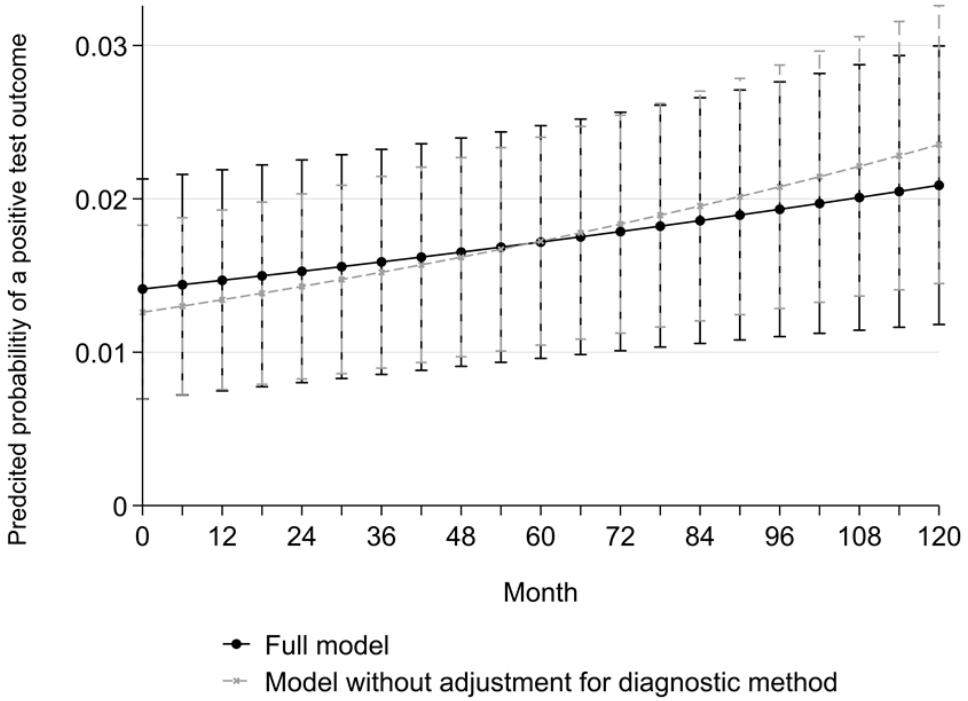


Figure 8.5: Predicted probability for a positive test outcome of an enterohaemorrhagic *E. coli* infection for the full multivariable model and a model without adjustment for methods across 10 years (in months) of the study period, 2007–2016, Switzerland

Discussion

We investigated the apparent epidemic increase of EHEC infections as seen in the rise of case notifications in the NNSID. We calculated the positivity as the rate of all positive diagnostic EHEC tests to the total number of EHEC tests performed. The number of positive tests in our sample of 11 laboratories comprised 61.3% of all notified cases between 2007 and 2016. The positivity gradually increased since 2007.

The impact of diagnostic tests on EHEC surveillance

The increase in positivity coincides with the introduction of multiplex PCR panels as a new diagnostic method for EHEC detection in Switzerland. The impact of changes in diagnostic approaches on public health surveillance has been highlighted before, especially in relation to the switch from culture-dependent to culture-independent diagnostics for foodborne diseases [14, 15]. Such diagnostic changes are especially important for EHEC, as the case definitions for EHEC in the European Union (EU) and in Switzerland are not limited to culture-confirmed cases, but include the detection of the Stx1 or Stx2 antigen or their respective genes [16]. Increases in EHEC notifications in Ireland are explained by the shift from culture-dependent to culture-independent diagnostic methods; the latter showing higher sensitivity and ability to detect non-O157 EHEC [17, 18].
The 11 Swiss diagnostic laboratories in the study switched to culture-independent methods for EHEC detection before 2007. Our data showed that the laboratories were using multiplex PCR panels (BD MAX, BioFire, Luminex) since 2007, but their introduction to routine diagnostics and subsequent replacement of other standard diagnostic methods only happened between 2011 and 2015. These panels comprise the largest proportion of all diagnostic tests performed for EHEC in Switzerland ever since.

Implications of using multiplex PCR panels for EHEC diagnosis

The introduction of multiplex PCR panels for gastrointestinal pathogens is the next paradigm shift in diagnostics for foodborne diseases after the switch to culture-independent tests.
Our data shows that EHEC test numbers increased considerably since the introduction of multiplex PCR panels. The increase in test volume

reflects a larger proportion of the population being screened for EHEC resulting in more positives notified to the NNSID [10]. The availability and use of gastrointestinal multiplex PCR panels has a large impact on testing behaviour. Previously, a test for EHEC was likely ordered by the treating physician if the patient was a paediatric case and/or reported a bloody stool and/or history of travel, due to higher probabilities to develop severe complications such as HUS [19-21]. The increased and wider-spread use of multiplex PCR panels leads to a larger screening of the population in two ways: (i) the suspicion of other gastrointestinal pathogens, such as *Campylobacter* spp., now also leads to an EHEC test, if the laboratory uses such multiplex PCR panels for the standard detection of *Campylobacter*; (ii) the physician orders a gastrointestinal panel directly when the patient presents with diarrhoea (i.e. syndromic testing). We assumed that the introduction of multiplex PCR for stool testing, and hence, co-testing for EHEC lacking this pre-selection, would result in a decreased positivity due to a lower pre-test probability for a positive test outcome. Surprisingly, this decrease is not reflected in our data. Instead, the increase in EHEC cases is disproportionally higher compared to the increase in test volume, resulting in the observed increase of positivity.

Part of the increased testing could also be due to a change in physicians' testing behaviour following the raising public awareness for EHEC infections. However, laboratory experts reported that tests for EHEC are rarely ordered by the treating physician which suggests little change in physicians' testing behaviour [22]. It seems, therefore, that positive test results for EHEC tend to be largely accidental and their clinical relevance for the individual patient is questionable. Hence, the interpretation of these findings remains complex for the physicians and has implications on public health surveillance. Questions concerning the appropriate treatment (no antibiotics, no antidiarrhoeal medicines for actual EHEC infections [23]) and respective reporting to the patient and the NNSID still need to be addressed.

Using multiplex PCR increases the number of cases found due to the higher sensitivity of (multiplex) PCR compared to other conventional diagnostic methods, and the increased probability to detect co-infections [24-27]. A study among staff members of meat-processing companies in Switzerland found that 3.5% were asymptomatic carriers of verotoxin-producing *Escherichia coli* (VTEC) [28]. Using multiplex PCR, such carriers could now be detected as having co-infections, whilst another gastrointestinal pathogen is causing the symptoms. While it is clear that changes in the diagnostic landscape can influence surveillance data

and trend monitoring, we believe this explains only part of the increase in EHEC case notifications in Switzerland.
Indications for a real increase in EHEC incidence independent of the diagnostic test method are threefold: First, our logistic regressions and predicted probabilities for a positive EHEC test outcome showed an increasing trend between 2007 and 2016 even after adjusting for the diagnostic method applied. Second, the predicted probabilities for a positive EHEC test show an upward trend for all methods (multiplex PCR, single PCR, culture-based and antigen test) during the study period. Third, two of the laboratories, which introduced multiplex PCR panels late or not at all, also showed an increase in positivity.
Therefore, we cannot rule out a real epidemiological increase in incidence of EHEC infections among the Swiss population.

Rising incidence of EHEC cases

To interpret a potential EHEC epidemic merits to also consider the epidemiological situation of HUS in Switzerland, as EHEC infections are the main cause to develop HUS. In Switzerland, reported HUS cases remained stable over the past years [10]. Thus, the increase in EHEC case notifications observed in the NNSID might represent mainly mild cases and/or to some extent "asymptomatic" co-infections with another infectious agent of higher pathogenicity causing the symptoms. We have no data on co-infections available to assess their relative contribution to the increase in EHEC case notifications. Though, STEC patients associated with a recent outbreak in Finland were classified as rather mild cases [29]. Furthermore, the authors reported that testing for STEC increased in Finland as well due to PCR screening of gastroenteritis patients.
The change in disease severity could further be explained with changes in the distribution of serogroups found among cases: the proportion of non-O157 EHEC associated with human disease increased in Switzerland, other European countries and the USA [30-32]. O157 EHEC cases are mostly associated with the development of severe disease (HUS) although the importance of non-O157 infections as a cause for HUS is being increasingly recognised [33-35]. Age and sex distributions of EHEC patients in Switzerland remained stable during the observation period 2007–2016. We, therefore, argue that risk groups for EHEC infections remained unchanged and are not the cause for an increase in incidence.
In an international context, the USA also reported an increased incidence of STEC cases in 2017 compared to 2014–2016, though not to the extent as Switzerland [31]. The USA also noted a stable incidence of

HUS in children in 2016 compared to 2013–2015, likely related to a decrease of O157 cases.
No other European country reported an increase in EHEC notification numbers to the extent observed in Switzerland (8-fold increase in cases between 2012 and 2016), except Romania, which had the highest relative increase between 2012 and 2016 (1 to 29 cases), associated with an outbreak in 2016 [32]. However, European countries' notification rates are as high as in Switzerland. In Finland, the increase in reported cases between 2012 and 2016 was 4-fold [32].

Limitations

We selected our sample of laboratories, among other criteria, based on their contribution to the latest notifications. This choice favoured laboratories which had switched to multiplex PCR and, therefore, may not represent the whole laboratory landscape in Switzerland.
We noted that in recent years NNSID case numbers and the number of positive test results recorded in the laboratories' individual datasets did not match. Positive cases were either underreported to the NNSID, or the NNSID excluded certain reports from their official statistics, or the number of positive test results in our sample was overestimated, e.g. due to an insufficient exclusion of repeated tests.
The correlation of "laboratory", "region" and "diagnostic method" hampered the evaluation of spatial trends. Inferences on specific greater regions in Switzerland largely depended on the laboratories chosen in our sample, e.g. the number of tests in each region per 100'000 population either relate to true differences in testing frequencies between regions or to under- or over-representation in our sample.

Conclusion

Since 2015 the notification numbers for enterohaemorrhagic *Escherichia coli* (EHEC) markedly increased in Switzerland. However, meaningful interpretation of such surveillance data is only possible if every aspect of the disease trajectory from changes in awareness (among physicians and patients) and testing behaviour to the choice of diagnostic method are taken into consideration.
Due to previously infrequent, but targeted testing for EHEC and the lack of culture-based test confirmation, EHEC surveillance has been heavily impacted by recent changes in diagnostic methods. The switch from targeted EHEC testing to co-testing of virtually all stool samples submitted

for "basic stool bacteriology" using multiplex PCR panels has notably increased the test volume for EHEC. This development led to a larger number of EHEC detection partly explaining the observed increase in notification numbers. However, the rise in EHEC cases is disproportionally high compared to the increase in test volume, resulting in a clearly increasing positivity for EHEC tests since 2007.
Hence, our study findings suggest that there is a real increase and epidemiological trend in EHEC infection incidence in Switzerland. The recently observed changes in the frequency of different serogroups and the stability of HUS cases suggests that the trend observed for EHEC is mostly attributable to rather mild cases.

Authors' contributions

CS and DM designed and conceived the study. Data collection and processing was performed by AS, with FF and CS. FF conducted the analysis. FF, AS, CS and DM interpreted the results. FF and AS wrote the first draft of the mansucript. All authors contributed to the revisions of the manuscript and approved the final version.

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9 Infectious disease surveillance: What can we conclude from analysing positivity rates of diagnostic testing?

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Working paper

9.1 Summary

Infectious disease surveillance systems are often based on reporting of laboratory-confirmed cases. Apart from changes in actual disease incidence, there are various factors which can influence the number of cases reported such as changes in diagnostic methods. Reporting the number of tests conducted and calculating the proportion of positive results is seen as a solution to overcome parts of these limitations associated with surveillance data.
Since 2016, laboratories in Switzerland are obliged to report annually the number of tests performed per month for selected notifiable diseases to the Federal Office of Public Health (FOPH). Results from preliminary analyses of these surveillance data are presented in this article with special emphasis on data usefulness and validity. Furthermore, the conclusiveness of positivity studies in general is discussed.
It is difficult to assess data validity of reports on testing frequency for several reasons: (i) multiple testing of the same patient during one disease episode is likely to occur but cannot be quantified, (ii) positivity rates heavily depend on individual laboratories' practices which are not known by the FOPH, and (iii) the "laboratory landscape" in Switzerland is highly complex and dynamic, making it difficult to compare reports from case-based reporting and from aggregated reporting of test and case numbers.
Calculation of positivity rates can complement surveillance data and help interpreting trends. However, it does still not allow to conclude on population incidence. The current way of collecting information on the frequency of testing in Switzerland requires individual data handling and follow-up with the diagnostic laboratories. Therefore, better ways of collecting valid information on testing frequency should be identified.

9.2 Introduction

Surveillance systems for infectious diseases mostly rely on reports from health professionals. In Switzerland, the Epidemics Act and its related ordinances define which observations are to be reported by physicians and by personnel of diagnostic laboratories [Das Eidgenössische Departement des Innern, 2015a; Der Schweizerische Bundesrat, 2015b; Die Bundesversammlung der Schweizerischen Eidgenossenschaft, 2012b]. It additionally defines the process and time limits for reporting and the information to be reported. Many observations are notifiable upon laboratory confirmation. Hence, the frequency of testing can heavily influence

the case numbers seen in the surveillance system, as noted by others as well [Gibney *et al.*, 2017; Janiec *et al.*, 2012; Kløvstad and Aavitsland, 2015; Lambert *et al.*, 2010; Van Cauteren *et al.*, 2015b]. Negative test results usually do not need to be reported. Making negative test results notifiable and calculating test positivity rates (the proportion of positive test results out of all tests performed) have been suggested to overcome this limitation [Janiec *et al.*, 2012; Kløvstad and Aavitsland, 2015; Lambert *et al.*, 2010]. However, this will still not allow concluding on population incidence as several factors have an influence on the number of tests conducted. The physicians' awareness for a disease, for example, can impact on testing frequency. Screening-like testing practices of physicians can strongly increase test frequency, especially if disease episodes can be mild or even asymptomatic (e.g. *Chlamydia trachomatis*; [Kløvstad and Aavitsland, 2015; Schmutz *et al.*, 2013]). On the side of the laboratory, changing practices of co-testing of different pathogens (e.g. routine parallel testing of enterohaemorrhagic *Escherichia coli* (EHEC) when *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. are requested) can result in changes in test numbers (chapters 7 and 8).

We previously conducted different studies looking at trends in positivity rates for selected notifiable diseases in Switzerland to better understand reporting trends observed in the National Notification System for Infectious Diseases (NNSID) (Bless *et al.* [2017]; Schmutz *et al.* [2013]; chapter 8). We found increasing positivity rates for EHEC between 2007 and 2016 (chapter 8), increasing positivity rates for *Campylobacter* spp. and decreasing positivity rates for *Salmonella* spp. between 2003 and 2012 [Bless *et al.*, 2017] and stable positivity rates for *Chlamydia trachomatis* in one canton of Switzerland (Basel-Stadt) between 2002 and 2010 [Schmutz *et al.*, 2013]. Currently, we are investigating positivity rates for *Legionella* spp. All aforementioned notifiable diseases showed increasing trends in the NNSID for the time period positivity was looked at, except for *Salmonella*.

With the implementation of the revised Epidemics Act in Switzerland in January 2016, information on the number of tests performed has to be reported annually for a number of notifiable diseases, additional to the individual case reports by diagnostic laboratories. These laboratory statistics have to be supplied for *Campylobacter*, carbapenemase-producing *Enterobacteriaceae*, *Chlamydia trachomatis*, *Francisella tularensis*, hepatitis C virus (HCV) (since January 2018), hepatitis E virus (HEV) (since January 2018), human immunodeficiency virus (HIV), *Legionella* spp., *Neisseria gonorrhoeae*, *Salmonella* spp. and Zika virus (since March 2016) [Das Eidgenössische Departement des Innern, 2015a].

Before 2016, the number of tests performed had only to be reported for HIV, influenza and *Legionella*.
The purpose of this article is twofold: first, a preliminary analysis of the data from the first two years of reporting of laboratory statistics (since the implementation of the new Epidemics Act) is conducted with special emphasis on the data's usefulness and validity. Second, the relevance and significance of positivity studies to interpret surveillance data in general is discussed. Hence, this chapter is a reflection on whether positivity rates and related denominator data are indeed the solution to overcome limitations with surveillance data for interpretation of trends.

9.3 Methods

Data on the "statistic of reports on laboratory findings" were sent by diagnostic laboratories in Switzerland to the Federal Office of Public Health (FOPH) according to Swiss law. Data were entered into an electronic database at the FOPH. Data from laboratory statistics on all notifiable diseases were extracted for the years 2016 and 2017. For most pathogens (all except *Francisella tularensis* and HIV), the number of tests, and thereof the number of positive results, stratified by diagnostic method and calendar month had to be reported. The official reporting form is available at `www.bag.admin.ch/infreporting` and in appendix D of this thesis.
Data analysis was exploratory, focussing on data quality and validity. Case-based notification data for 2016 and 2017 were extracted for certain diseases to compare case numbers from individual reports with the reported number of positive results from laboratory statistics.
For the present article, data on *Campylobacter* was analysed exemplary for others. Data from laboratory statistics ("statistic of reports on laboratory findings") were extracted as of 3rd August 2018; case-based notifications as of 21st June 2018.

9.4 Results and discussion

For the year 2016, 52 laboratories reported a total number of tests performed for *Campylobacter* spp. of 110'971; thereof, 9'119 with a positive result. For the year 2017, 54 laboratories reported test numbers stating that 105'348 tests for *Campylobacter* spp. were performed with a total of 8'868 positive results. These numbers correspond to an overall crude positivity rate of 8.2% and 8.4% in 2016 and 2017, respectively. Re-

Table 9.1: Number of positive tests for *Campylobacter* spp. according to individual "reports on laboratory findings" and according to "statistic of reports on laboratory findings" and total number of tests performed for *Campylobacter* spp. according to "statistic of reports on laboratory findings" as reported to the Federal Office of Public Health, 2016–2017, Switzerland

Year	Method	Number of positive tests		Number of tests	Positivity rate
		from case notifications	from laboratory statistics	from laboratory statistics	(in %)
2016	Detection of antigen	0	3	112	2.68
2016	Detection of antigen (IgG)	0	6	261	2.30
2016	Detection of antigen (IgM)	0	4	261	1.53
2016	Detection of nucleic acid	719	2'299	26'459	8.69
2016	Culture/isolation	8'902	6'807	83'878	8.12
2016	Unknown/not specified	18	0	0	
2016	**Total**	**9'639**	**9'119**	**110'971**	**8.22**
2017	Detection of antigen (IgG)	0	4	273	1.47
2017	Detection of antigen (IgM)	0	2	253	0.79
2017	Detection of nucleic acid	902	2'957	37'560	7.87
2017	Culture/isolation	8'211	5'905	67'262	8.78
2017	Microscopy	5	0	0	
2017	Unknown/not specified	47	0	0	
2017	**Total**	**9'165**	**8'868**	**105'348**	**8.42**

ported test numbers stratified by test method are summarised in table 9.1.

9.4.1 Multiple tests and reports per disease episode

As far as possible, the FOPH merges multiple reports (on clinical or laboratory findings) received for the same individual on one disease episode into one record for analysis and reporting of surveillance data. Furthermore, reports from individuals living abroad and from cases not fulfilling the case definition are excluded. This procedure of data cleaning was omitted in the present analysis given that laboratories are unlikely to follow the same procedure when reporting the summary statistics for the number of tests and the number of positive tests performed during one year. Hence, case numbers from individual case notifications as reported here must not be compared with case numbers reported in previously published analyses of surveillance data.

There are several reasons why multiple notifications are sent to the FOPH for one disease episode: (i) Multiple samples were sent to and have been tested by the laboratory. This can include multiple samples of the same type (e.g. 2–3 stool samples to increase sensitivity, recommended especially for parasites; or to control disease evolution [e.g. antibody response] or treatment outcome), and multiple samples of different specimen types (e.g. urine and sputum to test for *Legionella*); (ii) Multiple tests were conducted on one sample by the laboratory (either requested by the physician or based on the laboratories' routine procedures), for example to confirm a positive result (e.g. stool culture after positive result from polymerase chain reaction (PCR)) or to obtain additional information (e.g. antibiotic resistance profile; serotyping); (iii) Additional information (related to the test and/or the patient) became available to the laboratory which was forwarded to the FOPH. The two first-mentioned reasons for multiple notifications could also be reflected in laboratory statistics. However, how multiple tests for the same disease episode are reported by the diagnostic laboratories, hence, how they are reflected in test and case numbers, is unknown to the FOPH (except if spontaneously noted under "remarks" on the notification form) and is likely heterogeneous. Therefore, comparison of case numbers from individual notifications (report on clinical findings and/or laboratory findings) and reports on laboratory statistics (report on "statistic of reports on laboratory findings") is hampered and must be interpreted with caution.

Similarly, laboratory practices of confirmatory testing (e.g. confirming

every *Campylobacter*-positive result from multiplex PCR testing using culture-based methods) can have a large impact on test numbers and on the number of positive findings depending on how this is reported by laboratories – both, in individual case notifications and in reports on laboratory statistics. For example, some laboratories may report the individual case only after culture-confirmation while others are reporting PCR-positive findings already (potentially sending a second report after culture-confirmation). Remarks provided on laboratory statistics reporting forms indicate that some laboratories counted tests from culture-confirmation after PCR-testing twice (in test numbers for both diagnostic methods) while others counted them only once (often unclear in which category).
These laboratory practices of confirmatory testing (also referred to as "reflex testing"), together with the different handling of such multiple tests for one disease episode by the FOPH and the laboratories may explain that substantially more positive tests using culture-based methods were reported according to individual case notifications compared to laboratory statistics while the contrary is the case for detection of nucleic acid (i.e. PCR) (Table 9.1).

9.4.2 Data validity and positivity rates

One option to evaluate validity of the data reported on "statistic of reports on laboratory findings" reporting forms is to compare the number of positive tests with the number of positive tests reported according to case-based notifications. This option and its associated challenges were already discussed above. Another way to look at data validity is to calculate positivity rates, defined as the proportion of positive tests out of all tests performed. While positivity rates are likely to differ between diagnostic methods applied, they are expected to be similar across laboratories. Furthermore, variability of positivity rates should decline with increasing test numbers for statistical reasons. Hence, when plotting positivity rates by test numbers, observations should show the pattern of a funnel. Figure 9.1 shows the positivity rates for *Campylobacter* by laboratory, test method and year. Observations from PCR-diagnostics ("detection of nucleic acid") and culture-based methods follow the expected funnel pattern. Interestingly, however, some observations from culture-based methods form a second "cloud", characterised by low test numbers and high positivity rates. It seems likely that these observations represent laboratories applying culture-based methods only for confirmation of PCR-positive results given the diagnostic procedures re-

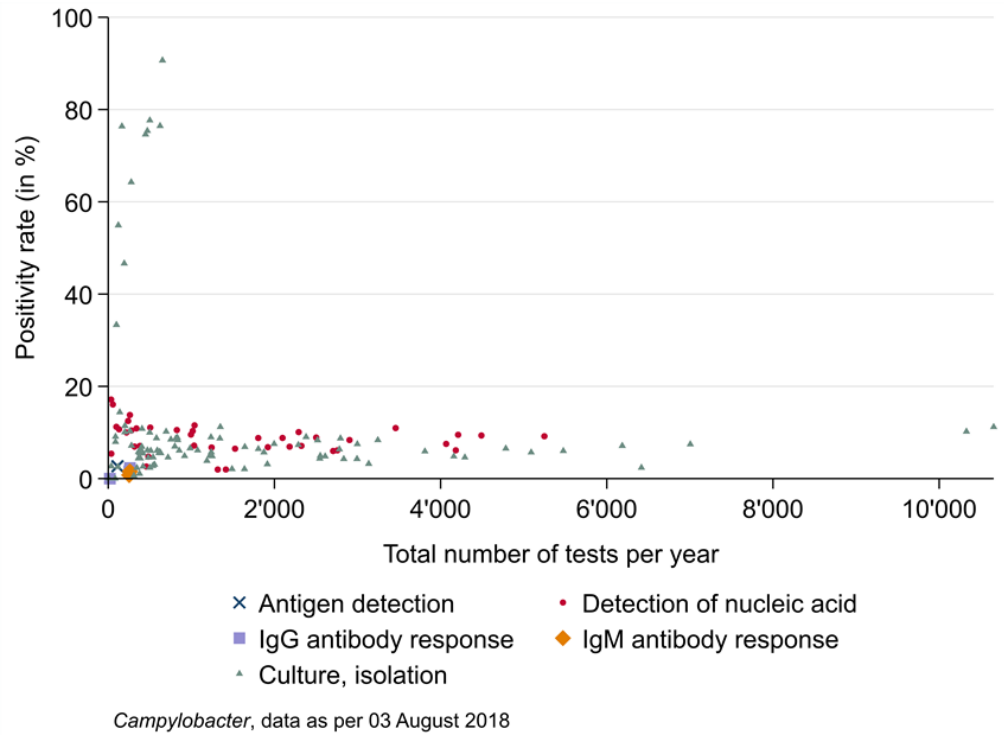

Figure 9.1: Positivity rate and total number of tests per year by test method for *Campylobacter* spp., according to reports on laboratory statistics, 2016–2017, Switzerland

ported by laboratory experts (chapter 7) and what was discussed above on confirmatory "reflex" testing. This would explain the low test numbers combined with high positivity rates.
It is possible that a laboratory conducts only one culture-based test in a given month. In this case, the positivity rate will either be 0 or 100%. If a laboratory reports that 7 out of 7 culture-based tests were positive in a given month, this seems already less likely (but still possible). However, it could be suspected that the number of negative tests instead of the number of positive tests is reported together with the total number of tests. Hence, very high positivity rates could also point at erroneous data. On the other hand, both, very high and very low positivity rates are reasonable given common testing procedures (high: confirmatory testing; low: screening) and hence, plausibility (internal validity) of values reported on laboratory statistics forms can hardly be assessed. One laboratory ("lab B") reported having performed 30 culture-based tests in May 2017, thereof 29 with a positive result (Table 9.2). These numbers seem unlikely if regarded separately. However, 25 "reports on laboratory findings" from a culture-based test were received from the same laboratory in this month. Hence, the 29 positive test results reported as summary statistic are plausible again and suggest that this laboratory applies culture-based methods for confirmation of positive test results obtained through another diagnostic method (likely PCR). Yet, lab B reported only one test for detection of nucleic acid (and 20 tests each for detection of IgG and IgM antibodies) in the same month.
However, the 7 out of 7 positive results reported by "lab A" in August 2016 are indeed explained by confirmatory testing, as indicated by a remark on the notification form: Lab A indicated performing PCR since May 2016 and applying culture-based methods for "screening/control". Furthermore, this laboratory reported having conducted 162 tests for detection of nucleic acid (e.g. PCR) in August 2016 of which 14 were positive.
In summary, it seems impossible to evaluate internal validity of the data reported on "statistic of reports on laboratory findings" notification forms in the absence of detailed information from the laboratory on diagnostic procedures.

9.4.3 Swiss "laboratory landscape": Complex and dynamic

There are laboratories operating on a national level in Switzerland with different branches throughout the country. For some companies, those

Table 9.2: Selected records of "statistic of reports on laboratory findings" on *Campylobacter* spp. to illustrate difficulty in evaluating plausibility of data comparing the number of positive results with the total number of tests reported from laboratory statistics and with the number of cases reported by the corresponding laboratory in the framework of individual case reporting, 2016–2017, Switzerland

Year	Month	Laboratory	Method	Number of positive tests	Number of total tests	Positivity (in %)	Number of reports on laboratory findings
2016	June	lab A	Detection of nucleic acid	12	172	7.0	0
2016	June	lab A	Culture/isolation	1	1	100	12
2016	July	lab A	Detection of nucleic acid	12	142	8.5	0
2016	July	lab A	Culture/isolation	3	3	100	14
2016	August	lab A	Detection of nucleic acid	14	162	8.6	2
2016	August	lab A	Culture/isolation	7	7	100	10
2017	April	lab B	Detection of nucleic acid	0	3	0	0
2017	April	lab B	Culture/isolation	19	21	90.5	19
2017	April	lab B	IgG antibody response	0	26	0	0
2017	April	lab B	IgM antibody response	0	26	0	0
2017	May	lab B	Detection of nucleic acid	1	1	100	0
2017	May	lab B	Culture/isolation	29	30	96.7	25
2017	May	lab B	IgG antibody response	0	20	0	0
2017	May	lab B	IgM antibody response	0	20	0	0
2017	June	lab B	Detection of nucleic acid	0	3	0	0
2017	June	lab B	Culture/isolation	52	55	94.5	43
2017	June	lab B	IgG antibody response	1	28	3.6	0
2017	June	lab B	IgM antibody response	0	28	0	0

sites are autonomous and can almost be seen as separate enterprises while other companies have central headquarters. Furthermore, there are (mostly regionally operating) independent laboratories which form a corporate group. Reporting can be organised at the local sites or managed by headquarters. It is difficult to merge individual case reports (from "reports on laboratory findings", reported on a daily basis) with summary statistics (from reports on "statistic of reports on laboratory findings", reported annually) given this heterogeneity and frequent changes in the "laboratory landscape" of Switzerland with rearrangements of such groups, company mergers, and discontinuation and start-up of businesses.
For example, labs "C" and "D" belong to "lab group 1". In 2016, no individual-based "reports on laboratory findings" from "lab D" are registered in the NNSID except for two cases in December while from "lab C" only individual-based reports are available but no report on "statistic of reports on laboratory findings"(Table 9.3). From March 2017 onwards, no reports at all from "lab C" were received. Instead, "lab D" reported individual-based laboratory findings but no laboratory statistics. Both, labs C and D are based in the canton of Ticino. It seems possible that lab C discontinued its business or rather joined "lab group 1", changed its name and moved to another place. However, this is purely speculative.
In conclusion, thorough understanding of the structure and operating procedures of the diagnostic laboratories in Switzerland is needed in order to correctly enter and merge notification data.

9.4.4 Comparable positivity rates from other studies

A previously conducted positivity study in Switzerland reported (age- and sex-standardised) positivity rates for *Campylobacter* increasing from 7.6% in 2003 to 11.1% in 2012 [Bless *et al.*, 2017]. This study collected test-based data from selected diagnostic laboratories directly. The findings from the current study suggest that the positivity rate decreased again. It has to be noted, however, that Bless *et al.* [2017] reported slightly lower rates for crude data compared to age- and sex-adjusted rates. Additionally, Bless *et al.* [2017] analysed data from a sample of five diagnostic laboratories which were selected based on the number of notifications received by the FOPH. This sampling procedure could have favoured laboratories with high positivity rates. Our preliminary analysis of summary statistics included data from all laboratories in Switzerland complying with their obligation to report. Furthermore, multiplex PCR

Table 9.3: Selected records of "statistic of reports on laboratory findings" on *Campylobacter* spp. to illustrate difficulty in merging records with case-based "reports on laboratory findings" by laboratory, 2016–2017, Switzerland

Year	Month	Laboratory group	Laboratory	Method	Number of positive tests	Number of total tests	Number of reports on laboratory findings
2016	October	lab group 1	lab C	Culture/isolation			8
2016	October	lab group 1	lab D	Detection of nucleic acid	0	41	
2016	October	lab group 1	lab D	Culture/isolation	8	85	
2016	November	lab group 1	lab C	Culture/isolation			10
2016	November	lab group 1	lab D	Detection of nucleic acid	1	39	
2016	November	lab group 1	lab D	Culture/isolation	8	63	
2016	December	lab group 1	lab C	Detection of nucleic acid			1
2016	December	lab group 1	lab C	Culture/isolation			4
2016	December	lab group 1	lab D	Detection of nucleic acid	2	44	
2016	December	lab group 1	lab D	Culture/isolation	3	151	2
2017	January	lab group 1	lab C	Culture/isolation			4
2017	January	lab group 1	lab D	Culture/isolation			1
2017	February	lab group 1	lab C	Culture/isolation			3
2017	February	lab group 1	lab D	Culture/isolation			3
2017	March	lab group 1	lab D	Culture/isolation			2
2017	April	lab group 1	lab D	Detection of nucleic acid			1
2017	April	lab group 1	lab D	Culture/isolation			5
2017	April	lab group 1	lab D	Unknown/not specified			1

Note: There were other laboratories belonging to lab group 1 reporting *Campylobacter*.

panels for routine testing of stool samples for gastrointestinal pathogens were introduced in several diagnostic laboratories in Switzerland between 2012 and 2016 and are likely to affect positivity rates (chapters 7 and 8).

A study conducted in Wales, United Kingdom (UK), reported a declining trend in the proportion of positive stool samples for *Campylobacter* from 8.9% in 1998 to 7.5% in 2008 for samples obtained by general practitioners [Janiec *et al.*, 2012]. At the same time, the stool sampling rates have increased by 40%. The Welsh positivity rates are within the same range as those found in Switzerland. The advantage of the Welsh system is that they profit from a national database which is fed by all diagnostic laboratories. Janiec *et al.* [2012] stated that "all laboratories in Wales follow a standard operating procedure for investigation of stool samples for bacterial pathogens" and that "there was no change in testing procedures throughout the study period". This is in strong contrast to the Swiss situation where the majority of diagnostic laboratories are private businesses and act independently.

In Norway, mandatory case-based surveillance data for *Chlamydia trachomatis* are supplemented by voluntary reporting of aggregated testing numbers stratified by age group and sex by diagnostic laboratories [Kløvstad and Aavitsland, 2015]. In contrast to Switzerland, Norwegian laboratories are requested to report "cases" rather than "laboratory tests". Chlamydia cases are defined as "a person with one or more positive laboratory tests for *Chlamydia trachomatis* in a urinary sample or a sample from anus, cervix, urethra, or vagina within a period of 60 days" [Kløvstad and Aavitsland, 2015]. Hence, the Norwegian system tries to overcome the problem of repeated testing in the same individual at the reporting level rather than at the level of analysis. Collecting testing numbers stratified by age group and sex allows identifying which population group is tested most frequently (e.g. to adapt campaigns promoting testing) and which population group yields the highest positivity rate, either due to most targeted testing or due to highest incidence.

Lambert *et al.* [2010] proposed to introduce mandatory reporting of laboratory tests with a negative result for influenza complementing reports on positive laboratory findings which are notifiable since 2001 in Australia. They suggest collecting the same information for positive and negative findings, thus, reporting of case-based data. Acknowledging that also positivity rates may be biased, e.g. due to co-testing of specimens for other pathogens, Lambert *et al.* [2010] argue that calculating the proportion of positive test results would still allow a better assessment of spatial and temporal trends in surveillance data.

9.4.5 Positivity rates do not suffice

Even though denominator data such as test numbers are factors to be considered when interpreting surveillance data, they are not a general solution to overcome limitations associated with case reports of laboratory-confirmed infections: it is still impossible to infer population incidence from case notifications if testing frequency is the only additional information obtained. There are too many factors which affect trends in test numbers upwards or downwards – exemplified in the following for an upward trend: (a) a "true" change in disease incidence, leading to more people falling ill, seeking help and being tested, (b) a change in disease severity (due to a change in pathogenicity or in human susceptibility), leading to more people seeking help and/or more people being tested, (c) a change in patients' help seeking behaviour, leading to more consultations and more people being tested, (d) a change in physicians' "criteria for testing" (e.g. based on symptoms or based on presence of selected risk factors) leading to a higher proportion of individuals being tested among those consulting a physician, (e) a change in the prevalence of risk factors "qualifying" for testing, (f) a change in laboratory diagnostics, e.g. from single pathogen testing to using a panel, hence samples are also tested for this pathogen if another pathogen included in this panel was requested by the physician, and (g) a change in one of the above-mentioned factors for a pathogen which is usually tested in parallel (e.g. with similar signs and symptoms and/or reasons for testing).
It is unlikely that only one of the above-mentioned factors changes considerably while all others remain constant, and there are about the same number of reasons explaining a change in positive test results. Consequently, trends in positivity rates can arise from a number of combinations of changes in testing frequency and case numbers and hence, an upward, downward or stable trend in positivity cannot be stringently assigned to an upward, downward or stable trend in disease incidence. Still, certain combinations of increasing and decreasing test numbers and positive results are more likely to result from an increase (or decrease) in disease incidence than others. For example, if both, the number of tests and the positivity rate increase (i.e. the number of positive results increases more strongly than the number of tests performed), it is very unlikely that the disease frequency in the population actually decreases. This situation was found for EHEC in Switzerland (chapter 8). Hence, looking at test numbers and positivity rates does provide additional information and can help interpreting trends in surveillance data.
Another important aspect to be considered for interpretation of posit-

ivity rates is the pathogen and its characteristic: for instance, an increase in test numbers for *Chlamydia trachomatis* is much more likely to result from a change in testing behaviour (e.g. screening additional risk groups) than an increase in test numbers for *Neisseria meningitidis*. For the latter, a change in the number of patients presenting with the respective symptoms seems more likely considering severity of invasive meningococcal disease.

9.5 Conclusions: Pros and cons of collecting information on test numbers

An analysis of test and case numbers in parallel (hence, positivity rates) can neither confirm nor disprove what is seen in the surveillance system of positive case notifications. However, both measures can either lead to the same or to different conclusions. It is reassuring that trends are interpreted correctly if conclusions drawn from looking at positivity rates are the same as those drawn from looking at notification data of laboratory-confirmed cases alone.
However, collecting information on test numbers is not straightforward. The first two years of reporting "laboratory statistics" (reporting of test numbers and positive results thereof, reported annually as aggregated numbers) have demonstrated that validity of data cannot be assessed easily and that follow-ups with laboratories for collecting a lot of additional information would be required to understand and clean the data. In summary, assessing test numbers (either as aggregated numbers or case-based) in a notification system can help to identify (major) changes in testing frequency. Researching reasons for observed changes can then be initiated in a timely fashion. However, further research is required to identify appropriate ways of collecting such information on test numbers on a routine basis given the highly dynamic sector of diagnostic laboratories and the heterogeneity in laboratory practices observed in Switzerland. It is questionable if the collection of denominator data in its current form is worth the effort of data acquisition and analysis.

Part III

ACUTE GASTROENTERITIS: PHYSICIANS' CASE MANAGEMENT AND PATIENTS' HEALTH SEEKING AND ITS INFLUENCE ON SURVEILLANCE DATA

10 General practitioners' viewpoint on acute gastroenteritis, campylobacteriosis and Swiss primary care

The first section of this chapter (section 10.1) provides a summary (incl. excerpts) of the published article "Acute gastroenteritis and campylobacteriosis in Swiss primary care: the viewpoint of general practitioners" [Bless *et al.*, 2016]. The article discusses how general practitioners (GPs) in Switzerland perceive and manage patients consulting with acute gastroenteritis (AG)* and campylobacteriosis. Understanding this case management is an important step in reconstructing the burden of illness pyramid. Further results that were obtained during the interviews with those GPs are presented in the second section (section 10.2). Those findings concern the GPs' perception of their role in the Swiss health system, their perception of the FOPH, the surveillance system, and the Swiss health system in general.

10.1 Summary of "Acute Gastroenteritis and campylobacteriosis in Swiss primary care: the viewpoint of general practitioners"

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RESEARCH ARTICLE

Acute Gastroenteritis and Campylobacteriosis in Swiss Primary Care: The Viewpoint of General Practitioners

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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.

Introduction

Infectious acute gastroenteritis (AG)* is caused by a wide range of gastrointestinal pathogens. Public health is concerned particularly with food- and waterborne pathogens which can cause disease outbreaks. In the Swiss National Notification System for Infectious Diseases (NNSID) a range of food- and waterborne pathogens are monitored. Notifications of campylobacteriosis – the most frequently reported foodborne pathogen in Switzerland – increased, reaching almost 8'500 cases in 2012. Increasing trends of *Campylobacter* have also been observed in the European Union (EU).

Information in the NNSID about cases of notifiable AG is restricted to laboratory-confirmed cases and information from diagnostic laboratories for many foodborne pathogens. There is insufficient information available on the burden of disease and the clinical presentation of infectious AG at primary care and at population level.

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 patients' 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.

Materials and methods

Face-to-face interviews were conducted based on a semi-structured questionnaire. The first part of the questionnaire covered GPs' perception of AG and campylobacteriosis including the perceived magnitude of the burden, the public health relevance, clinical presentation, and perceived patients' health care seeking behaviour, risk behaviours and risk groups. The second part of the questionnaire targeted case management focussing on diagnostic practices and treatment approaches and reasons for related decisions. The questionnaire was re-structured and adapted based on one key informant interview and five test interviews (four in German, one in French).

Interviews were conducted by three female social scientists and one male epidemiologist who were trained by a senior medical anthropologist in qualitative interviewing techniques. One-hundred-forty-six German-speaking and 29 French-speaking GPs who had managed campylobacteriosis patients in a previous case-control study and six purposely recruited French-speaking GPs were invited for study participation with an information letter sent by postal mail. During a follow-up contact

by telephone, GPs were asked for verbal informed consent. Interviews were conducted with consenting GPs usually in his or her own practice, lasted for 20–40 minutes and were tape recorded.
Interviews were transcribed immediately after conduct and analysed while data collection was ongoing. The question guide was refined and emerging themes were included in subsequent interviews. Codes for data analysis were continuously developed and assigned to GPs' narratives by a senior medical anthropologist using Weft-QDA software. Data analysis followed the principles of inductive content analysis as required by Grounded Theory.
The study was part of a project mandated by the Swiss Government studying the epidemic increase of human campylobacteriosis and was performed under the Swiss Epidemics Act. Therefore, no ethical approval was sought. The interviews focused solely on GPs' professional views, not on any personal aspects or data of individual patients. Participants did not receive any financial compensation for their participation.

Results

In total, 51 German-speaking and 18 French-speaking GPs participated in the study. Their median professional experience was 23 years (range: 3–39 years). GPs considered AG to be of little relevance both, for the patient and for public health in Switzerland. They stated that AG is important in travel medicine but uncommon in daily practice. GPs stated that campylobacteriosis patients occur in waves throughout the year, with peaks during summer linked to barbecuing and in winter linked to the consumption of meat fondue. GPs acknowledged that campylobacteriosis can be painful and disturbing even though it is a self-limiting and easy-to-treat disease. The type of work and social factors influence the duration of absence from work even though the patient's general condition is the main criterion. Sick leave lasts usually for several days to more than one week.
Perceived disease severity, past experiences, health insurance and the need for a medical certificate influence whether the physician is consulted immediately (within hours) or after some time (days) after onset of symptoms of AG. Telephone consultations with the practice nurse and/or the physician are common. Depending on the GP's preference, the patient is either advised to schedule a follow-up consultation by phone or at the practice, or to call again in case the symptoms do not improve.
The first consultation of a patient with AG usually includes anamnesis, clinical examination and point-of-care diagnostics (e.g. C-reactive pro-

tein (CRP) level). Diagnostics based on faecal specimens depend on a number of factors such as the patients' symptoms, general condition, disease duration, inflammatory signs, and exposure history. It includes mainly stool cultures for *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp.
Symptomatic treatment with anti-motility drugs, oral (for simple cases) or intravenous (for severe cases) rehydration is very common. Antibiotic therapy is considered useful, but prescribed cautiously as AG is usually self-limiting and GPs are aware of the occurrence of antibiotic resistance. Reasons favouring antibiotic therapy are comparable to those for stool diagnostics. Additionally, stool diagnostic results can influence antibiotic therapy.
Four distinct approaches to case management were apparent: "wait & see" including recommendations for diet, rehydration and symptomatic treatment, is mostly applied when the episode is recent and mild. "Treat & see" is based on the pragmatic reasoning that for antibiotic therapy ("treat"), there is no need to know the exact cause – if there is evidence for bacterial infection (e.g. elevated CRP). The third approach starts with obtaining a stool specimen ("test") but initiating empirical antibiotic therapy before knowing the test result. This "treat & test" strategy allows adapting treatment once diagnostic results are available. Finally, by applying "test & see", physicians try to avoid unnecessary antibiotic treatment. Antibiotics are only prescribed if bacterial pathogens are identified and symptoms persist. Most physicians appeared to follow various approaches depending on the respective situation. Hospitalisation and referral to specialists are rather uncommon.

Discussion

GPs perceptions of the epidemiology of campylobacteriosis in terms of seasonality (summer and winter peak), trends over the last 20 years (increasing trend; nowadays more frequent than salmonellosis) and age of patients affected (all age groups, but disproportionately frequent among young adults) is in line with what is seen in the NNSID. GPs are aware that their case management, apart from the patients' healthcare seeking behaviour, leads to underestimation of campylobacteriosis in the NNSID. The wide range of physicians' self-estimated frequency of requesting stool samples is also observed among GPs within and between other countries. Financial factors (e.g. costs for diagnostics and health insurance deductible) and the duration until results are available also affect the decision to perform stool diagnostics apart from factors consistent with published

literature on the clinical management of AG. Considering the lack of curative treatment for viral causes of AG, physicians make use of CRP levels to distinguish bacterial from viral AG. An increased CRP level favours bacterial AG and hence, the likelihood that the physician decides to perform stool diagnostics. Patients with travel history and severely affected patients are likely over-represented in the NNSID considering GPs' diagnostic behaviour.
Swiss GPs mainly follow the "wait & see" approach for patients consulting with AG. Due to the perceived long duration until culture-based stool diagnostic results are available, GPs favour "treat & see" and "treat & test" over "test & see". Ciprofloxacin (a fluoroquinolone) is frequently used for empirical antibiotic treatment of AG even though around 50% of *Campylobacter* spp. show resistance to fluoroquinolones.

Conclusions

Triage steps, reasons for and frequency of stool diagnostics need to be considered when interpreting NNSID data. Cases reported to the NNSID are more likely to be severe or to have travelled abroad compared to under-ascertained cases. Current developments in laboratory methods from culture-based stool diagnostics to multiplex polymerase chain reaction (PCR) panels could change physicians' case management approaches and hence, the proportion and selection of cases seen in the NNSID. Knowledge of physicians' case management and laboratory practices is, therefore, important for public health authorities to accurately interpret NNSID data.

10.2 Additional analysis & results: The general practitioners' role in the Swiss health system

10.2.1 GPs' knowledge on campylobacteriosis

GPs were not systematically asked about their knowledge on *Campylobacter* spp. and campylobacteriosis. However, several statements during the interviews pointed at their perception of incubation period, risk factors and clinical manifestation of the disease (the latter has already been discussed in the published article; section 10.1 and Bless *et al.* [2016]). While many facts mentioned were in agreement with published

literature, some statements pointed at uncommon, if not wrong, perceptions of incubation period or risk exposures, or lack of knowledge.
The incubation period for *Campylobacter* is said to be 2–5 days, sometimes 1–10 days [Mahon and Patrick, 2015]. But:

"[Vermutete Fälle von Campylobacteriose] Der anamnestische Hinweis ist da der plötzliche Ausbruch. Ungefähr 12 Stunden nach einer Mahlzeit. Das ist verdächtig. Vor allem, wenn auch andere die gleichen Symptome aufweisen." (MZ11)	*"[For suspected campylobacteriosis] the anamnestic indicator is the sudden onset. Approximately 12 hours after a meal. This is suspicious. Especially, if also others show the same symptoms."*

The most common risk factors for campylobacteriosis are: international travel, consumption of undercooked chicken, environmental exposure and direct contact with farm animals [Kaakoush *et al.*, 2015]. In terms of contaminated food, poultry products (mostly chicken, but also turkey and duck), unpasteurized milk, and water are common. Also other meat – beef, veal and pork – can harbour *Campylobacter*. Even though chicken are frequently infected with *Campylobacter*, eggs are generally not considered a risk factor for human infection [Fonseca *et al.*, 2014; Kaakoush *et al.*, 2015]. Apart from raw milk, other milk products were not found to be contaminated with *Campylobacter* [Modi *et al.*, 2015].

"Bei Campylobacter ist es natürlich klassisch, dass es über Nahrungsmittel aufgenommen wird. Also der klassische Weg ist über Eier, die befallen sind. Tiramisù zum Beispiel. Oder Pouletfleisch." (MZ04)	*"For Campylobacter it is the classic that it is transmitted through food. So, the typical way is through eggs which are contaminated. Tiramisù as an example. Or chicken meat."*
"Campylobacter ist oft im Poulet, also... Hühnerfleisch und auch Eier sind häufig kontaminiert... Das wissen die Leute häufig nicht." (PH04)	*"Campylobacter is often found in poultry, so... chicken meat and also eggs are contaminated frequently... This is often not known by people."*
[Über Nahrungsanamnese] *"Häufig beim Campylobacter ist Poulet... das Poulet, Glace auch*	[Talking about food anamnesis] *"Often with Campylobacter is chicken... the chicken, ice cream*

noch relativ viel, und Softeis. . . " (PH21)

quite frequently too, and soft ice cream. . . "

Interviewer : *"Et quels sont les facteurs de risque pour une infection au campylobacter ? Est-ce qu'il y a quelque chose en commun chez ces patients qui expliquerait. . . ?"*

Physician : *"J'arrive pas à dire. Comme on en voit tellement peu. Je sais pas."* (SFY09)

Interviewer: *"And what are risk factors for campylobacteriosis? Is there anything common among these patients which would explain this. . . ?"*

Physician: *"I cannot tell. Since you see this so infrequently. I don't know."*

Interviewer : *"Et dans leur* [*patients avec Campylobacter*] *alimentation, vous remarquez quelque chose qui pourrait provoquer l'infection ?"*

Physician : *"Non. C'est vrai qu'on leur demande toujours aussi s'ils ont mangé quelque chose de particulier qui leur paraissait pas frais, mais on ne trouve pas toujours."*

Interviewer : *"Une hypothèse c'est que ça vienne de la viande de poulet mal cuite."*

Physician : *"Le campylobacter ? Moi j'avais la notion pour les salmonelles mais pas pour le campylobacter, pour le poulet pas cuit. . . "* (SFY12)

Interviewer: *"And concerning their* [*campylobacteriosis patients*] *nutrition, do you notice something which could cause the infection?"*

Physician: *"No. It is true that one always asks if they ate something special which did not appear fresh, but this exposure is not always established."*

Interviewer: *"One hypothesis is that it is from undercooked chicken meat."*

Physician: *"Campylobacter? I personally knew this for Salmonella but not for Campylobacter, the chicken not cooked. . . "*

Interviewer : *"Et les risque. . . ma question c'était plutôt, d'où vient ce Campylobacter, est-ce qu'il y a un comportement. . . ?"*

Physician : *"Oui, alors. C'est vraiment l'ignorance totale, d'où viennent ces bactéries. Est-ce que les gens consomment beaucoup*

Interviewer: *"And the risks. . . my question was rather related to the source of Campylobacter, is there a behaviour. . . ?"*

Physician: *"Well, yes. It is really total ignorance from where these bacteria originate. Do people consume a lot of uncooked*

de légumes pas cuits, donc des salades, qu'ils ne les lavent pas, qu'ils ne... qu'ils ne lavent pas leurs fruits avant de les manger. Parfois on a même pas le temps de faire une immense enquête." (SFY07)

vegetables, like salads, which they don't wash, that they... that they don't wash their fruit before eating. Sometimes, one simply does not have the time to make a huge enquiry."

Campylobacter is not considered to strongly proliferate in foods [Burgess *et al.*, 2016].

"Man könnte mit einfachen Hygienemassnahmen, wie [zum Beispiel] das Fleisch nicht lange herumliegen zu lassen, Campylobacter deutlich reduzieren." (MZ24)

"With very simple hygiene interventions Campylobacter could be reduced, [for example] if it was not lying around for a long time."

10.2.2 GPs' perspective on stool testing

Physicians usually order "packages" and follow laboratory recommendations of the laboratory they work with. GPs focus on the patient when deciding for or against conducting stool diagnostics as expressed by one respondent:

"Sagen wir, wir machen die Stuhlprobe und haben jetzt den Erreger und es heilt ohnehin in fünf, sechs, sieben Tagen spontan aus. Was bringt uns das? Ausser, dass man jetzt vielleicht wichtige epidemiologische Daten gesammelt hat. Aber für den Patienten bringt das alles letztlich nicht viel. Zu wissen, welcher Erreger im Stuhl ist oder welchen man in Ägypten aufgeschnappt hat, bringt dem Patienten ja relativ wenig." (MZ18)

"Let's say we do a stool culture and we identify the pathogen and the illness recedes in five, six, seven days spontaneously anyway. What does this help? Except that maybe we collected important epidemiological data. But this doesn't help the patient much ultimately. It is of little advantage to the patient to know which pathogen is in the stool or which [pathogen] he caught in Egypt."

The GPs' approach seems pragmatic and based on experience:

Interviewer: *"Welche Rolle spielt die Erfahrung? Wenn ein Patient in Ihr Behandlungszimmer kommt, können Sie da schon auf den ersten Blick etwas über ihn sagen? Ich meine diesen berühmten medizinischen Blick, ob jemand krank ist oder nicht."*

Arzt: "*Ja. Das sieht man schon gut. Also, die Unterscheidung, ob jemand einen infektiösen Durchfall oder eher einen Reizdarm hat sieht man schon eher. Aber man muss gewisse Sachen einfach ausschliessen. Man muss sicher nicht bei jedem eine Stuhlbakteriologie machen."* (MZ21)

Interviewer: *"What role does experience play? When a patient comes to the practice, can you already pre-assess him or her? I refer to this famous medical vision [visual and/or general impression and feeling] whether or not someone is ill."*

Physician: *"Yes, you can notice this quite well, so the differentiation whether somebody has infectious diarrhoea or rather an irritable colon. This you can see quite well. But one must exclude certain conditions. One does certainly not need to do stool bacteriology with every diarrhoea case."*

Factors related to the patients' expectations and the physician's assurance can also influence decisions on stool testing, apart from medical signs and symptoms, patients' general condition, risk exposure, risk of transmission, and assuring accurate treatment:

Arzt: *"In der heutigen Zeit... die Leute erwarten dies bis zu einem gewissen Grad, dass man objektiv mit Laboruntersuchungen dokumentiert, oder?"*

Interviewer: *"Und nicht nur aufgrund der Untersuchung und Ihrer Erfahrung... "*

Arzt: *"Richtig."* (PH08)

Physician: *"Nowadays people expect it to a certain degree that one documents it objectively with laboratory investigations."*

Interviewer: *"And not only based on the examination and your experience."*

Physician: *"Exactly."*

"[...] pour avoir quand même une certitude de ce que je fais, vous voyez ? Après, si ça tourne mal, on me dira vous n'avez fait aucune analyse." (SFY07)

"[...] for still having certainty of what I do, you see. After all, if it turns worse, one will say you did not even perform an analysis."

Furthermore, also costs can play a role even though many physicians

stated that their decisions are not influenced by economic considerations.

Interviewer: *"Oder gibt es auch ökonomische Faktoren, welche die Testentscheidung beeinflussen?"*

Arzt: *"Also die Ökonomie spielt in diesem Sinne eine Rolle, indem man sagt, eine banale Durchfallerkrankung erfordert keine spezielle Diagnostik. Es wird symptomatisch behandelt und sollte innerhalb von 3 bis 4 Tagen wieder vorbei sein, selbstlimitierende Erkrankung, Selbstreinigung des Körpers."*

[...]

Interviewer: *"Spielt auch die Krankenkasse eine Rolle? Des Patienten?"*

Arzt: *"In diesem Falle jetzt nicht. Da habe ich mir jetzt wirklich noch nie Gedanken darüber gemacht und gedacht: 'Halt, Moment, bei dieser Krankenkasse kann ich jetzt keine Diagnostik betreiben.' Sondern da geht es effektiv nach der Klinik."* (PH02)

Interviewer: *"Or are there economic factors as well which influence the decision to do a test?"*

Physician: *"Well, the economy plays a role in a sense that one says that banal diarrhoea does not require specific diagnosis. It is treated symptomatically and should be over within 3 to 4 days, self-limiting disease, self-purification of the body."*

[...]

Interviewer: *"Do considerations regarding the patient's health insurance play a role, too?"*

In this case not. I really have never thought about this and thought: 'Wait, one moment, with this insurance I cannot do a diagnostic test.' What really counts is the clinic [*clinical symptoms*]*."*

"Pour la raison pour laquelle je fais peu de cultures, c'est pour les coûts. Ça coûte très cher une culture de selles. Quand on a un patient qui a une franchise élevée – non, disons, alors, s'il y une franchise basse c'est pas juste pour l'assurance – mais pour un patient si une diarrhée par téléphone ça lui fait 20 francs, une diarrhée au cabinet avec une culture de selles on est pratique-

"For the reason why I do only few cultures, it's because of the costs. Stool culture is very expensive. If a patient with a high deductible – no, let's put it this way, when it is a low deductible it is not just for the insurance – but for a patient if a diarrhoea [*is managed*] *by telephone it costs him 20 francs, for a diarrhoea in the practice with stool culture costs reach basically 200 francs! I*

ment à 200 francs ! Je trouve que ça représente des coûts énormes pour le patient et le système de santé. Et si dans les deux cas il va mieux en 3 jours, je trouve que ça n'a pas de sens de faire des grosses dépenses de santé." (SF17)

think that this represents enormous costs for the patient and for the health system. And if in both cases he [the patient] is better after 3 days, I think it makes no sense to spend a lot of money on health."

Finally, also the (long) duration until results are available is likely to influence testing behaviour, although few physicians explicitly mentioned that it prevents them from testing:

"Und wir machen Stuhlkulturen eher sparsam. Stuhlkulturen bringen uns überhaupt nichts. Bis wir das Resultat haben ist der Patient entweder wieder gesund oder... man kann ja nicht warten mit den Antibiotika, bis man endlich das Resultat hat [...]" (PH12)

"We do stool cultures rather sparingly. Stool cultures do not come with any benefit: until we have the result the patient is either healthy again or... one cannot wait to give antibiotics until one finally has the result [...]"

10.2.3 The GPs' perception of their role

Swiss GPs emphasise that their approach is patient-centred or even situation-centred and they deal with "the patient in his or her individual context". They also highlight the long-term relationship which is based on mutual confidence and trust. This confidence is considered essential and represents a key motivation and appreciation for working in primary health care as opposed to working in a hospital.
In line with their patient-centred approach, GPs' decisions for or against stool testing largely depend on the expected impact of the results on subsequent case management. Considerations on public health stay in the background:

"Plus on en [culture de selles] fait, plus on va en trouver, mais est-ce que ça va changer grand chose ? L'idée c'est quand même que ça change l'attitude, si un

"The more [stool cultures] you do, the more you will find, but would this change a lot? The idea is still that it changes the attitude, if a test does not change

test ne change pas l'attitude, c'est inutile. Après on dit considération de santé publique, c'est pour ça que vous êtes là, mais ça, si on nous prouve que c'est utile en terme de santé publique de dépister toul le monde, on peut le faire, mais c'est vrai que ça a un coût, et est-ce que ça va changer quelque chose ?" (SFY05)

the attitude, it is useless. Then, people argue for reasons of public health, and that GPs have to contribute to public health. If testing widely/screening is proven beneficial for public health, we can do it. Yet, it would still cost a lot. And will it change something?"

The physician working as a GP requires psychosocial skills. Furthermore, he develops the "medical vision" (assessment of the patient based on general impression and intuition) which helps to follow his or her pragmatic and experience- or intuition-based approach.

Arzt: *"Ich sage immer, dass wir in der Hausarztpraxis keine 'evidence-based Medizin' machen, sondern eine 'intuition-based Medizin' "*

[...]

Interviewer: *"Sie haben vorhin etwas sehr Interessantes gesagt, vor allem aus der sozialwissenschaftlichen Perspektive. Sie haben gesagt, dass es so ein Gefühl gibt bei der Diagnose... Können Sie dieses genauer beschreiben?"*

Arzt: *"Also, Sie merken einfach, ob jemand krank ist oder nicht..."*

Interviewer: *"Der medizinische Blick?"*

Arzt: *"Das ist der medizinische Blick und das ist die Erfahrung, oder? Das ist die Erfahrung! Und diese muss man sich erwerben."* (MZ20)

Physician: *"I always say that in general practice, we do not do evidence-based medicine, but an intuition-based medicine."*

[...]

Interviewer: *"Before you said something very interesting, especially from a social science perspective. You said, that there is this special feeling when diagnosing... Can you describe this in more detail?"*

Physician: *"Well, you just notice whether someone is ill or not..."*

Interviewer: *"The medical vision?"*

Physician: *"That is the medical vision and that is the experience, no? That is the experience! And this you have to acquire."*

"Vous savez, chaque praticien fait son... son travail de façon

"You know, each practitioner does his... his work in a per-

personnelle,... en quelque sorte." (SFY07)

sonal fashion,... to a certain degree."

Arzt: *"Es ist sehr viel Soft-Wissen dabei, also Soft... Gefühlsentscheidungen. Manchmal weiss man selbst gar nicht, warum man so entscheidet. Durch die jahrelange Erfahrung, hat man manchmal die Nase dafür."* (PH12)

Physician: *"There is a lot of soft-knowledge involved, soft... in the sense of intuition. Sometimes we don't even know ourselves why we decided this way. Based on years of experience we sometimes have the flair for it."*

"Vous savez, c'est toujours difficile en médicine d'être absolument systématique, c'est une impression aussi." (SFY11)

"You know, it is always difficult to be absolutely systematic in medicine, it is also an impression."

This dependence on intangible knowledge, soft skills and intuition could explain why some GPs feel that their discipline is neglected by colleagues of other disciplines, and politics:

"[...] dass die Hausarztmedizin, ähnlich wie in Deutschland, nicht die Wertschätzung geniesst, die sie eigentlich haben sollte. Dass man einfach auch von der Bezahlung, den Tax-Punkten her die Spezialisten eigentlich über Gebühr bevorteilt. Das ist genau wie in Deutschland. Der Spezialist verdient dann das doppelte und dreifache und arbeitet die gleiche Zeit. Ich will ihm das auch nicht in Abrede stellen – auch der arbeitet viel – wie wir nun halt eben auch! Man darf sich dann nicht wundern, dass dann immer weniger Leute die Hausarztmedizin ergreifen. Man gefährdet damit irgendwann mal diese breite Gesundheitsversor-

"[...] that primary care medicine, similar to Germany, does not get the recognition it merits. That specialists are unduly advantaged in terms of payment, tax points. That is just like in Germany. The specialist then earns the double or triple, but works the same time. I don't want to deny this – also he is working a lot – but we do so too! You cannot be surprised, after all, that fewer and fewer people choose primary care medicine. At some point this jeopardises the broad health care, if we [GPs] once do not exist anymore. I don't know if the political level is aware of this. Because basically it is always difficult... A politician

gung, wenn es uns dann mal nicht mehr gibt. Ich weiss nicht, ob das in der politischen Ebene so klar angekommen ist. Weil im Grunde ist das natürlich immer schwieriger... sie schliessen als Politiker ein Kantonsspital, was staatlich ist – auch in Deutschland, ein Unispital, das geschlossen wird – das ist natürlich für sie als Politiker ungünstiger, als wenn drei, vier Arztpraxen zu machen. Das geht so im Grundrauschen unter. Ob es da in Vechta oder in Weinfelden, exemplarisch gesehen, 15 oder 13 oder 12 Hausärzte hat... interessiert ja den Politiker vielleicht nicht. Aber ob es ein Spital hat in dem Ort oder nicht... das ist schon wieder etwas, was dann in der Presse auftaucht und vielleicht auch den Politiker die Wiederwahl kostet. Also im Grunde müsste man eigentlich eher von diesem Spezialisten-Gedanken weg kommen und das Gesundheitssystem eher wie eine Pyramide verstehen wo es eine Grundversorgung braucht [...]" (MZ18)

closes a cantonal hospital which is public – in Germany too, a university hospital that is closed – that is less favourable for a politician than if three, four practices are closing. This will get lost in the ambient noise. By way of example, if there are 15 or 13 or 12 general practitioners in Vechta or Weinfelden... might not be of interest to the politician. But if there is a hospital in this place or not... this is something which is also noted by public media and could also go at the expense of the politician's re-election. So basically, one should get away from this specialist-thinking and see the health care system as a pyramid which needs primary health care [...]"

10.2.4 The GPs' view of the Federal Office of Public Health

Physicians were also asked about their perception of the Federal Office of Public Health (FOPH) apart from their approaches to diagnosis and treatment of AG and campylobacteriosis. This question about the FOPH was phrased very broadly, hence, not referring to a specific task or field of responsibility or action of the FOPH such as health insurance, health policy, consumer protection or public health.

Opinions about the FOPH differed among GPs. Given that the question about the FOPH was phrased very broadly, the GPs' perception was largely dependent on the division or task of the FOPH the physician was referring to. Own past experiences with the federal authority were influencing factors. Also personal preferences and expectations about information sources (e.g. on guidelines) influenced the GPs' opinion about the federal office. Statements about the political aspects of the FOPH's work (e.g. tariff structure or lack of support in strengthening family medicine) and on personnel dealing with "administrative tasks" (e.g. permission to work as a GP in a private practice) were rather negative while the scientific collaborators and the parts on infectious diseases, disease surveillance and vaccination recommendations (including travel medicine) tended to be perceived positively.
Several GPs thought that the FOPH was not important or "far away" – sometimes in a negative, but often in a neutral sense. They felt that the federal authority was too distal from primary health care implementation to understand "real", everyday issues. Furthermore, GPs have no interaction with the FOPH during their daily work and, thus, are not aware of the tasks and responsibilities of the FOPH.
Expectations on part of the GPs towards the FOPH are high during international emergencies (e.g. severe acute respiratory syndrome (SARS), H5N1 [bird flu] epidemic, H1N1 [swine flu] pandemic). In these situations, physicians expect to get advice and support from the FOPH. At the same time, they claim that the FOPH overreacted with regard to its response to epidemic and pandemic threats in the past. Consequently, they claim the population was scared and contacted the physician who then had to deal with the anxiety of his patients.
In terms of information provided by the FOPH on a regular basis, many GPs considered the vaccination regimen as very useful, especially in the context of travel medicine. The weekly journal of the FOPH, the "BAG Bulletin", was appreciated very much by some physicians while others thought it did not provide useful information. Some GPs claimed to read it every week while others were not sure if it still exists as they stopped receiving the printed version of the "blue booklet". Physicians frequently mentioned Swiss medical journals (mostly sent to them for free), continuous education and quality circles as useful sources to keep up-to-date.

10.2.5 GPs and the FOPH: Lack of mutual understanding

The qualitative study among Swiss GPs provided important insights into the case management of AG and campylobacteriosis in Switzerland. Additionally, the study allowed exploring the GPs' perception of and expectations towards the FOPH. Ideally, the findings of this latter part should be complemented by looking at the perception of and expectations towards primary care from the FOPH's perspective. However, already the unilateral point of view indicates that there is a need for improving mutual understanding of tasks, responsibilities and challenges. Similar to laboratory experts claiming that the FOPH staff is "difficult to contact" (chapter 7), GPs feel that the FOPH is "distant". This perception of distance could result from lack of interaction between the two actors (FOPH and GPs) of the Swiss health system but also from their different perspectives (individual-based *vs.* population-based). The FOPH could probably improve its reputation among physicians by informing physicians more directly and proactively about its work and openly name associated challenges, e.g. showing the need to and interest in understanding the current practice in diagnosis and treatment of infectious diseases. Given information sources used by Swiss GPs according to the study, the FOPH could use local medical journals as a communication channel. Medical societies, events for continuous education and local quality circles could be targeted for more personal contact platforms.

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

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ORIGINAL PAPER

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

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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 1-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 4 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.

Keywords Acute gastroenteritis · Sentinel surveillance · Primary health care · Switzerland · Antibiotics · Infectious intestinal diseases

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 UK [6].

Bacterial pathogens causing AG which have to be reported to the National Notification System for Infectious

Claudia Schmutz and Philipp Justus Bless contributed equally to this paper.

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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 UK [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 *Escherichia 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 (under-reporting) [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 under-reporting 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 3 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 (1) estimating the incidence and burden of AG seen at the primary care level, (2) describing the physicians' case management (diagnostics, treatment) of AG patients and (3) estimating the work loss due to AG of cases presenting to a physician.

Methods

A 1-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").

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, 6'930 physicians were practising 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.

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 24h 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.

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). 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, dates 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 7 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.

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. 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 4'800 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.

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 was 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 cutoff value for regularly reporting physicians are 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 1'000 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 interval (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 were 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).

Results

Physician and patient characteristics

In total, 3'867 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), 3'734 cases were used for analyses of weekly questionnaires. 2'200 cases were retained for the analyses of supplementary questionnaires. The detailed inclusion process is described in figure 11.1. Out of 172 physicians registered in the Sentinella system in 2014, 154 of the regularly reporting physicians reported at least one case of AG

Table 11.1: 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)	3'734	2'200
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)

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 11.1). The subsample of cases with supplementary questionnaires was comparable to cases reported on weekly forms in terms of basic patient characteristics (Table 11.1).
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 11.2). 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.

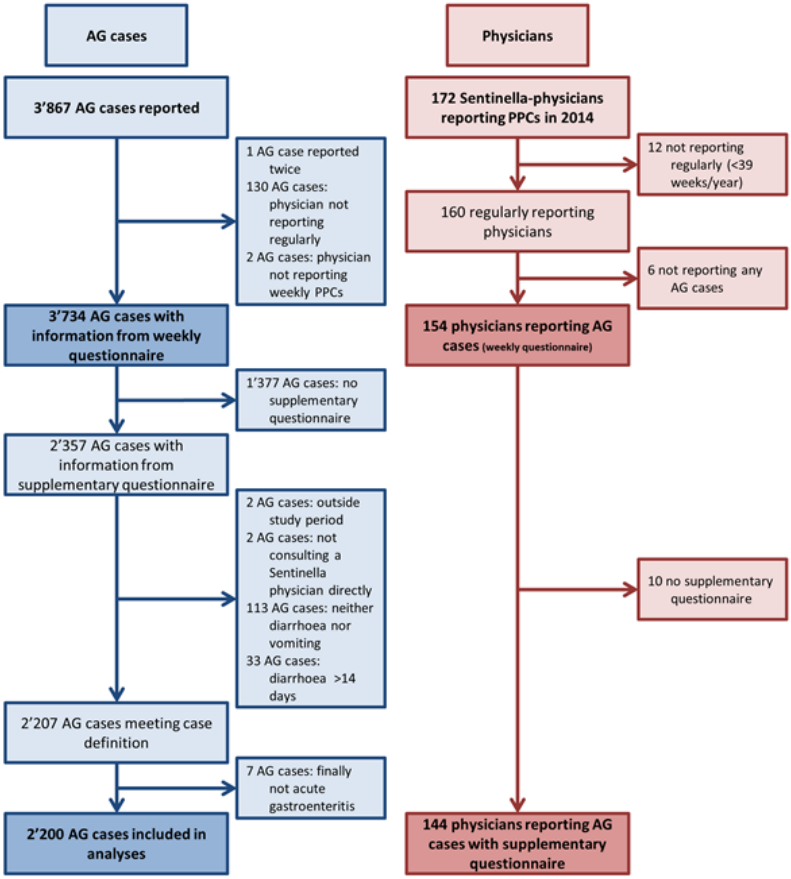

Figure 11.1: Study profile of notified cases and reporting physicians. Acute gastroenteritis study, Swiss Sentinel Surveillance Network, 2014.
AG acute gastroenteritis, *PPC* physician-patient contact

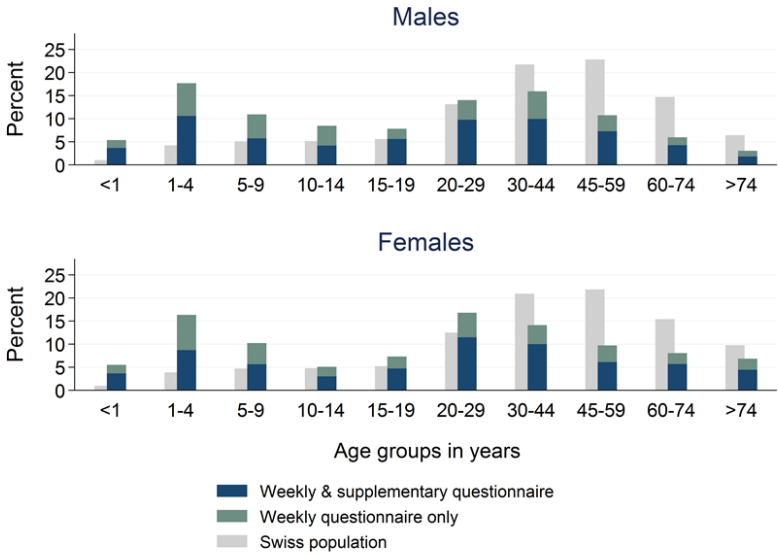

Figure 11.2: Age distribution by sex among acute gastroenteritis cases reported by Sentinella-physicians on weekly and/or supplementary questionnaires. Swiss Sentinel Surveillance Network, 2014; age distribution of Swiss population (official numbers [17]) added for comparison

Burden of AG at primary care level

Each week, 15–139 cases (median 69, IQR 54–80) were reported (Figure 11.3). 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 1'000 PPCs per week (IQR 4.6–6.7) was observed. The notifications correspond to 2'146 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 11.4.

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 11.2). 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 11.2). 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 seven 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.

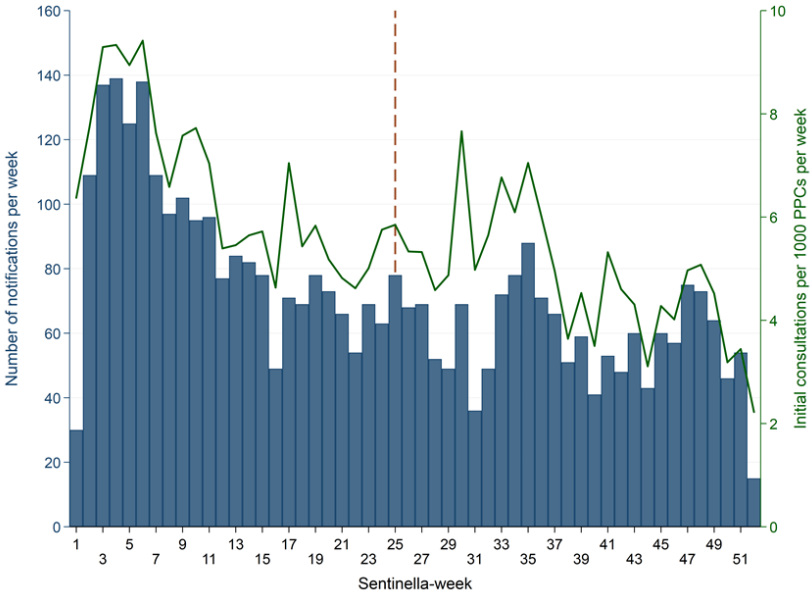

Figure 11.3: Acute gastroenteritis cases reported by physicians from the Swiss Sentinel Surveillance Network in 2014 (28.12.2013–26.12.2014): weekly case numbers (bars) and number of initial AG consultations per 1'000 physician-patient contacts (PPCs, "consultations") per week (line).
Vertical, dashed line: date of change of sampling scheme (from subsample of cases with supplementary questionnaires to supplementary questionnaire for every reported case)

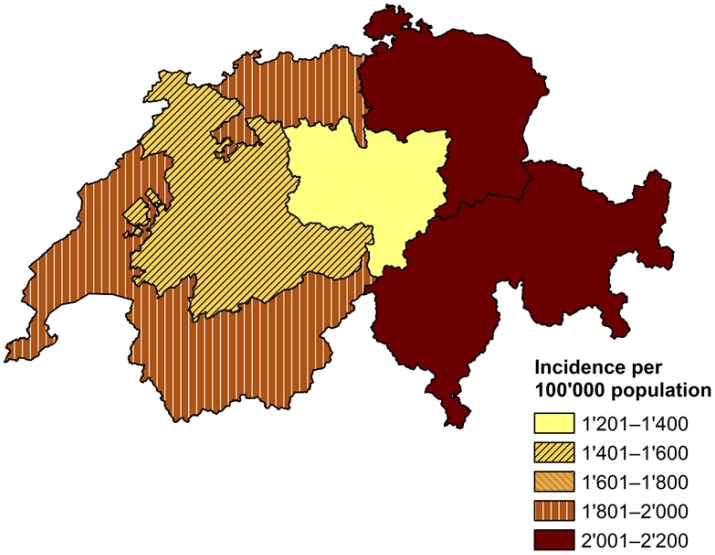

Figure 11.4: Calculated incidence of first consultations due to acute gastroenteritis at primary care level in Switzerland by Sentinella-region, based on standard extrapolation. Swiss Sentinel Surveillance Network, 2014.
Note: an outlier (one physician reporting 400 cases) was excluded from this extrapolation by region.
Source of map shapefile: Swiss Federal Office of Topography

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 11.3). 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 7 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 7 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 11.3). 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

Table 11.2: 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=2'200)		
Diarrhoea	1'940	87.9 (85.6–89.9)
Diarrhoea with blood and/or mucus	249	10.8 (8.5–13.7)
Loss of appetite	1'345	63.5 (58.4–68.4)
Abdominal pain/cramps	1'329	61.1 (57.0–65.1)
Nausea	1'296	60.4 (56.6–64.1)
Vomiting	1'227	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=2'115)		
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)
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=2'200)		
1	1'742	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

pathogens were identified in 11.5% (95% CI 5.4–22.9) of the 98 cases with a positive stool test result.

Table 11.3: 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*=2'176)	286	12.3 (10.1–14.8)
Stool test performed (*N*=2'176)	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)
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

Table 11.4: 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=2'089)	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)
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=1'909)		
Fluid replacement with tea, broth	1'089	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

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 11.4). 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 spasmolytics (15.0%, 95% CI 11.5–19.2). Antibiotics were prescribed in 8.5% (95% CI 6.5–11.0) of cases (Table 11.4).

The Sentinella-physicians initiated stool testing and prescribed antibiotics at the first consultation in 33 cases (unweighted results, table 11.5). Stool diagnostics revealed the 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 11.4). 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 11.4). 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’ impres-

Table 11.5: Time point of prescription of stool testing and antibiotic treatment among acute gastroenteritis patients consulting primary care physicians, Swiss Sentinel Surveillance Network, 2014

	No antibiotics prescribed	Antibiotic prescribed at first consultation	Antibiotic prescribed at follow-up consultation
No stool test initiated	1'713	70	11
Stool test initiated at first consultation	68	33	7
Thereof with positive result for a pathogen susceptible to antibiotic therapy[a]	12	20	5
Thereof with positive result for a pathogen not susceptible to antibiotic therapy[a]	4	1	
Stool test initiated at follow-up consultation	56	3	22
Thereof with positive result for a pathogen susceptible to antibiotic therapy[a]	10	2	11
Thereof with positive result for a pathogen not susceptible to antibiotic therapy[a]	4		1

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

[a] Not considering possible antibiotic resistances and treatment recommendations

sion (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).

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.

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 US [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]. The 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.

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.

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 contact 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 7 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].

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 1'000 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].

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 socioeconomic 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.

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Compliance with ethical standards

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).

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.

Electronic supplementary material

The online version of this article (doi:10.1007/s15010-017-1049-5) contains supplementary material, which is available to authorized users. Please visit `https://doi.org/10.1007/s15010-017-1049-5`.

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Part IV

THE SOCIAL AND FINANCIAL BURDEN OF GASTROINTESTINAL DISEASES ACROSS THE BURDEN OF ILLNESS PYRAMID

12 Estimating healthcare costs of acute gastroenteritis and human campylobacteriosis in Switzerland

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Estimating healthcare costs of acute gastroenteritis and human campylobacteriosis in Switzerland

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SUMMARY

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.

Key words: Acute gastroenteritis, campylobacteriosis, healthcare costs, Switzerland.

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

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Summary

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.

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, 8'480 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). 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 €1'305 (United States [10]) per case in the community ([9-20] in table 12.1). 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 €6'141 (United States [12]) ([8,10-12, 17, 20, 26] in table 12.2). 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 12.2). 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 Authority [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 (Supplementary material) and laboratory positivity rates of *Campylobacter* spp. (Supplementary material). 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.

Methods

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

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).

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

Table 12.1: 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 costs, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
					Direct healthcare costs	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]	1'384	1'305[d]	11'636
Mangen, 2015 [11]	Netherlands	2011	14 foodborne pathogens; including sequelae	4'810'000	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]	806–1'227	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

Table 12.1: (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 health-care cost, per case (in €)	Direct health-care costs, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
					Direct health-care costs	Patient costs (e.g. travel costs)	Productivity losses	Others[b]					
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	1'028–1'128
Hellard, 2003 [9]	Australia	1999	Highly credible gastroenteritis	15'173'430	X		X		AUD 1.65	3[d]	46	14[d]	208

Table 12.1: (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 costs, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
					Direct healthcare costs	Patient costs (e.g. travel costs)	Productivity losses	Others[b]					
Lindquist, 2001 [19]	Municipality of Uppsala, Sweden	1999	Foodborne illnesses	500'000[i] (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]	3'151	472	3'151

[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.

Table 12.1: (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 health-care cost, per case (in €)	Direct health-care costs, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
					Direct health-care costs	Patient costs (e.g. travel costs)	Productivity losses	Others[b]					

[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 12.2: 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 costs, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
						Direct healthcare costs	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[e]	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]	1'392–6'141	1'177–5'189
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

Table 12.2: (continued)

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 costs, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
						Direct healthcare costs	Patient costs (e.g. travel costs)	Productivity losses	Others[b]					
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.

Table 12.2: (continued)

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 costs, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
						Direct healthcare costs	Patient costs (e.g. travel costs)	Productivity losses	Others[b]					

[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].

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. 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].

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].

$$\textit{Patients in management model } D = \textit{cases hospitalized due to } \text{ICD-10 } \textit{code } \text{A04.5}$$

$$\textit{Patients in management model } C = \textit{cases in } \text{NNSID} - \textit{patients in management model } D$$

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).

$$\textit{Patients in management model } B = \frac{\textit{cases in } \text{NNSID}}{\textit{positivity rate } \left(= \frac{\textit{positive tests in x labs}}{\textit{all tests in x labs}}\right)} - \textit{cases in } \text{NNSID}$$

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.

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

The data sources used for the extrapolation from individual to population-based costs are summarized in figure 12.1a.

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.

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

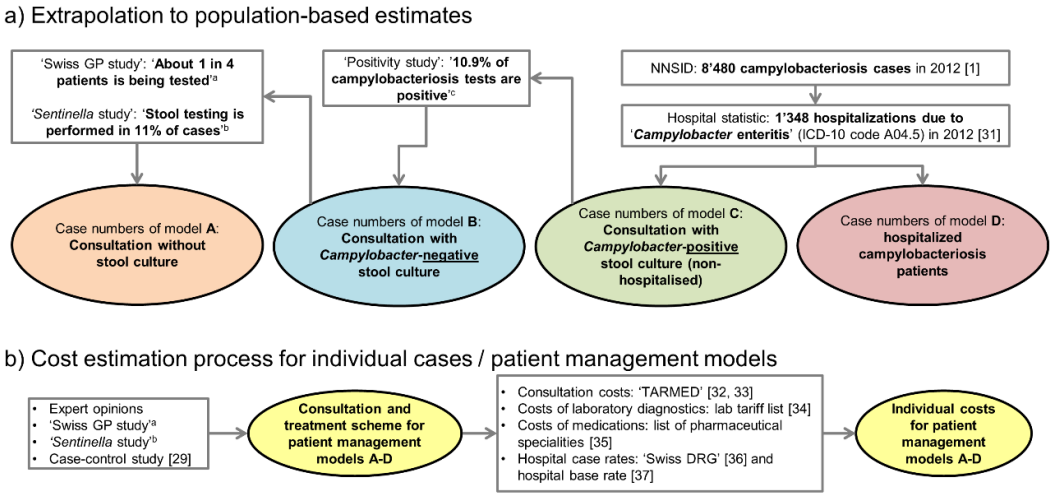

Figure 12.1: Overview of data sources used for (*a*) extrapolation of treatment costs and (*b*) for cost estimation for acute gastroenteritis and campylobacteriosis patients.

[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).

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 12.1b.
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).

Data analysis

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). Afterwards, experts were asked whether they considered the estimated proportions reasonable. The two scenarios do not imply any chronology of the steps involved.
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 electro-

cardiograms. 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.

Results

Frequency of different patient management models in Switzerland

In the NNSID, 8'480 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). 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), 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% (420/3'794) of patients had stool testing performed (Supplementary material). 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, 1'348 hospitalizations were reported which is the maximum so far (Figure 12.2). 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 (8'480 cases), this proportion would result in 1'230 hospitalizations (patient management model D). Patient management model C includes all notified cases except those being hospitalized (1'348), resulting in 7'132 patients annually in Switzerland.

Individual case management costs for AG and campylobacteriosis patients

The costs per case are highly variable ranging from €30 (patient management model A) to €4'828 (patient management model D). The cost

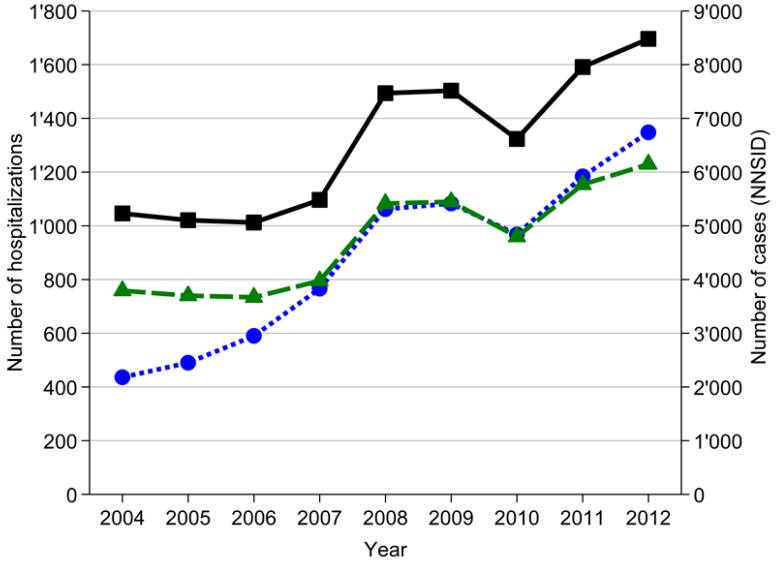

Figure 12.2: Number of hospitalizations due to ICD-10 code A04.5 '*Campylobacter* enteritis' in Switzerland from 2004 to 2012 (blue dotted line with circles, left axis, [31]), number of hospitalizations extrapolated from results of a case-control study in Switzerland [29] assuming hospitalization of 14.5% of cases registered in the National Notification System for Infectious Diseases (NNSID) (green dashed line with triangles, left axis) and number of case notifications from the NNSID [1] (black solid line with squares; right axis).

Table 12.3: Healthcare costs associated with the management of acute gastroenteritis and campylobacteriosis for four patient management models with two scenarios each (values reflect costs in €)

	Patient management model A		Patient management model B		Patient management model C		Patient management model D	
	Consultation without stool test		Consultation with negative stool culture[a]		Consultation with positive stool culture[a]		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[e])	4'727.36
			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 consultation	12.68	5 min telephone consultation	12.68		
Total, minimal scenario		29.81		156.68		220.59		4'759.06
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

Table 12.3: (continued)

	Patient management model A	Patient management model B	Patient management model C	Patient management model D	
	Consultation without stool test	Consultation with negative stool culture[a]	Consultation with positive stool culture[a]	Hospitalization	
				+ 15 min second consultation[b]	31.69
Total, extended scenario	72.93	206.87	270.78		4'827.53
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		
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).

Table 12.3: (continued)

	Patient management model A	Patient management model B	Patient management model C	Patient management model D
	Consultation without stool test	Consultation with negative stool culture[a]	Consultation with positive stool culture[a]	Hospitalization

[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).

items attributed to the different patient management models and scenarios and associated costs are presented in table 12.3. (For a list of unit costs see supplementary table S2.)
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 €179–1'033 (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).

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 (Table 12.4). 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).
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).

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.

Table 12.4: Estimated healthcare costs for the treatment of acute gastroenteritis and campylobacteriosis in Switzerland. Costs for individual cases are based on resource use estimates presented in table 12.3

	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**	**7'132**	**1'348**
In minimal scenario	503'566	186'715	41'591	2'496	674
In extended scenario	125'891	46'679	27'727	4'636	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.

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 figures S1 and S2). 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.

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 notifica-

tion data together with the hospitalization rate found in the case-control study (1'348 *vs.* 1'230 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]).

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, 1'243 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). Individual (healthcare) costs for these patients may be low. However, the high quantity of these patients might still lead to considerable costs.

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 campylobacteriosis (Tables 12.1 and 12.2). 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 2'544–39'008 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 12.2) 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 12.1).

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 inter-sectorial public health interventions and increasing awareness in the population at all levels.

Supplementary material

For supplementary material accompanying this paper visit `http://dx.doi.org/10.1017/S0950268816001618`.

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Declaration of interest

None.

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13 The burden of gastroenteritis in Switzerland (BUGS) study: a research proposal for a one-year, prospective cohort study

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Abstract

Objectives: Acute gastroenteritis (AG) is a usually self-limiting, but common disease worldwide. In Europe, incidence estimates range from 0.3–1.5 AG episodes/person-year. For Switzerland, available information on AG is restricted to notifiable foodborne diseases and findings from research studies starting at primary care level. The aims of this one-year, population-based prospective cohort study are to assess the incidence, burden of disease, aetiology and socio-economic impact of AG in the Swiss general population. Additionally, the prevalence of bacterial gastrointestinal pathogens and bacteria harbouring antimicrobial resistances in the asymptomatic population shall be assessed.
Results: Weekly follow-up of the cohort consisting of 3'000 participants will provide incidence estimates of AG. Furthermore, information collected will be used to assess risk factors for experiencing an episode of AG, to explore determinants for help seeking, and to characterise the socio-economic impact of AG including absence from work and inability to perform daily activities. Aetiology of AG is determined by investigating stool samples from symptomatic participants. Finally, stool samples from participants collected during an asymptomatic period will be used to assess the prevalence of enterohaemorrhagic *E. coli*, *Campylobacter spp.*, *Salmonella spp.* and *Shigella spp.* as well as of resistance to different antibiotics (extended-spectrum beta-lactamase-, fluoroquinolone- and carbapenemase-resistance).

Introduction

Acute gastroenteritis (AG)*, manifesting with signs and symptoms of diarrhoea, vomiting, abdominal pain or cramps, fever, dehydration, nausea and/or loss of appetite, is usually self-limiting, but leads to a considerable burden of disease, health system use and socio-economic impact. Studies in several European countries estimated the incidence of AG at 0.3–1.5 episodes per person and year [1-14]. Furthermore, it was found that a considerable 11% of patients with infectious enteritis develop post-infectious irritable bowel syndrome [15, 16]. Incidence of AG for Switzerland is assumed to be comparable, but data is limited to notifiable pathogens reported to the Federal Office of Public Health (FOPH) based on the Epidemics Act. Several studies from other European countries have shown that (i) only 6.4%–37.8% of all AG episodes lead to consultation of a physician [1-9, 11, 12, 14], and (ii) 0.2%–1.8% of episodes are reported to national surveillance systems

[1, 11, 14]. These proportions are highly variable between countries and pathogens due to different help seeking behaviour, case management and surveillance systems [17]. From a study in the Swiss Sentinel Surveillance Network, Sentinella, we estimated that around 175'000 individuals consulted a physician due to acute gastroenteritis in Switzerland in 2014 [18]. Around 12% of cases were asked to submit a stool specimen and hence, could potentially – if positive – be reported to the National Notification System for Infectious Diseases (NNSID) if their sample tested positive for a notifiable pathogen and was reported by the diagnostic laboratory. However, the proportion of AG patients consulting a physician is currently not known for Switzerland. Consequently, inference from the above-mentioned frequencies and proportions to the incidence and burden of AG at population level is not possible.
Therefore, the present study primarily aims at measuring the incidence of acute gastroenteritis in the general population in Switzerland. Secondary objectives are to describe the burden of disease and the socio-economic impact of AG, to assess its aetiology and to investigate the frequency of selected risk exposures. Finally, the carriage rate of selected pathogenic bacteria and bacteria harbouring selected antibiotic resistances among the "healthy" (non-diarrhoeal) population in Switzerland is assessed.

Main text

Study design and methodology

A one-year, prospective cohort study is conducted to determine the incidence of AG in the general population in Switzerland. The study will assess signs and symptoms of AG and exposure to selected risk factors (incl. antibiotic use). In case of symptoms, the help seeking behaviour of patients, inability to work or to perform usual daily activities, perceived illness experience and socio-economic consequences of the illness will be explored. Furthermore, the aetiology of AG is investigated by examining stool samples from a subsample of participants reporting gastrointestinal symptoms. Finally, the prevalence of selected bacterial gastrointestinal pathogens (enterohaemorrhagic *Escherichia coli* [EHEC], *Campylobacter*, *Salmonella* and *Shigella*) and bacteria with selected antibiotic resistances (extended-spectrum beta-lactamase [ESBL], carbapenemase, fluoroquinolone, and mobilised colistin resistance [mcr]-1) is assessed among participants during an asymptomatic period.

Study setting, recruitment process and eligibility

A representative sample of the Swiss population will be requested from the Federal Statistical Office. The cohort is recruited by postal mail. The procedure for cohort recruitment is shown in figure 13.1. Invitation letters include a study information document, an informed consent form, a contact information questionnaire (for obtaining participants' contact details and for selection of the preferred language and means of communication) and a short screening questionnaire to assess study eligibility. Eligibility criteria for participating in the study are: living in Switzerland; speaking German, French or Italian; age $\geq$14 years; not suffering from cancer of the bowel, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibrosis, coeliac disease or another chronic illness with symptoms of diarrhoea or vomiting.

Data collection and management

Upon return of the signed informed consent and the completed contact information and screening questionnaires, eligible study participants receive a baseline questionnaire, a stool sampling kit including an information and instruction sheet on stool sampling, and the first weekly questionnaire. The content of each questionnaire is summarised in table 13.1. Participants will continuously receive the weekly questionnaire during one year (52 weeks; figure 13.2). Participants receive an additional questionnaire ("illness questionnaire") in case of reporting gastrointestinal signs and symptoms. Furthermore, participants are advised to immediately report occurrence of diarrhoea and/or vomiting actively to the study team by phone, e-mail or SMS (during the day, including weekends) (Figure 13.3). This "active reporting system" is used to select AG episodes for microbiological investigation based on a pre-defined algorithm considering moderate and severe cases of illness as defined by Riddle, *et al.* [19]. In case the study subject's AG episode is selected, the study team will advise him/her to use the stool sampling kit received at the beginning of the study and send a stool sample to the study laboratory as fast as possible. After sending in a stool sample, the participant's stool sampling kit will be replaced. The list of diagnostic tests performed on stool samples from symptomatic participants is provided in table 13.1.

Each week, a pre-defined number of randomly selected participants (see sample size calculation) will receive a stool sampling kit to send in a stool sample immediately. Those stool samples will be tested for selected pathogenic bacteria and presence of certain antibiotic resistances

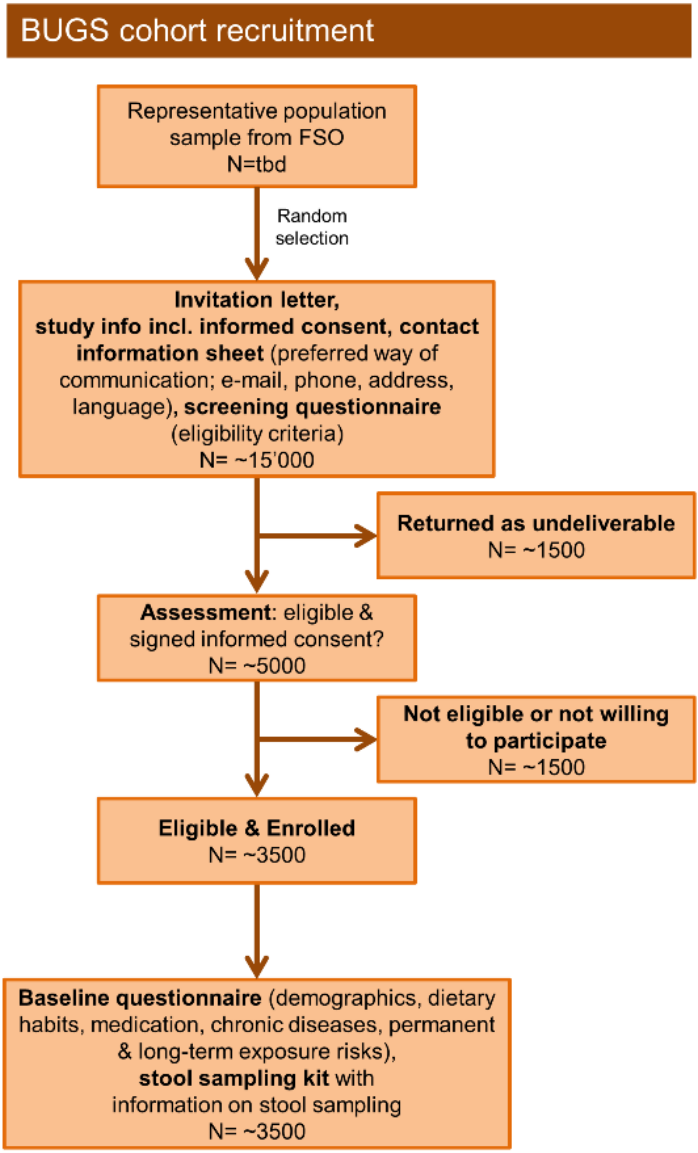

Figure 13.1: Operational flowchart of cohort recruitment for the burden of gastroenteritis in Switzerland (BUGS) study
FSO: Federal Statistical Office; tbd: to be defined

Table 13.1: Overview and content of different questionnaires used and other data collection for the burden of gastroenteritis in Switzerland (BUGS) study

Data collection tool	**Means of application**	**Frequency**	**Content**
Contact information questionnaire	Paper-based	1x before enrolment	Address, e-mail, phone number, language, preferred means of communication (electronic questionnaire with link sent by e-mail [default] or paper-based questionnaire sent by postal mail)
Screening questionnaire	Paper-based	1x before enrolment	General demographic characteristics (age, sex), characteristics to assess eligibility; for those not willing to participate: reason for non-participation
Baseline questionnaire	Electronic and paper-based	1x at the beginning of the observation period	Baseline characteristics: detailed demographic characteristics, dietary habits, regular medication intake, chronic diseases, permanent and long-term exposure risks (e.g. occupational), general health seeking
Weekly questionnaire	Electronic and paper-based	Weekly (52x)	Occurrence of gastrointestinal signs and symptoms and short-term / transient risk exposures (e.g. food consumption, travel)
Illness questionnaire	Electronic and paper-based	After experiencing gastrointestinal signs and symptoms	Disease determinants, health and help seeking, health care utilisation, (self-)medication, consultations, absence from work, ability to perform usual daily activities

Table 13.1: (continued)

Data collection tool	Means of application	Frequency	Content
Stool sample (sympto-matic)	Sampling kit sent to participant at baseline; upon instruction by study personnel participant sends to study laboratory	Selected episodes of acute gastroenteritis	Stool sample investigated for: • Bacteria: *Campylobacter spp.*, *Salmonella spp.*, *Shigella spp.*, *Yersinia spp.* (all culture & PCR); *Clostridium difficile* (RDT & PCR); *Plesiomonas shigelloides*, *Vibrio spp.*, EAEC, EPEC, ETEC, EHEC (all PCR) • Viruses: adenovirus, astrovirus, norovirus, rotavirus, sapovirus (all PCR) • Protozoa & parasites: *Cryptosporidium*, *Cyclospora cyetanensis*, *Entamoeba histolytica*, *Giardia lamblia* • Selected samples (depending on risk profile): additionally for cestodes, trematodes, nematodes and protozoa
Stool sample (asympto-matic)	Sampling kit sent to participant; Participant sends to study laboratory	Max. 1x during observation period; random selection	Stool sample investigated for: • Antibiotic resistance: ESBL, carbapenemase, fluoroquinolones; if carbapenemase-positive: MCR-1 • Bacteria: *Campylobacter spp.*, *Salmonella spp.*, *Shigella*/EIEC, EHEC (all PCR)
Stool sample questionnaire (asympto-matic)	Electronic and paper-based	Max. 1x during observation period; random selection	Risk factors for carrying antibiotic-resistant bacteria, recent antibiotic consumption, visits to or stay in medical institutions, contact to animals and/or raw food

PCR: Polymerase Chain Reaction; RDT: Rapid diagnostic test; EAEC: enteroaggregative *Escherichia coli*; EPEC: enteropathogenic *E. coli*; ETEC: enterotoxigenic *E. coli*; EHEC: enterohaemorrhagic *E. coli*; EIEC: enteroinvasive *E. coli*

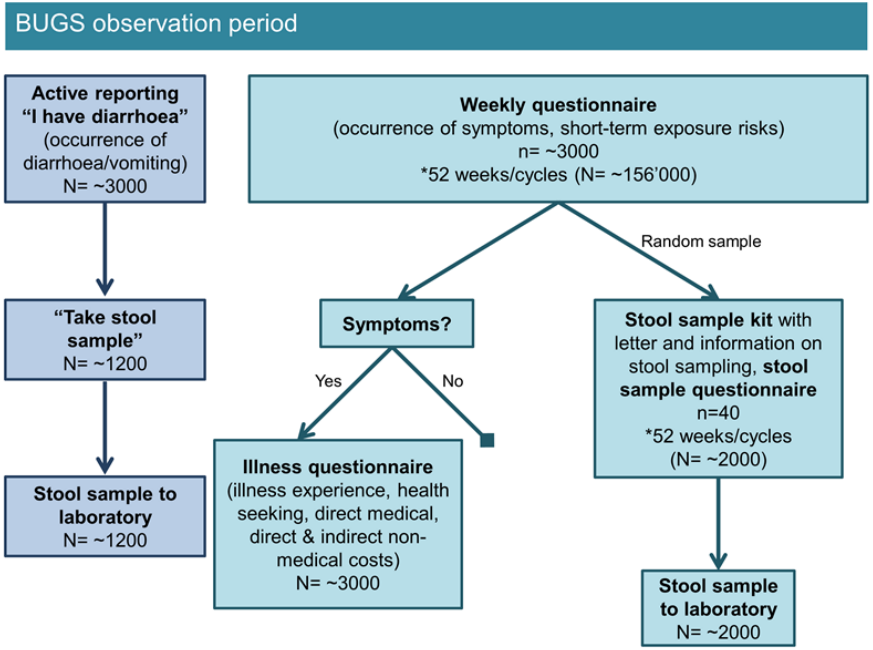

Figure 13.2: Flowchart of cohort observation period for the burden of gastroenteritis in Switzerland (BUGS) study

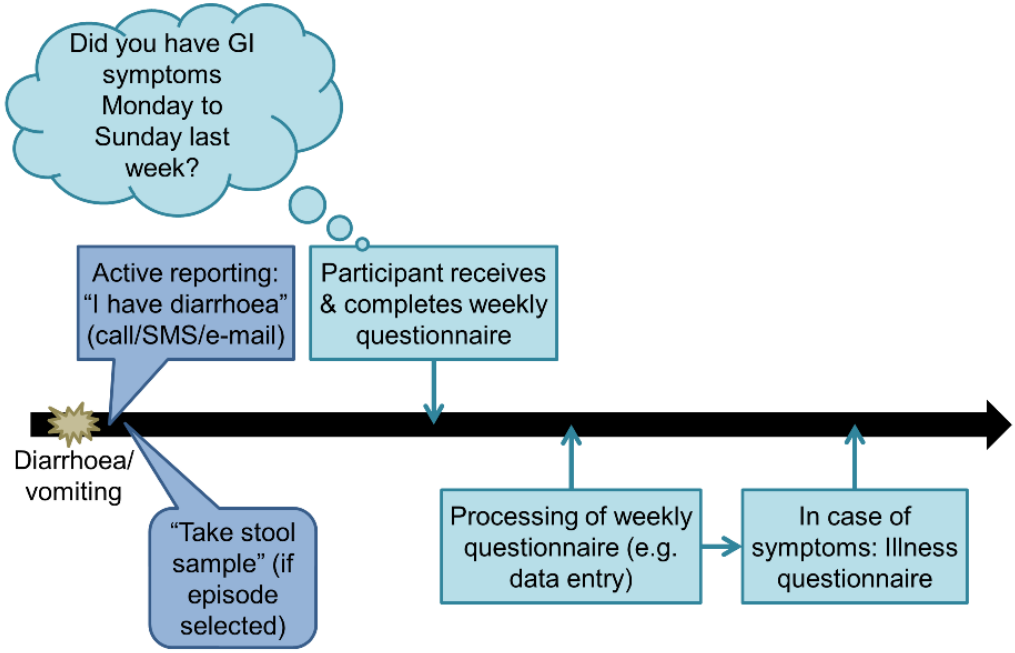

Figure 13.3: Timeline from occurrence of symptoms until sending of illness questionnaire for the burden of gastroenteritis in Switzerland (BUGS) study
GI: gastrointestinal

with the aim to assess respective prevalences in the asymptomatic population (Table 13.1). The stool sample will be discarded if the participant reported diarrhoea with or without vomiting in the 4 weeks preceding sampling. Sampling is conducted weekly throughout the observation period to account for potential seasonal differences in prevalence. Each participant is selected at most once for "asymptomatic sampling".
All questionnaires apart from the contact information and screening questionnaires will be available in electronic- and paper-format. By default, participants will receive an e-mail containing a personalised link to the electronic questionnaires. However, during recruitment, they may opt for paper-based questionnaires sent by postal mail. LimeSurvey, an open source software set-up on a secured server at our institution (Swiss TPH), will be used for electronic data collection. The software allows completion of the questionnaire in a standard internet browser using desktop or laptop computers, tablets or smartphones.
Electronic questionnaires will be programmed to require an answer to ensure completeness of the data collected but will include an option "I do not want to answer" or "not applicable" (where appropriate) in order to prevent a forced-choice bias.
Paper questionnaires are entered by study personnel at the study centre using a LimeSurvey data entry mask which is slightly adapted from the one used by participants (e.g. containing an additional field "no answer given" for each mandatory question). A sample of 10% of paper questionnaires is entered twice for data quality control. Discordant results are checked against paper originals. A full double entry is conducted for the "contact information questionnaire" as correct address details are crucial for successfully contacting participants.
Quality control of data from study laboratories (stool sample results) will be with the diagnostic laboratories, operating according to their standard operating procedures in their daily routine. The study team will only check plausibility of the data and values.
Electronic data are stored on secured network drives accessible only by the study team. Data on the network drive is backed-up regularly, according to institutional policy. Electronic data is stored in original file formats and in comma-separated values (csv) format, where appropriate, to ensure long-term accessibility.

Sample size calculation

We calculated the minimal sample size based on different parameter assumptions for comparisons between two distinct groups and for within-

subject comparisons between two distinct periods. Underlying formulas and results are provided in additional file 1 (Appendix E).
A cohort size of 3'000 individuals is envisaged to allow analysis of secondary outcomes and comparisons between groups and to assert enough power in case assumptions were too optimistic based on the different sample size calculations. We plan to start the observation period with a cohort size of 3'500 individuals in order to achieve an average cohort size of 3'000 after withdrawals and loss to follow-up during the 52 week study period. Assuming a participation rate of 25% (including loss of people not meeting the eligibility criteria) and a loss to follow-up of 20%, 15'000 people will be contacted initially. For planning purposes, we assume an average cohort size of 3'000 throughout the one-year observation period. The sample size (n) needed to reach a specific relative precision (ϵ) for the microbiological outcomes in asymptomatic participants (prevalence of antibiotic resistances and selected pathogenic bacteria) was calculated using the following formula (based on [20]):

$$n = \frac{1.96^2 * (1 - P)}{\epsilon^2 * P}$$

For the prevalence of ESBL, a relative precision of 20% is envisaged at a 95% confidence level. Assuming a prevalence (P) of 5–6% (based on [21, 22]), a sample size of 1'505–1'825 is needed. Considering that the previous prevalence estimates are from groups of potentially higher prevalence than the general population (staff members of meat-processing companies with likely higher exposure risk; and primary care patients), we plan to investigate 2'000 samples. Hence, every week 40 subjects are randomly selected. Given the very low prevalence of Carbapenemase-resistance (0.1%; personal communication) and mcr-1 (not found in 1'000 samples; personal communication) it is questionable whether these resistances will be found at all in our cohort. The prevalence of fluoroquinolone-resistance in *E. coli* has not yet been investigated in the asymptomatic Swiss population. Fluoroquinolone resistance prevalence in *E. coli* is at around 20% based on resistance data generated during routine medical care [23]. Hence, using the same sample size as for ESBL (N=2'000) should allow for an estimate with a relative precision of at least 20% even if the prevalence in the general Swiss population is somewhat lower than 20%.
The presence of pathogenic bacteria (EHEC, *Campylobacter spp.*, *Salmonella spp.*, and *Shigella spp.*) can only be investigated in 1'600 samples of asymptomatic participants (of 2'000 collected) due to financial constraints. For this investigation, the main interest is on EHEC

prevalence in asymptomatic people. Considering that this prevalence is expected at around 7–10% (personal communication) a sample size of 1'600 will still allow for a relative precision of 15–18%.

Approach to analysis

Definition of AG disease episode

The primary outcome of our study is presence or absence of an AG episode and the incidence of AG in the general population. For this purpose, an episode of AG is classified according to a modified version of the definition suggested by Majowicz *et al.* [24]: a case of gastroenteritis is an individual with $\geq$3 loose stools in 24 h, with or without vomiting, but excluding those (a) with cancer of the bowel, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibrosis, coeliac disease, or another chronic illness with symptoms of diarrhoea, or (b) who report their symptoms were due to drugs, alcohol, or pregnancy. An episode is defined to begin on the first day and end on the last day of reported diarrhoea and/or vomiting, followed by a diarrhoea- and vomiting-free period of 3 days [25].

Statistical analysis

Data cleaning and analysis will be conducted with the statistical software Stata and/or R. All steps performed to clean and analyse the data are documented in scripts (R) or do-files (Stata).
The cohort will be characterised in terms of demographic characteristics, health status, dietary habits and permanent or long-term risk exposures as reported at baseline. Similarly, cohort participants lost to follow-up will be compared to those remaining in the cohort.
The primary outcome defined at the level of person-week is presence or absence of an AG episode. Risk factors for experiencing an episode of AG will be determined using multivariable mixed logistic regression analyses with the individual included as a random effect. A basic multivariable model including the biologically most plausible variables, region and season will be defined a priori. Generalised estimating equation models (GEE) will be considered in case of convergence issues of the mixed logistic regression models.
Secondary analyses will include calculating the incidence of AG as the number of AG episodes per person-year under observation and the incidence of gastrointestinal signs and symptoms (including episodes not fulfilling the case definition of AG). Furthermore, transient risk factors

for experiencing an episode of AG will be explored in uni- and multivariable mixed logistic regression models, including the individual as random effect. Exposure information from the week preceding the AG episode will be used. Determinants for presenting to the health system (pharmacies, primary care, specialists or hospitals) in case of AG are also investigated, again using uni- and multivariable mixed logistic regression models (with the individual as random effect). Predictor variables include signs and symptoms, and perceived severity of AG, demographic characteristics (age, sex, occupational status), co-morbidity, and type of health insurance. Additionally, the socio-economic impact such as absence from work, inability to perform usual daily activities and the need for care by family members or friends related to AG disease episodes will be described.
Results from stool sample investigations from symptomatic participants will be used to estimate pathogen-specific incidence rates of AG.
Finally, the prevalences of bacteria harbouring ESBL-, carbapenem- and fluoroquinolone-resistance, and of EHEC, *Campylobacter*, *Salmonella* and *Shigella* in the asymptomatic population is calculated.

Ethical considerations

Health-related personal data and stool samples from participants are collected for this study. Therefore, the study is subject to the Federal Act on Research on Human Beings and requires ethical approval. Approval will be sought from the responsible local ethical committee(s) for a non-clinical trial study with minimal risks. All participants will be asked for written informed consent before enrolment. The study will be conducted according to the principles of Good Epidemiological Practice [26] and the Declaration of Helsinki [27].
Participants will be advised to seek health care as they would do without participating in this study. Similarly, it will be emphasised that investigation of stool samples in the framework of this study does not replace stool sample investigation potentially initiated by their health care provider. Results of stool investigations of symptomatic participants conducted as part of this study are obtained with a time delay due to study logistics. Hence, microbiological results will be known to the study team too late to affect treatment considering the short disease duration of most AG episodes and, therefore, will not be communicated to participants or their physicians.
Participants are informed if antibiotic resistances are identified in their stool samples during an asymptomatic period and advised to inform

their physician in case of illness.

Operational issues

Data confidentiality and personalisation

Ideally, questionnaires should be anonymous as soon as they contain health-related personal information. However, we must be able to link the different questionnaires completed by each study participant. To minimize the risk that unauthorised people are able to link the participants' names to their questionnaire data, we plan to implement several measures: each participant is given a person identification code ("person ID") as well as a questionnaire identification code ("questionnaire ID"). The person ID is used in all files/data sets containing personal information. The questionnaire ID is used in all files/data sets containing information obtained from questionnaires or from laboratory testing. The key file, linking the person ID and the questionnaire ID will be password protected and stored separately from the other data sets. Access to this key file will be limited to the principal investigator, the study coordinator and an additional person (substitute of the study coordinator). For paper-based questionnaires, both codes (person ID and questionnaire ID) are printed on the empty questionnaires. However, as soon as receipt of the completed questionnaires is registered in the study centre, the person ID will be removed (cut off). In order to avoid that both codes are easily visible and recognised as such by unauthorised persons, one of the codes (the person ID) is printed in directly readable format (Arabic letters and numerals) and the other code is printed as a QR- or bar-code. Also, the two codes are not labelled with "person ID" or "questionnaire ID". For electronic questionnaires only the "questionnaire ID" will be used and no names are stored in LimeSurvey (where questionnaire data is entered and stored during the entire data collection phase). In order to complete the questionnaire, participants will receive an e-mail including a link to the questionnaire containing the questionnaire ID.

Active reporting system needed

For investigating the aetiology of AG, stool samples need to be obtained quickly after disease onset as AG is usually a short, self-limiting disease. Therefore, the information on signs and symptoms obtained through the weekly questionnaire is too much delayed to be the basis for selection of episodes for aetiological investigation (especially in those completing the paper-based questionnaires; figure 13.3). We expect reporting delays of

1–13 days in those completing electronic questionnaires and of at least 3–10 days (best case scenario) for paper-based questionnaires which will severely impact the likelihood to detect pathogens. To address this limitation, we plan to set up an "active reporting system" for participants (see "data collection and management"). These parallel ways of collecting data on diarrhoea and vomiting have advantages and disadvantages: on the one hand, we can compare reporting completeness of the two methods. On the other hand, participants are required to actively think of the study when experiencing signs and symptoms, and have to report their symptoms twice – potentially increasing reporting fatigue and reporting bias due to sensitisation. Further, the active reporting system requires that study personnel being able to communicate in all three study languages is on call every day, including weekends and public holidays.

Limitations

Our study will be subject to limitations. Participation bias is likely to occur. Considering the rather long observation period (one year with weekly follow-ups), a certain amount of participants will be lost to follow-up or withdraw from the study; these participants might differ from those completing the entire follow-up period. Similarly, reporting fatigue might occur, especially in those experiencing more than one episode of AG. However, all those biases and limitations are unavoidable in cohort studies and their mitigation is difficult. To address reporting fatigue, we consider establishing a project newsletter to give participants feedback about interim results of the study and additional information related to the topic to highlight the importance of their contribution to research. Inverse probability weighting will be considered if characteristics of our final cohort differ from those of the general population.

Furthermore, compliance in actively reporting signs and symptoms as well as in providing stool samples is crucial. Therefore, its importance will be emphasised repeatedly to study participants. We suspect that compliance might be associated with the (perceived) severity of the disease episode. However, we can only try to assess this bias at the end of the study by comparing data from active reporting/stool sampling and data from weekly questionnaires.

Recall bias and telescoping have been described as major challenges in studies on AG. We believe that this bias might not be a notable problem in our study considering the rather short recall period of 1 week.

Participants travelling will still receive the electronic questionnaire but those completing paper-based questionnaires will be able to complete the questionnaire only once they returned. This might lead to different compliance and recall bias in those two groups. On the other hand, it provides an opportunity to assess potential differences in results between the two methods.

Declarations

Ethics approval and consent to participate

Approval for this study will be sought from the responsible local ethical committee(s) for a non-clinical trial study with minimal risks. All participants will be asked for written informed consent. The study will be conducted according to the principles of Good Epidemiological Practice and the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and material

Data sharing not applicable to this article as datasets were not yet generated for the presented study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DM and CS conceptualised the study and wrote the manuscript. Both authors approved the final manuscript.

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Part V

DISCUSSION AND CONCLUSIONS

14 Discussion

Surveillance of infectious diseases in Switzerland mainly relies on two systems: the National Notification System for Infectious Diseases (NNSID) and the Swiss Sentinel Surveillance Network (*Sentinella*). However, both systems are subject to different degrees of underestimation* of disease frequency. There is insufficient knowledge on how disease incidence or prevalence in the general population relates to the number of notified cases in Switzerland. Therefore, the aim of this doctoral research was to improve the understanding of this burden of illness pyramid using the example of foodborne infections, exemplified in studying *Campylobacter*, *Salmonella* and enterohaemorrhagic *Escherichia coli* (EHEC) among others.

Trends in the frequency of *Campylobacter* and *Salmonella* were assessed analysing data from the NNSID from 1988 to 2013 (chapter 4). The two pathogens, presenting with similar signs and symptoms, showed inverse trends pointing at changes in disease incidence. Indeed, several interventions to control *Salmonella* spp. were implemented after the peak levels in the early 1990ies and appear to have been successful. In contrast, no limits at all for *Campylobacter* spp. in food were in place between 2006 and 2013 in Switzerland. Analysis of surveillance data of hepatitis A, another disease which may be transmitted through contaminated food, revealed difficulties in interpreting long-term trends given frequent changes in notification forms (chapter 5).

Results from positivity studies for *Campylobacter* and *Salmonella*, hence, studies taking into consideration the number of tests conducted apart from the number of positive results, lead to the same conclusions as analysis of notification data alone: *Campylobacter* is increasing while *Salmonella* is decreasing (chapter 6). At the same time, stool testing frequency was found to be increasing for both pathogens. Part of the increase in case numbers for *Campylobacter* can, therefore, be attributed to increased testing while the observed decrease in *Salmonella* notifications seems even more significant considering this aspect. Understanding diagnostic procedures and testing behaviour was consequently deemed essential. Increased testing volume was also considered the main reason for the observed strong increase in EHEC notifications since 2015, as stated by laboratory experts (chapter 7). However, analysis of laborat-

ory data suggested that increased testing only partially explained the strong increase (chapter 8). We, hence, concluded that the occurrence of epidemic events cannot be ruled out in the case of EHEC.
Swiss general practitioners (GPs) mostly follow a "wait & see" approach when managing cases of acute gastroenteritis (AG)* as seen in a qualitative (chapter 10) as well as in a quantitative assessment (chapter 11). Both studies showed that only a minority of patients (one in four to one in ten patients) is prescribed stool testing and hence, the illness has a chance to be captured by the surveillance system if a notifiable pathogen is found. In brief, there is already a rather small chance to start with for an AG episode to proceed to higher levels of the burden of illness pyramid and potentially being notified. Finally, all steps along the burden of illness pyramid are associated with costs. In absence of available data on costs associated with AG in Switzerland, we estimated that AG and campylobacteriosis resulted in substantial healthcare costs of €29–45 million in 2012 (chapter 12). Patients with AG neither approaching a GP nor being hospitalised were not considered in these cost estimates. Similarly, absence from work and other indirect costs were not considered. Further research at the population level to understand the full burden of disease of AG is urgently needed in Switzerland given the large burden associated with AG identified through our research already when looking only at levels starting from primary care. Consequently, a research proposal was developed to explore the incidence, burden of disease, social and societal impact of AG (chapter 13).
The research presented in this thesis was conducted in close collaboration with and support of federal authorities (Federal Office of Public Health (FOPH), Federal Food Safety and Veterinary Office (FSVO)). This public-public partnership was mutually beneficial: it allowed us (the researchers) to get direct and easy access to existing structures (e.g. *Sentinella*) and data (e.g. disease notifications). *Vice versa*, our multifaceted research could be targeted to the needs of public authorities, assuring that research is close to application. This improved acceptance of the research conducted, guaranteed support of our projects by federal authorities and increased the chance of further use and dissemination of research results by those stakeholders or consideration and implementation of recommendations originating from our research. Furthermore, our research supported the federal offices in several ways (e.g. implementation of measures or recommendations, justify priorities) by providing sound, scientific evidence of long-standing hypotheses and by quantifying disease burden. Publication of results lead to media reactions (Appendix, section F.1), raising attention to the topic by the public

and increasing external validity of our research.
This chapter consists of three main parts. In the first part, the different levels of the burden of illness pyramid are discussed in the light of the research results presented in this PhD thesis and findings from other countries (section 14.1). The second part critically reflects on the Swiss NNSID: whether the NNSID fulfils its purpose (subsection 14.2.1), whether the purpose of the NNSID fulfils 'our' (the researchers', epidemiologists', public health experts') expectations (subsection 14.2.2), and finally suggestions for improving the NNSID are made (subsection 14.2.3). The third part then illustrates how the ideal case management of AG looks like from different perspectives and discusses the various and partly conflicting wants and needs of patients (subsection 14.3.1), physicians (subsection 14.3.2) and of the public health community (subsection 14.3.3).

14.1 Reconstructing the burden of illness pyramid

14.1.1 From infection to disease notification

Several steps are involved until a case is reported to national surveillance, as already mentioned in the introduction of this thesis (section 1.1 and figure 1.1): after an individual is exposed to a certain pathogen, the person has to be infected and/or develop (gastrointestinal) symptoms. Then, the individual has to seek medical care. The physician has to request a (stool) sample from his patient. The patient has to comply with this request and the sample has to be sent to the diagnostic laboratory. At the diagnostic laboratory, the sample has to be analysed. If a pathogen can be identified by the laboratory and if this pathogen is notifiable, the laboratory has to report it to the FOPH. Finally, if the laboratory complies with its obligation to report and the reporting form is entered at the FOPH, only then, the case is registered in official disease surveillance statistics.
At each step, some cases are "lost" and hence, what is registered in the NNSID does not reflect the actual disease incidence in the population. However, the proportion of cases reaching the tip of the 'burden of illness pyramid' depends on the pathogen, the patient, the physician, the laboratory and the federal administration and hence, can neither be compared across pathogens nor across countries or health systems. The different levels of the burden of illness pyramid and factors associ-

ated with the transition from one level to the next are discussed in the following sections.

14.1.2 Before primary care: The "invisible" part of the burden of illness pyramid

The lowest levels of the burden of illness pyramid, those before primary care, are the most difficult to explore, understand and comprehend. At this stage, no healthcare professionals are involved and hence, the healthcare system does not "see" those cases. Considering that most traditional surveillance systems collect information from actors of the health care system, i.e. physicians and/or diagnostic laboratories, these lower levels are not captured. In Switzerland, the incidence of AG and the proportion of individuals approaching a physician are not known but will be explored in an upcoming prospective cohort study (Burden of gastroenteritis in Switzerland (BUGS) study; chapter 13).
A study in the United Kingdom (UK) showed that 533–1'530 cases of infectious intestinal disease (IID) occurred per 1'000 person-years [Viviani *et al.*, 2016]. The incidence found in this retrospective telephone survey differed depending on the recall period (7 *vs.* 28 days). Furthermore, incidence rates found by Viviani *et al.* [2016] were higher than those found in a prospective cohort study conducted in the UK at around the same time (274 cases/1'000 person-years [Tam *et al.*, 2012]). They concluded that alterations in study design (e.g. recall period or case definition) can strongly impact on study findings.
Tam *et al.* [2012] found that 25.3 cases per 1'000 person-years consulted their GP in the aforementioned cohort study, hence, around 9% of community cases. A retrospective survey in the Netherlands found a community incidence of IID of 964 cases/1'000 person-years with 8% of cases visiting a physician [Doorduyn *et al.*, 2012]. Duration of symptoms of $\geq$3 days, blood in the stool and young age were predictors for consulting a GP. Similarly, an Australian study found that disease duration, presence of fever or chills, respiratory symptoms, and earache increased the odds of visiting a physician due to infectious gastroenteritis while stomach cramps decreased the odds [Chen *et al.*, 2016]. In a study among campylobacteriosis patients in Switzerland, participants mentioned severity and lack of improvement of symptoms as reasons for care seeking [Bless *et al.*, 2014]. One third of patients (32.7%) consulted the physician directly, but some had consulted friends and family (42.8%), a pharmacy (19.5%), the internet (14.5%) and/or called a medical hotline (5.0%) before visiting a physician. In the aforementioned Australian study, 36.1%

of gastroenteritis cases visited any type of healthcare professional (e.g. pharmacists or doctors) while 13.4% visited a physician [Chen *et al.*, 2016]. Similarly, our qualitative study among Swiss GPs provided evidence that there is a substantial proportion of people with AG who do either seek help at pharmacy level or by contacting the practice nurse, apart from not seeking help at all (section 10.1 and Bless *et al.* [2016]). As mentioned above, traditional surveillance systems (referred to as the "indicator-based component" of epidemic intelligence* [Paquet *et al.*, 2006]) do not cover these lower parts of the burden of illness pyramid. In recent years, numerous so-called "event-based internet surveillance systems" have been developed. The "'event-based component' [of epidemic intelligence] refers to unstructured data gathered from sources of intelligence of any nature" [Paquet *et al.*, 2006]. Information sources include news feeds, social media, search engine queries, and users actively reporting health events [O'Shea, 2017]. This has the advantage that they do not rely on information from healthcare professionals [O'Shea, 2017] and hence, also levels below primary care can be covered. Additionally, processes for notification are shorter and therefore, faster. However, so far, such event-based internet surveillance systems have mainly been used for early detection of emerging infectious diseases or outbreaks. Milinovich *et al.* [2014] found a correlation between a selected internet search term and notifications for 17 infectious diseases in Australia. However, they also highlighted that there is a complex interplay between internet searches, media attention, and actual disease incidence. Therefore, more detailed analyses are needed to further explore the potential of using search terms for monitoring disease occurrence. It seems that event-based surveillance is able to detect *changes* in disease occurrence. By contrast, and similar to traditional surveillance, it is probably not suitable to measure actual disease prevalence or incidence considering that it is not possible to directly infer from baseline levels of search term activity to disease prevalence. Syndromic surveillance is another option for early detection of outbreaks. Syndromic surveillance can be based on different data sources ranging from clinical observations over laboratory data to drug sales and use of web pages and helplines [Dupuy *et al.*, 2013]. Clinical observations and laboratory data require contact with the healthcare system and hence, are again subject to underestimation. One example of syndromic surveillance based on clinical observations is the study on AG conducted within *Sentinella* (chapter 11). The use of data on drug sales, use of web pages and helplines are all subject to the same limitations as discussed above: they are probably able to detect changes in disease frequency but baseline levels of disease activity cannot

be directly quantified. Finally, in the context of One Health*, surveillance in the veterinary sector has been proposed for earlier detection of outbreaks of emerging zoonotic diseases, thereby reducing costs for outbreak control [The World Bank, 2012]. However, most surveillance systems are passive and hence, rely on signs and symptoms of the disease or syndrome under surveillance. Therefore, this One Health approach using veterinary syndromic surveillance is not suitable for foodborne diseases such as *Campylobacter* as this zoonosis is mostly asymptomatic in poultry, cattle, and pigs which are important sources of human *Campylobacter* infections in Switzerland [Horrocks *et al.*, 2009; Jonas *et al.*, 2015; Kittl *et al.*, 2011]. Furthermore, human AG is frequently caused by viruses having no animal reservoir (e.g. Norovirus, rotavirus) [Hall and Lopman, 2015; Patel, 2015]. Therefore, in order to quantify the lowest levels of the burden of illness pyramid, research studies such as the BUGS study (chapter 13) are needed.

14.1.3 At primary care: physicians' case management is patient-oriented

Patients with AG consult a physician two days (median) after onset of symptoms, according to the *Sentinella* study (chapter 11). Campylobacteriosis patients in a case-control study reported a median time interval between first symptoms and consultation of three days [Bless *et al.*, 2014]. Nevertheless, physicians frequently report to follow a "wait & see" approach for patients with AG (section 10.1 and Bless *et al.* [2016]). This is in line with American guidelines for the management of acute diarrhoea in adults recommending stool diagnostics "in cases of dysentery, moderate-severe disease, and symptoms lasting >7 days" [Riddle *et al.*, 2016]. However, testing is also recommended according to those guidelines "in situations where the individual patient is at high risk of spreading disease to others, and during known or suspected outbreaks". Several studies reported that protracted or long course of disease, poor general condition, blood in stool, and reporting recent travels were important factors favouring stool diagnostics [Bless *et al.*, 2016; Hennessy *et al.*, 2004; McNulty *et al.*, 2012, 2014; Scallan *et al.*, 2005; Schmutz *et al.*, 2017a; Van Cauteren *et al.*, 2015b; Van den Brandhof *et al.*, 2006]. Hence, physicians consider mainly patient characteristics and patients' well-being when deciding for or against stool testing. Public health considerations play only a minor role in this decision, mainly if the case is linked to the healthcare sector (either working or living in an institution), or to the hospitality or food industry (section 10.1 and Bless

et al. [2016]). Decisions for testing were also reported to be driven by patient characteristics (e.g. age, length of hospital stay, clinical details) in a study about the management of patients with suspected infectious diarrhoea in hospitals in England [Buchanan *et al.*, 2015].
Physicians estimated to request stool samples for 18% of patients (range: 5–60%) (section 10.1 and Bless *et al.* [2016]). The *Sentinella* study found a slightly lower proportion of 12% (chapter 11). A wide range and heterogeneity in stool sampling rates were reported in other countries, with individual physicians reporting stool sampling rates ranging from zero per cent to 100% [McNulty *et al.*, 2014; Van Cauteren *et al.*, 2015b; Van den Brandhof *et al.*, 2006]. The number of stool tests conducted varies also strongly throughout the year as seen in the positivity studies (chapter 6 and 8). Apart from seasonality in disease incidence, this could also be due to seasonality in the prevalence of "risk factors for stool testing" such as travel activity.
Stool sample investigation does not only depend on the decision of the physician, but also on compliance of the patient. A qualitative study in the UK revealed that embarrassment, fear of results and lack of information on why and how to collect the stool were barriers for patients to providing stool samples [Lecky *et al.*, 2014]. Fear of results might be more strongly related to colorectal cancer screening than to acute infectious gastroenteritis. Embarrassment was partly mentioned in connection with handing over the sample to the receptionist, considering that the reception is a public area where other people may listen to the conversation or observe the situation. This factor might be different in Switzerland as some physicians would instruct patients to directly sending the stool sample to the diagnostic laboratory by postal mail. Furthermore, participants mentioned concerns about hygiene (handling faeces could contaminate own hands and objects; waste disposal) and generally considered it "dirty" to handle their own stool. The *Sentinella* study indicated that in 94% of cases where the physician decided to do stool diagnostics a sample was actually sent to the laboratory (12.3% *vs.* 11.6%) (chapter 11). Consistently, Swiss GPs reported that compliance of patients to provide a stool sample is generally not an issue (chapter 10). However, they also stated that if the patient would refuse stool sampling, they would usually not insist as results are not crucial for therapy in most cases of AG. For patients, there might be a trade-off between embarrassment and perceived benefit of getting the results. This trade-off might favour perceived benefit in case of acute infection and suffering (in the case of AG) as opposed to preventive screening.

14.1.4 After primary care: beyond sensitivity and specificity of diagnostic methods

Traditional stool culture for gastrointestinal pathogens is increasingly replaced by culture-independent methods such as multiplex PCR panels in Switzerland (chapters 7 and 8) and elsewhere [Gibney *et al.*, 2017; Iwamoto *et al.*, 2015; Marder *et al.*, 2017; May *et al.*, 2017]. This leads not only to changes in diagnostic sensitivity and specificity but also to changes in testing frequency, mainly due to co-testing for multiple pathogens. For example, if the physician ordered tests for two or three single pathogens, a laboratory using multiplex polymerase chain reaction (PCR) panels is likely to test the sample using the panel (given the requested pathogens are included in the panel) instead of using single tests for each pathogen due to economic considerations (chapter 7). Test results from pathogens included in the panel but not ordered by the physician would then usually be reported by the laboratory if positive due to ethical reasons (chapter 7). However, there are also laboratories considering not to report results of tests not ordered to the physician (as already routine in case of blood exams). Such information on co-testing and ways of reporting of results from tests not ordered is usually not collected by surveillance systems. However, it can impact on surveillance data as shown at the example of EHEC in Switzerland, where it lead to a strong increase in case numbers (chapters 7 and 8), and *Campylobacter* in the United States of America (USA), where culture-confirmed cases decreased while notification rates adjusted for culture-independent diagnostic tests remained stable [Gu *et al.*, 2018].
It was mentioned that not only EHEC but also other pathogens causing diarrhoeal diseases should be detected more frequently with the increasing use of multiplex PCR panels [Bundesamt für Gesundheit and Nationales Referenzzentrum für enteropathogene Bakterien und Listerien, 2015]. However, the authors hypothesised that this was not the case because there is still enough expertise and equipment available to confirm positive PCR results using culture-based methods. This is not the only explanation for the lacking (strong) increase even though culture-confirmation was indeed required for *Campylobacter* to fulfil the case definition of the NNSID (until 2017; in 2018, the FOPH changed the case definition for *Campylobacter* to include also cases with PCR-confirmation only. This change is valid retroactively for cases notified since January 2013 [personal communication]). According to laboratory experts, testing for EHEC was rarely specifically requested while *Campylobacter*, *Salmonella* and *Shigella* all were routinely tested. Hence, the

use of multiplex PCR panels did probably not have a large impact on test numbers for *Campylobacter*, *Salmonella* and *Shigella* while it had a tremendous impact on test numbers for EHEC (and other pathogens which are not notifiable). Therefore, it is conceivable that the increasing use of multiplex PCR panels had a much larger impact on EHEC test and case numbers than on the other three notifiable bacterial pathogens included in most panels (*Campylobacter*, *Salmonella* and *Shigella*).
Nevertheless, also changes in diagnostic methods affecting sensitivity and specificity must obviously be taken into account when interpreting surveillance data, as described by Bless [2018]; Gu *et al.* [2018]; Hurd *et al.* [2012] using the example of *Campylobacter*.
Statements from physicians and laboratory experts indicated that the selection of diagnostic tests by the physician – both, concerning the inclusion of pathogens and the method applied – is not only dependent on subject-specific or medical reasons but is also influenced by presentation of options on laboratory test order forms (unpublished observation). Studies in Finland, Israel and the Netherlands have shown that physicians' ordering behaviour can be altered by changing how laboratory test options are presented on order forms [Kahan *et al.*, 2009; Seppänen *et al.*, 2016; Shalev *et al.*, 2009; Zaat *et al.*, 1992]. Hence, also changes in something "simple" such as a laboratory test order form can influence surveillance data. Given that diagnostic laboratories in Switzerland operate in the private sector, harmonisation of order forms is hardly achievable.
Furthermore, testing algorithms offered and used by diagnostic laboratories are likely also influenced by economic considerations. It has been shown that the workload at the laboratory and the overall turnaround time of the sample can be reduced by screening samples first using PCR followed by culture of PCR-positive samples (compared to culture only) [Van Lint *et al.*, 2016].
In summary, medical decisions and technical features such as sensitivity and specificity of diagnostic methods are not the only factors influencing under-diagnosis*. Laboratory test order forms and "translation" of physicians' laboratory orders into actual selection of tests at the laboratory are also factors to be considered.

14.1.5 At the tip of the iceberg: the notification system is not static

Finally, physicians and laboratories have to comply with their obligation to report notifiable observations. Self-reported knowledge of physicians

and employees of laboratories about the notification system is generally "good" in Switzerland, according to an evaluation report of 2012 [von Stokar *et al.*, 2012].
Analysis of hepatitis A, B and C notification data showed that for all three diseases, no report on clinical findings was received by the FOPH for about 14–15% of cases (chapter 5, Richard *et al.* [2017, 2018]). This is in line with previous analyses reporting that for 6% to 21% of cases of gonorrhoea or invasive meningococcal disease reports from physicians were missing [von Stokar *et al.*, 2012]. Furthermore, a report on laboratory findings was missing for 6% of hepatitis A cases. Additionally, for a study on EHEC, laboratories were asked to send stool samples or EHEC isolates to the National Reference Centre for Enteropathogenic Bacteria and Listeria (NENT). Comparison of samples received by the reference laboratory and notifications recorded at the FOPH revealed that for around 10% of 900 samples no corresponding notification could be identified (personal communication). There might be other reasons for those discrepancies apart from non-compliance in reporting. Nevertheless, it is reasonable to assume that there is some under-notification* in Switzerland. Yet, a quantitative assessment of under-notification has not been conducted systematically.
The challenges associated with surveillance systems do not end once the notification arrives at the point of notification (in Switzerland: the FOPH) and hence, the case is captured by the system (here: the NNSID). Further issues include the reliability and validity of the data as well as quality of data entry and proper documentation of changes in data entry procedures, data entry masks, and notification forms (see also subsection 14.2.1). Analysis of hepatitis A notification data in Switzerland (chapter 5) has shown that (a) changes in notification forms occur frequently, (b) changes in both, data entry and forms are difficult to track, and (c) certain sections of reports on clinical findings (e.g. assumed place and source of exposure) are poorly filled in. The number of variables included in the surveillance system changed (increased) over time in Australia [Gibney *et al.*, 2017], indicating changes in notification forms which may make interpretation of long-term trends difficult. Furthermore, notification forms used in Australia and Canada may even differ between states (or province/territory) [Neave *et al.*, 2016]. In Switzerland, notification forms are provided at national level (by the FOPH).
In conclusion, cases registered in the surveillance system are not only subject to underestimation, resulting in a non-random selection of cases occurring at population level. Heterogeneity in surveillance data is further increased, and comparability reduced, by changes in notification

forms and procedures, under-notification and incompleteness of data.

14.1.6 From disease notification back to infection

The research work presented provides insights into and quantitative estimates for the most important steps from attending primary care to being notified to the NNSID. Figure 14.1 summarises the multiplication factors as we found them from our different studies for the different levels of the burden of illness pyramid and extrapolation of NNSID case numbers of *Campylobacter*, *Salmonella* and EHEC to consultation frequencies at primary care level. Estimated multiplication factors did not distinguish between pathogens except for positivity rates. When calculating backwards from pathogen-specific case numbers, estimated consultation frequencies at primary care differ widely. This is not surprising considering that prevalence and incidence of these pathogens, and the proportion of cases seeking care, getting tested and finally notified differ. Additionally, it has to be noted that estimated numbers at all except the top two levels of the pyramid are not pathogen-specific and are, therefore, not cumulative. In other words, AG cases tested for *Campylobacter* spp. and *Salmonella* spp. will be included in both, *Campylobacter* and *Salmonella* estimates. Therefore, based on our extrapolation, "true" consultation frequencies at primary care level are likely in the range of 230'000 (lowest estimate for EHEC) and 1.1 million (highest estimate for *Salmonella*) per year. These estimates are substantial in size but have to be interpreted with care as they are subject to several additional limitations. Certain multiplication factor estimates did not include the hospital setting. For example, the proportion of individuals requested to provide a stool sample was taken from the *Sentinella* study (chapter 11). This study involved GPs only. Physicians working in a hospital may use a different case management strategy. Additionally, the positivity studies on *Campylobacter* and *Salmonella* (chapter 6) did only include private sector laboratories (no hospital laboratories). Positivity rates of hospital laboratories may differ. Finally, multiplication factors and case numbers used for this calculation originate from different years which could also affect extrapolation results.
The *Sentinella* study (chapter 11) and the study on healthcare costs (chapter 12) also provided estimates of consultations due to AG at primary care level: the *Sentinella* study estimates (174'610 first consultations due to AG) were lower while the estimates from the assessment of healthcare costs (311'192–707'255 patients consulting due to AG or campylobacteriosis) were comparable to the "downward calculation" presen-

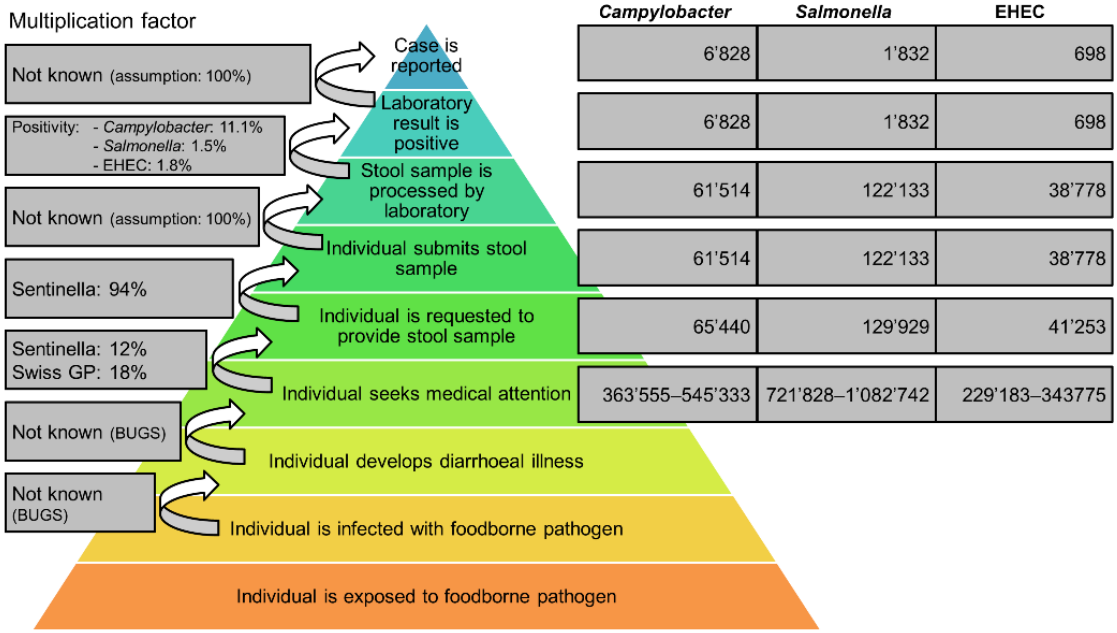

Figure 14.1: Estimation of case numbers at different levels of the burden of illness pyramid for foodborne infections. Note that numbers across pathogens are not cumulative and do not reflect estimated numbers for this specific pathogen. Estimated multiplication factors are from different years
Positivity: see studies on positivity rates, chapters 6 and 8; Sentinella: see study within the Swiss Sentinel Surveillance Network, chapter 11; Swiss GP: see study among Swiss GPs, chapter 10; BUGS: see study on burden of gastroenteritis in Switzerland, chapter 13

ted in this chapter (Figure 14.1). It has to be considered that the latter two calculations were based on the same information sources (the health-care cost estimations using mostly preliminary results of the same studies as the calculation in this chapter). Additionally, those two calculations started from the top of the pyramid and calculated downwards while the *Sentinella* extrapolation relied on consultation frequencies at primary care level in Switzerland considering the proportion of consultations by Sentinella-physicians and the proportion thereof which is due to AG. All calculations are based on several assumptions making it difficult to assess which of them is most reliable and closest to reality. Furthermore, estimates were calculated for different calendar years. Nevertheless, all estimates point at a substantial burden due to AG at the primary care level in Switzerland which is partly preventable. Furthermore, the estimates are indicative of a large, yet unquantified burden to the Swiss economy and society.

14.2 The National Notification System for Infectious Diseases: a critical reflection

14.2.1 Does the NNSID fulfil its purpose?

When judging about the performance of a system, its intended purpose has to be taken into account. The purpose of the NNSID is the early detection and surveillance of communicable diseases [Die Bundesversammlung der Schweizerischen Eidgenossenschaft, 2012b]. This should support to prevent epidemics and further spread of those diseases, and to evaluate if control measures were effective. Critique was raised that data from the Swiss NNSID do not allow distinguishing between changes in disease frequency at population level and changes in other factors influencing case numbers [Bundesamt für Gesundheit and Nationales Referenzzentrum für enteropathogene Bakterien und Listerien, 2015; Schmutz *et al.*, 2013, 2016]. The same was reported for surveillance systems of other countries [Henao *et al.*, 2015; Janiec *et al.*, 2012; Lake *et al.*, 2010]. In the subsequent paragraphs, the NNSID's performance is assessed, roughly following the handbook of the European Centre for Disease Prevention and Control (ECDC) for surveillance system evaluation (chapter 3) [European Centre for Disease Prevention and Control, 2014]. These guidelines were chosen as they were recent (from 2014) and developed for the European Union (EU) with the aim to improve comparability of country-specific data collected within The European Surveillance Sys-

tem (TESSy). Switzerland does not belong to the EU and hence, does not participate in TESSy but it still reports case numbers for selected diseases to ECDC. Therefore, it would be ideal if the Swiss surveillance system was comparable to those of the EU countries considering the geographic proximity and the (relative) similarity of health systems. Still, guidelines of the Centers for Disease Control and Prevention (CDC) for evaluating public health surveillance systems (task D) [German *et al.*, 2001] were considered in addition to complement the assessment.

External completeness – Under-notification

According to the ECDC handbook, external completeness refers to the level of under-notification, hence, the cases correctly diagnosed by not reported to the surveillance system (note, however, that the term "under-reporting" is used in the handbook) [European Centre for Disease Prevention and Control, 2014]. In contrast, sensitivity of a surveillance system includes under-notification, under-diagnosis and under-ascertainment* of cases. For a discussion on the sensitivity of the Swiss surveillance system, please see the next section.

Both, the actual external completeness and the target level of external completeness depend on the pathogen studied. Diseases for which a high level of external completeness is important include highly contagious diseases, diseases with high case-fatality, rare diseases, (re-)emerging diseases, new strains, and diseases for which eradication or control is envisaged [European Centre for Disease Prevention and Control, 2014]. For other diseases in the surveillance system, lower levels of external completeness may be acceptable. Acceptable levels for external completeness of notifications should be defined before conducting a formal evaluation.

One way to assess external completeness is comparison of notifications received from physicians and from laboratories for diseases for which both reports are required. Von Stokar *et al.* [2012] looked at five diseases in Switzerland (invasive meningococcal disease, measles, gonorrhoea, tick-borne encephalitis and hepatitis B) and reported that between 2.8% and 21% of cases missed physician reports in 2008 or 2009, depending on the disease. Analysis of Swiss hepatitis A notification data revealed that a report on clinical findings was missing for 14% of cases between 1988 and 2016 (chapter 5). Data for this kind of assessment is readily available at the FOPH and hence, analysis should be conducted on a routine basis for all notifiable diseases.

Another method for assessing external completeness is comparison of

surveillance data with databases of data providers (i.e. laboratories and physicians) or with medical records. For our positivity studies we received data from diagnostic laboratories directly and compared it to case numbers reported by the corresponding diagnostic laboratories according to the NNSID database. Comparison of positive laboratory reports received from the laboratories directly and cases recorded in the NNSID for EHEC revealed that numbers differed by up to 21% annually for the time period from 2007 to 2016 (chapter 8).
Capture-recapture studies are a third way of assessing external completeness. However, appropriate data sources are limited to compare the NNSID data with. Only the subset of hospitalised cases reported in the NNSID could be compared with hospital statistics. Mortality statistics are not very suitable either as (fortunately) the majority of cases reported to the infectious disease surveillance system will not be fatal. *Sentinella* seems suitable in the first instance. However, case definitions often differ between the NNSID and *Sentinella* – if the same diseases are surveyed at all – and notifications lack a common identifier. Hence, the proportion of patients captured by both systems cannot easily be quantified. However, other countries have evaluated reporting completeness using capture-recapture studies. For example, in Wallonia, Belgium, a completeness rate of 65% for notification of Legionnaires' disease was found [Jacquinet *et al.*, 2015]. A similar rate of 60% was found for Creutzfeldt-Jakob disease (CJD) in Belgium [Litzroth *et al.*, 2015]. It was concluded that the surveillance system was able to detect changes in CJD incidence. Low reporting completeness was found in the Netherlands for pertussis-related hospitalisations and deaths [Van der Maas *et al.*, 2017]. Similar to Switzerland, cases must be reported to the Dutch notification system upon laboratory-confirmation. Hence, hospitalisations occurring after laboratory-confirmation may be missed. Despite limitations, capture-recapture studies should be considered to formally assess external completeness of the NNSID.

Sensitivity and specificity

The ECDC handbook defines sensitivity as the "proportion of the actual cases that were reported to the system"; Specificity, on the other hand, is the "proportion of non-cases identified as such and not reported to the system" [European Centre for Disease Prevention and Control, 2014]. Therefore, sensitivity and specificity also depend on the disease considered and are not universal to a surveillance system. Reconstruction of the burden of illness pyramid from consultation at primary care to

disease notification using the example of foodborne infections has shown that underreporting* is substantial in Switzerland (subsection 14.1.6), and hence, sensitivity of the NNSID is low. However, diagnostic tests used have changed: the increasing use of multiplex PCR panels – for gastrointestinal infections but also for other diseases – increases test numbers and case detections and, hence, sensitivity (chapter 7). On the other hand, rare diseases may not be at the forefront of physicians minds and hence, may not be considered at all or diagnosed with a substantial delay (chapter 5), again at the cost of sensitivity. Considering that many observations are notifiable upon positive laboratory diagnosis and that diagnostic methods are of high quality in Switzerland, both, specificity and positive predictive value (PPV) of the surveillance system are assumed to be high.

Another aspect affecting sensitivity of the surveillance system is access to healthcare. Access to healthcare is assumed high considering that health insurance is compulsory in Switzerland and that 78% of the population reported having consulted a physician within the last 12 months according to the Swiss health survey in 2012 [Bundesamt für Statistik, 2017b]. The BUGS study (chapter 13) will provide further information for assessing sensitivity of the NNSID by looking at patients' help seeking behaviour and quantifying under-ascertainment.

The CDC guidelines define a second approach to measure sensitivity of a surveillance system apart from underreporting: the "ability to detect outbreaks, including to monitor changes in the number of cases over time" [German *et al.*, 2001].

Sensitivity to detect outbreaks or changes in disease frequency can still be good even if underestimation is substantial as long as factors affecting underestimation remain constant. A change in one or several of those factors can either affect sensitivity or the PPV of the system. The PPV of an outbreak or "alert" could be considered instead of looking at the PPV of an individual case. However, no proportion of correct alerts can be estimated in the absence of knowing the number of "true" changes in disease occurrence (or outbreaks). However, experiences with EHEC (chapters 7 and 8), *Legionella* [Fischer *et al.*, 2017; Gysin, 2018] and *Chlamydia trachomatis* [Schmutz *et al.*, 2013] – all showing an increase in notified cases which does not necessarily represent an increase in disease frequency at population level – point at a rather low PPV of the NNSID.

External validity

External validity is assessed by comparing data from the surveillance system with data from another system, ideally from a source considered the "gold standard". A common method used is record linkage using different data sources, e.g. medical records, or death certificates. A study comparing measles case notifications concluded that the NNSID had a lower sensitivity but a higher specificity compared to *Sentinella* in terms of case detection [Richard *et al.*, 2008]. However, the NNSID's performance was better for identifying outbreaks.
Hospital and mortality statistics are another source for comparison of case numbers. However, different case definitions hamper easy comparisons. Furthermore, the three systems (NNSID, hospital and mortality statistics) collect information at different time points during the course of disease additionally complicating comparability. Comparison of data on hepatitis A from the three aforementioned systems has shown that case numbers from hospital statistics are comparable with the number of cases reported to be hospitalised according to the NNSID – but only when excluding secondary diagnoses from hospital statistics (chapter 5). More deaths due to hepatitis A were recorded in mortality statistics than in the NNSID.
Studies assessing external validity of data collected through the NNSID are recommended.

Usefulness of the surveillance system

A system can be considered useful if it fulfils its purpose and results are used for public health action. However, it can also be useful if it generates evidence for action beyond its intended purpose [German *et al.*, 2001]. Data from Swiss surveillance systems (NNSID and *Sentinella*) have been used for several studies presented in this thesis (chapters 4, 5, 6, 8, 9, and 12). They stimulated research [Bless *et al.*, 2014; Schmutz *et al.*, 2013], and served as basis for research articles [Richard *et al.*, 2017, 2018; Schuler *et al.*, 2014] as well as for detection of outbreaks [Delaporte *et al.*, 2011; Knoblauch *et al.*, 2015; Stephan *et al.*, 2015]. Furthermore, notification data influenced policy. For example, the Swiss national programme against human immunodeficiency virus (HIV) expanded its scope to include also other sexually transmitted infections due to the increase in *Chlamydia trachomatis* infections, syphilis and gonorrhoea [Federal Office of Public Health, 2010]. Finally, data from the NNSID and from *Sentinella*, published in the "BAG Bulletin", are regularly taken up by public media (Appendix, section F.2). These are all

factors indicative of the system's usefulness. Similarly, increasing *Campylobacter* case numbers lead to the establishment of the so-called "Campylobacter-Plattform" in 2008, a multi-stakeholder platform consisting of representatives from research, from cantonal and federal authorities, and from the poultry industry [Federal Veterinary Office, 2008], aiming at reducing *Campylobacter* case numbers in Switzerland. However, despite continuous high levels of *Campylobacter* case notifications, the platform was abolished in 2016 [Bundesamt für Lebensmittelsicherheit und Veterinärwesen, 2016].
Factors defining usefulness of a system vary between users [European Centre for Disease Prevention and Control, 2014]. Therefore, a list of intended and actual users of the systems would be required to formally assess the NNSID's and *Sentinella*'s usefulness.

Simplicity

The process of notification is shown in appendix B. Given the administrative structure of Switzerland, the reporting entities have to report to one of 26 cantonal health authorities, and selected reports must be sent to the federal health authority. Furthermore, the NNSID still relies on paper-based notification forms transmitted to the cantonal physician and/or the FOPH by postal mail or fax (or telephone in case of observations notifiable within 2 hours). Notifications received by the cantonal authorities are forwarded to the federal authorities again by postal mail or fax. The notification process could significantly be modernised and simplified if notifications could be filled in directly in an electronic system. This would then automatically and efficiently transmit the notification to the appropriate authorities (federal and concerned cantonal authorities). Also Germany still uses paper-based notification for physicians to report to local health authorities [Robert Koch-Institut, 2017]. In contrast to Switzerland, however, notification forms are entered into an electronic system at the local level and forwarded to the state and federal health departments electronically.
Information requested for reports on laboratory findings are mostly technical (such as type of specimen and diagnostic method) and therefore routinely collected, known and easily recordable at the laboratory. However, reports on clinical findings also include information which may not be known by physicians if they did not explicitly ask for during the consultation (e.g. exposure history; see also "Data quality" in this subsection, 14.2.1, for a discussion of resulting consequences).
Furthermore, the Swiss system is rather complex when it comes to inter-

vening in public health matters such as contact tracing and prophylaxis among contacts: responsibilities are dependent on the circumstances. The cantonal authority (cantonal physician) is responsible for case management of a case within his own canton [Der Schweizerische Bundesrat, 2015b]. Cantonal authorities may collaborate if several cantons are involved (e.g. in case of small clusters or if the patient was travelling), but the federal authority may also take over the responsibility. Finally, the federal authority (the FOPH) is responsible if the case was travelling abroad, hence, for communication with international authorities.

Flexibility – responsiveness to changing needs

Following reports of numerous countries of autochthonous transmission of Zika virus disease and clusters of microcephaly and other neurologic disorders in Brazil, the World Health Organization (WHO) declared a Public Health Emergency of International Concern on 1st February 2016 [World Health Organization, 2016]. On 5th March 2016, a revised DHA Ordinance entered into force declaring Zika virus a notifiable disease in Switzerland [Das Eidgenössische Departement des Innern, 2015b]. Similarly, notification of hepatitis E was introduced on 1st January 2018 in response to the increasing awareness that hepatitis E is endemic in Europe and not only travel-associated [Bundesamt für Gesundheit, 2017a; Das Eidgenössische Departement des Innern, 2015a]. Hence, the NNSID is able to quickly respond to changing needs – at least in case of emerging diseases.

The obligation to reconsider the list of notifiable observations and the content of the notifications at least once a year is stipulated in the "DHA Ordinance on the reporting of observations on human communicable diseases" [Das Eidgenössische Departement des Innern, 2015a]. Content (or at least wording) of notification forms was changed quite frequently for hepatitis A and *Legionella* (chapter 5; Gysin [2018]) – and likely also for other diseases. For example, the clinical sign of jaundice was prompted in at least three different ways: it was listed as one of the signs and symptoms under the heading "clinical signs" from 1988–1990, it could be checked as "reason for laboratory testing" from 1991–1998, and was listed again under "manifestation" or "clinical manifestation" from 1999 onwards. Whether this kind of flexibility of the system is favourable is, however, questionable considering that such changes can make interpretation of long-term trends difficult. Case definitions were also changed repeatedly. For example, in 2018 the case definition for *Campylobacter* was adapted to include also cases with laboratory-confirmation using

culture-independent methods as confirmed cases (personal communication). Case definitions used by ECDC are also regularly updated; also at the European level, the case definition for *Campylobacter* newly includes laboratory-confirmed cases using nucleic acid detection methods as confirmed cases in the 2018 update [European Commission, 2018].
Implementation of electronic reporting for laboratories was planned already for 2012/13 [von Stokar *et al.*, 2012] but is still pending (as of August 2018).
In conclusion, the NNSID is responsive to changing epidemiological needs. However, when it comes to adapting to technological advances, the NNSID's flexibility is limited.

Data quality

A substantial proportion of "unknown" or "not specified" responses to certain variables has been noted for different notifiable diseases, especially regarding exposure information and risk factors (chapter 5, Gysin [2018]). The assumed place of exposure was unknown or missing for 41% and 70% of acute and chronic hepatitis B cases, respectively and for 25% and 68% of acute and non-acute hepatitis C cases recorded in the NNSID [Richard *et al.*, 2017, 2018]. Poor completion of suspected country of exposure was also reported in Australia [Gibney *et al.*, 2017]. The study among Swiss GPs has further shown that taking the exposure history is not among the top priorities during a consultation for some physicians – at least for diarrhoeal diseases (section 10.2). This is likely also the case for other diseases which would explain the poor completion of exposure information by the physician on notification forms.
The physician is required to complete the form as soon as the criterion for notification is fulfilled [Das Eidgenössische Departement des Innern, 2015a]. Considering that this criterion for notification is often dependent on laboratory-confirmation of the disease, the physician knows that he is requested to complete the notification form only after the consultation. The physician may not routinely collect all information requested on the notification form, e.g. on exposure history, given that it is not required for case management. Hence, filling in the form after seeing the patient further contributes to incomplete information if no follow-up consultations are scheduled and not all information required was obtained and recorded during the initial consultation. Extra efforts would be required by the physician in order to be able to answer all questions on the notification form (e.g. "preventively" collecting the information needed even though the suspected case might not be confirmed); else, data quality is

at stake.
Moreover, considering the validity of data even if all information was obtained, it reflects one point in time but certain factors such as hospitalisation status could change. In this regard, also new diagnostic methods providing faster results could change the time point of completion of the notification form because the criterion for notification is fulfilled at a different point in time during the course of disease. This could influence content of the notification.
For HIV, influenza and *Legionella* the number of tests conducted had to be reported by diagnostic laboratories already before implementation of the new Epidemics Act in 2016. For example, for *Legionella* this information is required since 2006 [Gysin, 2018]. However, reporting is incomplete and has not been enforced. Sometimes even fewer tests than cases (positive tests) were recorded for *Legionella* [Gysin, 2018]. Knowledge gaps on laboratory routine procedures in testing make it difficult to evaluate data quality of reports on the "statistic of reports on laboratory findings" (i.e. the number of tests performed and the number of positive tests thereof) which are notifiable since 2016 (chapter 9).

Acceptability of the surveillance system

The interviews with Swiss GPs and laboratory experts (chapters 7 and 10) indicated that there are differences between them concerning acceptability of the surveillance system but they generally see the need for a notification system. On the other hand, they mentioned that they have to provide a lot of information for little return (e.g. statistics as reported in the bulletin of the FOPH, the "BAG-Bulletin"). Von Stokar *et al.* [2012] found that some physicians would wait notifying a case until they were reminded to report it by the cantonal physician (who sends reminders based on reports from laboratories). Diagnosing a notifiable disease is not everyday business for most physicians. Therefore, they might not have a routine procedure and might not be aware of all notifiable diseases. In contrast, in laboratories, reporting is frequently automated or there is at least a defined procedure for reporting.
On the other hand, physicians in an Australian study reported that they did not notify a case of *Campylobacter* because the laboratory would notify it anyway, they did not know the reason for not reporting, or they did not consider the notification important [Grills *et al.*, 2010]. Hence, increasing the physicians' awareness that every single notification is important and that the information provided by physicians is complementary to the laboratory notification are key to improve acceptability and

compliance.
Another reason for higher acceptability and compliance by laboratories compared to physicians could be that notification forms for laboratories require fewer information and information which is easier to obtain (e.g. age and sex of the patient) compared to physician notifications (e.g. risk factors and exposure).
Acceptability of a system is subjective and its proper assessment would require a separate study. Nevertheless, based on the indications discussed above, it can be concluded that the NNSID is accepted by Swiss system actors. Despite, its acceptance could be improved by providing feedback (e.g. in the form of more frequent, timely and targeted analyses of notification data; more than "simple" tables with case numbers in the weekly "BAG Bulletin") and increasing awareness of the importance of every single notification. In line, physicians in Australia reported that improved feedback beyond "automatically generated summary reports" would increase their compliance to notify [Grills *et al.*, 2010].

Representativeness

Cases captured by the NNSID are unlikely to be representative of the cases occurring in the general population in Switzerland – at least in the case of foodborne diseases. The study among Swiss GPs and the *Sentinella* study (chapters 10 and 11) have shown that, for example, patients reporting recent travel are much more likely to be tested in case of AG and hence, are more likely to be captured by the system. Furthermore, patients with severe disease, poor general health state or comorbidities are more likely to seek care and to be tested. Physicians' (mis-)perception of risk factors can additionally influence their approach to diagnosis as well as their awareness of a certain disease influencing case-ascertainment.
Representativeness is likely to vary between diseases. The factor of underestimation is probably lower for highly virulent pathogens and their representativeness in the NNSID is higher. In contrast, the case ascertainment bias is presumably higher for pathogens frequently causing asymptomatic or mild infections.

Timeliness of reporting and outbreak detection

Timeliness is partly inherent to the system set-up (e.g. defined time frame for reporting as stipulated in the Epidemics Act) and partly dependent on the persons and processes involved. Notification is required

within 2 or 24 hours or 7 days, depending on the pathogen [Das Eidgenössische Departement des Innern, 2015a]. Furthermore, help seeking behaviour of patients, diagnostic approaches of the physicians, specimen collection and transportation, laboratory methods used by laboratories, compliance with the reporting requirements and data processing at the cantonal and federal authorities are influencing timeliness of reporting. New diagnostic methods such as multiplex PCR panels replacing traditional culture-based methods for stool testing reduce the time to diagnosis. However, patients with AG do not immediately seek help and physicians frequently follow a "wait & see" approach (section 10.1 and chapter 11), both delaying case detection. Richard *et al.* [2008] reported that timeliness of case detection was better in *Sentinella* than in the NNSID but it should be improved in both systems.
Another aspect of the surveillance system's timeliness is the time to detection of an "event" (a potential cluster or outbreak). This is dependent on the processing of the data received, on data analyses and on information sources used. In order to increase the chance to react timely in case of a foodborne outbreak, the time frame for notification was reduced to 24 hours for most foodborne pathogens in Switzerland [Das Eidgenössische Departement des Innern, 2015a]. However, the timeliness of the NNSID could certainly be further improved by introducing electronic reporting, allowing for an almost simultaneous information of cantonal and federal authorities and minimising time needed for data entry. Additionally, automated outbreak detection tools could be applied for rapid identification of clusters in case reports. First positive experiences are reported from Germany where such a system was implemented in 2013 [Salmon *et al.*, 2016].

Stability

Reliability and availability of the surveillance system itself (not the data collected within the system) are key factors of stability according to the CDC guidelines [German *et al.*, 2001]. The studies conducted as part of this thesis do not assess stability of the NNSID; however, no events have been noted pointing at a lack of stability. Yet, the system's stability could potentially still be improved, e.g. by implementing electronic notification, considering that data processing at the cantonal and federal authorities is mostly manual and hence, dependent on availability of workforce.

Conclusions on the system's performance

This rough evaluation of the Swiss surveillance system showed that the NNSID is a useful, well accepted and stable system. Sensitivity of the system at case-level is low but sensitivity of outbreak detection still seems acceptable. The system is able to adapt to changing epidemiological needs but lacks flexibility to accommodate technical improvements such as electronic reporting. Introducing electronic reporting could increase timeliness of the system as well as simplicity and data quality. Combining and comparing notification data with data collected through other systems (e.g. hospital and mortality statistics) is recommended to evaluate the data in terms of external completeness and validity, and to further increase data use.
In summary, the NNSID does fulfil its purpose but should still be improved in various aspects. It has to be noted that this is not a formal evaluation of the Swiss surveillance system. A detailed evaluation following all steps described in the ECDC handbook [European Centre for Disease Prevention and Control, 2014] goes beyond the scope of this thesis but is strongly recommended. Furthermore, costs and cost effectiveness of disease surveillance were not considered but should be included in a future evaluation.

14.2.2 Does the purpose of the NNSID match our expectations?

A more refined definition of the NNSID's purpose in combination with targeted research systematically evaluating all system characteristics is needed to further assess the system's performance.
Critique about the NNSID which was raised may not only signal failures of the system but could also be attributed to high or wrong expectations towards the system. A surveillance system is not designed to provide answers to all epidemiological research questions. Hence it cannot be expected that it replaces epidemiological research. As discussed above (subsection 14.2.1), simplicity is a key factor of a surveillance system. Therefore, keeping the public health surveillance system simple, flexible, acceptable, timely and stable and complementing findings by separate research studies is likely more efficient and appropriate than overloading the surveillance system with complementary research questions.
In that sense, it might be worthwhile considering alterations to the existing NNSID. For example, the burden of notification could be reduced for physicians by decreasing the amount of data requested, especially

for data with poor quality (e.g. exposure information). Complementary research could be mandated using the resources saved to gather this information, when needed. This approach would have the advantage that studies could be targeted to specific research questions circumventing limitations inherent to surveillance systems such as case ascertainment bias.
Additional possibilities to improve the NNSID are discussed in the following subsection.

14.2.3 How could the NNSID be improved?

An evaluation of the NNSID was conducted in 2011 based on a mandate from the FOPH, as referred to already before [von Stokar *et al.*, 2012]. The evaluation report concluded that the NNSID is a well functioning and accepted system. Nevertheless, several recommendations to improve the NNSID were given, mainly in terms of compliance and quality, some of which are listed below:

- Regularly assess compliance of reporting taking into account other information sources such as SwissDRG and medical statistics of hospitals
- Simplify process of reporting by merging initial and complementary report to improve compliance
- Implement an electronic notification system (which can ideally be linked to practice-, hospital-, and laboratory-software information systems) to improve compliance
- Improve knowledge about the NNSID among those required to notify (e.g. on the selection of notifiable observations, time limit for reporting and process of reporting)
- Actively inform about functionality and benefit of the NNSID through different information channels
- Actively communicate changes in the NNSID to those concerned
- Specify contact persons who are readily available in case of questions about technicalities of the NNSID
- Involve cantonal physicians to inform about the NNSID as they are in close(r) contact with physicians
- Involve professional associations and stakeholders to act as role models and implement clear processes within institutions (hospitals, laboratories) defining responsibilities

Optimising communication and increasing compliance

Some of the recommendations by von Stokar *et al.* [2012] have been addressed. For example, initial and complementary reports have been replaced by one notification form (report on clinical findings) for all but four notifiable observations with the implementation of the new Epidemics Act in 2016.
The benefit and importance of the NNSID was discussed controversially among Swiss GPs participating in the qualitative study (section 10.2). Both, laboratory experts and GPs from the stakeholder consultation (chapters 7 and 10) mentioned the difficulty to identify and contact responsible persons at the FOPH. Hence, the FOPH should still try to improve communication and specify personal contact partner(s). Furthermore, the contacts established during the laboratory visits should be maintained or even strengthened, and expanded to include more laboratories, generating a community of practice of actors of the Swiss surveillance system. Regular exchanges should be organised, e.g. as monthly telephone conferences complemented by an annual meeting. If this approach proves successful, a similar network and exchange with physicians should be considered.
The suggestion by von Stokar *et al.* [2012] to involve cantonal physicians as mediators between physicians and the FOPH seems promising: GPs participating in the qualitative study mentioned closer contact with cantonal physicians than with the FOPH and perception of cantonal authorities was generally more positive than perception of the FOPH (chapter 10). It has to be noted, however, that the recommendations of von Stokar *et al.* [2012] and most of the study findings originate from times before introduction of the new Epidemics Act.
With the implementation of the new Epidemics Act, the FOPH released a "manual on notifiable diseases" [Bundesamt für Gesundheit, 2018a] as well as a poster with an overview of all notifiable diseases and pathogens [Bundesamt für Gesundheit, 2018]. The latter was displayed in several laboratories, as noted during the visits (chapter 7). This suggests that the poster was considered attractive and acts as a good tool to increase visibility of the notification system. Weekly reporting of influenza during the influenza season was mentioned several times by Swiss GPs and considered useful (unpublished observation). Communication of surveillance data on influenza should, therefore, be used as a role model also for other diseases considering that this reporting is well-known and perceived positive by both, physicians and public media.
Findings from the qualitative study among Swiss GPs (section 10.2)

suggest that events for continuous education and Swiss medical journals (e.g. *Swiss Medical Weekly* or *Primary Care*) are suitable tools to reach a high proportion of GPs in Switzerland. Therefore, these communication channels should be used more actively by the FOPH to inform about issues related to disease surveillance, including changes in the notification system but also to communicate results from analyses of notification data. Publishing articles in existing local medical journals is suggested rather than creating an own journal or newsletter considering that physicians reported being overwhelmed by the flood of information. In addition, active participation of staff from the FOPH at conferences and events for continuous education should be increased to foster direct personal contact between system actors.

Content of notification forms

Reliability and usefulness of risk factor and exposure information (personal risk factors, exposure risks, potential source and place of exposure) collected in surveillance systems must be questioned: first, the information is often incomplete (chapter 5; Gibney *et al.* [2017]; Richard *et al.* [2017, 2018]). Second, the information relies on proper and systematic anamnesis by the physician completing the form. However, the study among Swiss GPs indicated that anamnesis on risk factors is not the most important part of a consultation for some physicians, at least concerning food anamnesis in case of diarrhoeal diseases (section 10.2). Furthermore, the physicians' correct knowledge on incubation period, potential sources of exposure and risk factors is crucial for accurate anamnesis and completion of notification forms but must be questioned (section 10.2). Neave *et al.* [2016] evaluated notification forms from Australia, New Zealand, the UK and Canada for selected diseases and made recommendations about which variables should be collected on notification forms to inform public health policy in the context of imported infections. They recommended the collection of at least the following variables: "*Travel-related information:* recent international travel; reason for travel; dates of entry to and departure from the countries visited during the disease incubation period; and vaccination details. *Demographic information:* traveller's and parent's country of birth; country of usual residence; length of time resident in current country; postcode. There was no agreement about whether ethnicity should be collected. *Disease severity information:* hospitalisation; death."
Following these recommendations, completely refraining from obtaining information on possible exposure may not be appropriate. However,

every variable of the notification form should be evaluated, carefully considering validity, reliability and importance. Moreover, wording of questions should be cautiously and deliberately chosen. For example, there is a slight, but potentially important difference in asking "in which country has the patient been during the incubation period" (objective information) and "in which country has the patient likely been infected?" (information with some subjective component, including interpretation of the physician). Subtle changes in wording of notification forms can influence responses, but the extent can hardly be quantified (chapter 5). Therefore, it is recommended to refrain from those changes if ever possible. Collecting objective information (e.g. where has the person been) rather than partly subjective information (e.g. where has the person been exposed) is recommended to reduce heterogeneity in surveillance data and increase reliability.

Electronic notification

Electronic notification has not been implemented in the NNSID yet, but is still planned to be implemented in the future. Implementing electronic notification can improve the NNSID in several ways: first, it is likely to increase compliance by reducing the time needed for notification (less paper handling; quicker search for appropriate form). Second, quality of the data could be improved (e.g. automatically highlighting fields with missing or erroneous information, no data entry of paper forms). Third, under-notification could be reduced if the electronic reporting system is linked to the practice-, hospital-, or laboratory information system and generates automatic reminders that a certain diagnosis is notifiable. Fourth, timeliness could be improved by simplifying the reporting process. The *Sentinella* network offers both, electronic and paper-based notification. Electronic notification was chosen by more than half of participating physicians (chapter 11). Currently, the FOPH considers switching to electronic notification only in the *Sentinella* system and asked participating physicians still reporting on paper forms about their willingness to switch [Sentinella, 2017]. More than a third of respondents each were willing to switch immediately (26/70) or in case paper-notification is ceased (25/70). One fourth of respondents still preferred paper-based forms (18/70). For 14 of 70 respondents offering electronic notification only would be a reason to quit *Sentinella*. These experiences and results indicate that electronic notification would be well-accepted among the majority of Swiss physicians. Nevertheless, there is still a minority with a negative attitude towards electronic reporting. Proact-

ive information of physicians (and others required to report) will, hence, be very important when changing to electronic notification in other surveillance systems, e.g. the NNSID.
In the Netherlands, introduction of an electronic reporting system between the municipal and the national health services lead to improved timeliness and completeness of notifications despite reports from clinicians and laboratories were still sent using conventional phone, fax or e-mail to report to the municipal level [Ward *et al.*, 2005]. Similarly, Gibney *et al.* [2017] suggested that increasing case numbers seen in the Australian surveillance system are partly attributable to changing from manual notification of clinicians to automatic notification of laboratories.

Comprehensive *vs.* sentinel surveillance

During the evaluation of the NNSID it was also discussed if the nationally compulsory notifications could be replaced by a sentinel surveillance system [von Stokar *et al.*, 2012]. It was shown that the NNSID is less sensitive than *Sentinella* to detect cases of measles, despite the former relying on two information sources (physicians and laboratories) while the latter is exclusively supported by physicians [Richard *et al.*, 2008]. Nevertheless, the NNSID was more sensitive to detect outbreaks. Additionally, *Sentinella* lacked specificity and both systems showed weak timeliness. Considering that outbreak detection is one of the main purposes of disease surveillance, a comprehensive system such as the NNSID should not generally be replaced by sentinel surveillance.

Collection of summary statistics (denominator information)

Knowledge of denominator information such as the number of tests performed is important for interpretation of case numbers, as shown by our positivity studies (chapters 6 and 8; Schmutz *et al.* [2013]). Reporting of summary statistics for laboratories has been introduced more widely with the new Epidemics Act: Laboratories have to report the number of tests conducted for certain diseases once a year (chapter 9). Knowing this denominator would allow rough analyses similar to our positivity studies (chapters 6 and 8; Schmutz *et al.* [2013]). Repeated tests in the same individual cannot be considered when analysing those data in contrast to our positivity studies where individual-based information was collected. Experiences from the aforementioned studies suggest that interpretation of findings do not change considerably if repeated tests are not considered – at least when looking at trends. On the other hand, preliminary analysis of summary statistics from the first two years of

reporting has identified several limitations (chapter 9). One of those limitations – confirmatory ("reflex") testing – was not routinely applied by diagnostic laboratories for the pathogens considered in our positivity studies during the time periods studied. It is conceivable that systematic reflex testing does affect positivity considerably and hence, should not be ignored. In this case, collection of aggregated (*vs.* individual-based) data on test numbers would no longer suffice. Furthermore, validity and usefulness of data collected through current notification forms on "statistic of reports on laboratory findings" must be questioned (chapter 9).

14.3 The ideal case management for acute gastroenteritis from different perspectives

14.3.1 The patients' perspective: reducing illness duration and social impact

Laboratory-confirmed campylobacteriosis patients in Switzerland reported consulting a physician mainly due to severity, persistence or lack of perceived amelioration of signs and symptoms [Bless *et al.*, 2014; Suter, 2014]. The need for a medical certificate was spontaneously reported as a reason for consultation in 4% of cases only. However, this finding might be influenced by the fact that the study was conducted during the festive season. Furthermore, the need for a medical certificate may not be the primary reason for consultation in severely affected patients (such as laboratory-confirmed campylobacteriosis cases) while it might be a more prominent reason among moderately affected patients with AG. The expectations of the patients towards the physician have not been assessed in the aforementioned study. Swiss physicians reported that patients rather expect some sort of "action" (e.g. treatment or laboratory investigation) as opposed to what physicians called "watchful waiting" (chapter 10).

Generally, little is published about patients' expectations when consulting a physician due to AG. Both, patients' reported reason for consultation in the Swiss case-control study on campylobacteriosis [Bless *et al.*, 2014] and physicians' perception of patients' expectations (chapter 10), point at a reduction of illness duration, and measures mitigating signs and symptoms and therefore reducing suffering and social impact as the main expectations of patients consulting a physician due to AG. A study investigating antibiotic prescription in patients with acute diarrhoea vis-

iting emergency departments in the USA found that 91% of patients expected prescription of an antibiotic and/or another medication [Karras *et al.*, 2003]. A study among participants of the Swiss inflammatory bowel disease (IBD) national cohort revealed that individuals' most important expectations were good coordination between GPs and specialists, receiving information on adverse events of treatment, and easier drug treatments [Pittet *et al.*, 2018]. However, those expectations are likely different in IBD patients compared to AG patients considering the chronic nature of IBD. A study exploring reasons for attending an urgent care centre in England found that patients with a "minor illness" (as classified by a GP) mentioned quick access to care as a main reason for consulting the centre (as opposed to a GP) [Amiel *et al.*, 2014]. Furthermore, more than half of patients expected receiving prescription medication.
Patients' expectations towards the physician when consulting due to AG will be explored in detail in the framework of the BUGS study (chapter 13).

14.3.2 The physicians' perspective: reducing suffering and caring for the vulnerable

There are no Swiss guidelines on the management of acute diarrhoea. The Swiss Society for Gastroenterology refers to international guidelines [Schweizerische Gesellschaft für Gastroenterologie, 2018]. American guidelines for the management of acute diarrhoea in adults suggest initiation of stool diagnostics "in cases of dysentery, moderate-severe disease, and symptoms lasting >7 days" in line with common practice reported by Swiss physicians (chapter 10; Riddle *et al.* [2016]). In those cases, diagnosis serves to enable targeted treatment of the individual patient. Assessing aetiology is usually not considered in mild to moderate and recent cases as it hardly affects treatment for mainly two reasons: first, AG is usually self-limiting and hence, symptomatic treatment and/or dietary recommendations are generally sufficient (chapter 10). Second, physicians want to help the (suffering) patient immediately rather than in a few days when diagnostic results are available. In this perspective, the use of new multiplex PCR panels seems to have advantages over traditional culture by providing results in hours rather than days (once the stool sample arrived at the laboratory). Fast results provide the basis to adjust treatment based on the aetiology of disease. Ideally, this then helps to reduce both, suffering of the patient and empirical antibiotic therapy. The latter should be avoided in the light of antibiotic resist-

ances [Review on Antimicrobial Resistance, 2016].
The GP acts as the counterpart of the patient which is reflected in various aspects of his attitude towards diagnosis, treatment and perception of AG in general: as discussed above and in chapters 10, 11 and 14.1.3, the decision for or against stool diagnostics is mainly dependent on the patient's health status rather than on public health considerations. Similarly, the decision for or against prescription of antibiotics is based on the individuals' well-being rather than on the general aim to reduce antimicrobial use in the population (chapter 10; Review on Antimicrobial Resistance [2016]). This leads to pragmatic decisions and empiric therapy, and puts microbiological findings in the rear. A qualitative study among English GPs found that high patients' expectations for relief and lack of time during consultation to explain inappropriateness of antibiotics were barriers for appropriate antibiotic prescription in the general practice outpatient setting [Yates *et al.*, 2018]. Furthermore, a recent literature review concluded that the link between over-prescribing of antibiotics by physicians and the increase of antimicrobial resistance is neither immediate nor apparent to the physician while missed bacterial infections with potentially serious patient outcomes are clearly coupled [Krockow *et al.*, 2018].
When asked about the importance of diarrhoeal diseases, many GPs responded that diarrhoea is not a problem because it is self-limiting, easy to treat and generally not dangerous (chapter 10). They stated that AG is frequent, but harmless. Hence, GPs' reasoning suggests that they did not consider the public health aspect of diarrhoeal diseases or their economic impact in their response. Also when asked about the influence of costs on their decision for or against stool diagnostics, GPs' answers were patient-focused (testing only if it is to the benefit of the patient to reduce costs for the individual) rather than population-oriented (testing for knowing the aetiology and typing to foster outbreak detection and to plan targeted interventions) (chapter 10). Assessing potential exposure is not a priority for some physicians (chapter 10). Similarly, McNulty *et al.* [2014] reported that occupational risks and contact with farm animals were frequently only recorded by physicians if spontaneously reported by the patient. Furthermore, a study analysing data from a listeriosis outbreak investigation concluded that the physicians' food history taking appeared unstructured [Kiefer *et al.*, 2016]. All above-mentioned factors suggest that also physicians are mainly interested in AG (the syndrome, as it presents as an illness/disease) as opposed to foodborne disease* (with a focus on the transmission pathway).
Apart from reducing suffering of the patient, one of the physicians' main

concerns is to identify vulnerable patients and patients at risk of complications and sequelae such as infants, elderly people and patients with co-morbidities (chapter 10). Public health considerations seem to play a minor role. In line, aetiological diagnosis is not generally recommended [Riddle *et al.*, 2016]. Furthermore, counselling on preventive measures is only recommended for individuals at high risk of complications and for travellers [Riddle *et al.*, 2016]. This recommendation seems questionable as contact with a person with acute diarrhoea was the only preventable risk factor identified in a French study [Arena *et al.*, 2014].

14.3.3 The public health or epidemiologists' perspective: identifying sources and outbreaks and preventing spread of disease

From a public health perspective, investigating the aetiology of a disease is central. In the case of AG, the aetiology should be assessed if there is a high risk of human-to-human transmission and during outbreaks [Riddle *et al.*, 2016]. Knowing the aetiology is key to identify outbreaks, to check if clustered cases are indeed linked to each other, to link outbreak cases to suspected sources and/or to implement targeted interventions. Therefore, the public health specialist concerned with prevention and control of outbreaks is rather interested in foodborne disease (the aetiological perspective) than in AG (the symptomatic perspective).
In terms of diagnostic methods, culture or a combination of culture and culture-independent methods is preferred over culture-independent methods alone from a public health point of view [Macfarlane-Smith *et al.*, 2018; Riddle *et al.*, 2016]. Culture-based methods are crucial to obtain isolates which are important for identifying clustered cases and potential sources through typing. Shea *et al.* [2017] argued that isolates are the "most effective tool" for maintaining and improving food safety. In contrast, in the hospital setting, the use of multiplex gastrointestinal (GI) panels could help infection control by quickly identifying patients for which isolation (in the sense of quarantine) is indicated. A study from the USA showed that among 158 patients with a negative test for *C. difficile* and/or rotavirus using conventional methods, about a fifth was positive for another GI pathogen using the FilmArray® Gastrointestinal (GI) Panel [Rand *et al.*, 2015]. Among those, 60% were not isolated appropriately. On the other hand, isolation could have been suspended for 25 patients testing negative with the panel. Also, culture-independent methods help reducing the use of antibiotics as well as the length of hospitalisation, and are, therefore, preferred from an economic point of view

[Beal *et al.*, 2018]. For laboratories, using culture-independent methods such as multiplex PCR panels is financially attractive as well as already mentioned before – even when followed by reflex testing in case of PCR-positive results [Shea *et al.*, 2017; Van Lint *et al.*, 2016]. In conclusion, from a public health perspective, there are factors favouring culture-dependent methods and factors favouring culture-independent methods. Screening samples with culture-independent methods followed by isolation/culture-confirmation in case of positive screening results seems a viable compromise. Nevertheless, the prolonged time delay from taking the sample to starting bacterial culture must be taken into consideration when choosing this approach [Shea *et al.*, 2017]. In the future, next-generation sequencing (NGS) could be an alternative diagnostic approach combining advantages of PCR (fast results) and culture-based methods (allowing epidemiological investigations, e.g. transmission dynamics) [Gardy and Loman, 2018]. Gardy and Loman [2018] even suggested that NGS could be used as a basis for a global surveillance system given that the technology becomes affordable (both, in terms of money and resources needed) and data is made available worldwide.
In Switzerland, laboratories mostly operate in the private sector. Hence, the decision which diagnostic methods to apply is with the laboratories themselves. Nevertheless, federal authorities could issue recommendations and guidelines. Furthermore, on a political level, testing procedures can be influenced by adapting the official tariff lists for reimbursement of costs by the compulsory health insurance. The potential impact of such changes on laboratory diagnostics has been described using the example of *Aeromonas* spp. [Tritten *et al.*, 2014].
Aetiological assessment and susceptibility testing are highly recommended given the increasing problem of antimicrobial resistance and global efforts to reduce antibiotic prescription [Review on Antimicrobial Resistance, 2016]. Similarly, the Strategy on Antibiotic Resistance Switzerland (StAR) aims at using antibiotics only in case of a proven bacterial infection without alternative treatment options [Der Schweizerische Bundesrat, 2015a]. The review on antimicrobial resistance highlighted the need for rapid, low-cost point-of-care diagnostics [Review on Antimicrobial Resistance, 2016]. Furthermore, they suggested that "high-income countries should make it mandatory that by 2020 the prescription of antibiotics will need to be informed by data and testing technology wherever it is available". Multiplex PCR panels provide faster results than traditional culture techniques. However, they are neither low-cost nor point-of-care diagnostics. Furthermore, they do not allow antimicrobial susceptibility testing. Hence, other diagnostic tools are most likely needed

to tackle the increasing problem of antimicrobial resistance. StAR also mentions the need to develop new laboratory tests which are inexpensive, provide rapid results and have "a strong practical emphasis" [Der Schweizerische Bundesrat, 2015a]. "Competent learned societies, the reference laboratories and industry" are responsible for the development and implementation of these new tools according to the Swiss strategy. Independently, financial responsibility needs to be clarified: can the patient be obliged to pay for diagnostics if diagnostics are performed for the sake of population health – without immediate benefit for the individual? Compliance of Swiss GPs in following such recommendations of universal testing must be doubted given their patient-centred view and their perceived unimportance of microbiological results for the majority of individuals.

Knowing the aetiology of AG is not only important to identify outbreaks, to adjust control measures (e.g. patient isolation) and to reduce antimicrobial prescription but also to improve population health at large by implementing targeted interventions for prevention. For example, it is of utmost importance to know if the majority of AG is caused by bacteria (the most common ones being zoonotic agents) or by viruses (mostly with the human as main or sole reservoir). Similarly, the estimated proportion of foodborne origin is highly dependent on the pathogen (Table 1.1; [Hald *et al.*, 2016; Havelaar *et al.*, 2015]). For example, humans are the only known reservoir for norovirus. Its transmission occurs mainly from person-to-person or via contaminated food or water (the food and water being contaminated by infected individuals) [Hall and Lopman, 2015]. Outbreaks are very common, especially in places where many people convene, such as hospitals, nursery homes, schools, cruise ships, restaurants and hotels. Prevention and control, therefore, relies on proper hygiene including hand hygiene, disinfection of the environment and patient isolation [Hall and Lopman, 2015]. In contrast, campylobacteriosis cases are mostly sporadic and frequently linked to contaminated food (mostly meat, contamination originating from the infected animal or spread during the slaughtering process) or infected animals [Mahon and Patrick, 2015]. Direct transmission from infected humans is considered rare. Consequently, prevention starts at controlling contamination at animal level, throughout the food chain ("from farm to fork") and ends at the consumer level with campaigns on kitchen hygiene. In summary, while some prevention efforts (e.g. general hygiene interventions) might help mitigating the risk of infection with several foodborne or gastrointestinal pathogens for humans, others are pathogen-specific (e.g. mandatory freezing of poultry-liver for retail to reduce

Campylobacter) and are, therefore, relying on aetiological assessment.

15 Conclusions

The burden of illness pyramid for foodborne infections was investigated using different research approaches. These have shown that the burden of AG in Switzerland is considerable. Many cases seen at primary care level are mild or moderate and can easily be managed by GPs. However, these cases still cause a considerable burden due to their frequency. In line, healthcare costs of an individual mild case of AG may be low, but the sum is still noteworthy and underestimated. Furthermore, even mild cases result in work loss which could not be quantified within the scope of this research but must be substantial. Cases seen in the notification system do not represent a random selection of patients with AG considering the rather sparing use of stool diagnostics. Hence, the NNSID overrepresents severe or co-morbid cases and those with specific risk factors for infection or testing, like recent travels. Furthermore, there are many pathogens causing AG which are not notifiable, such as norovirus and rotavirus. Cases appearing in the notification system are much lower in numbers than those missed but individual healthcare costs are higher. Strategies for saving healthcare costs should, therefore, target mild and severe cases as well as cases caused by notifiable and non-notifiable pathogens. Assessment of non-healthcare costs such as work loss is recommended to prioritise interventions and to evaluate their cost-effectiveness.

The number of human *Campylobacter* and EHEC infections is increasing while the number of *Salmonella* and hepatitis A infections is stable or even decreasing in Switzerland according to notification data. The trends observed for the first three pathogens mentioned are also supported by positivity studies taking into account the number of tests conducted. Those analyses have shown that the NNSID is a useful system to identify outbreaks but it is not sufficient for characterising the epidemiology of foodborne diseases in Switzerland. It needs to be complemented by research for confirming presence of and investigating suspected disease outbreaks. Furthermore, complementary research should be used for assessing epidemiological determinants such as patients' and physicians' behaviour, the burden of disease at population level and obtaining other supplementary information for setting priorities and informing policy.

Sentinella is a useful sentinel surveillance system to complement findings from the NNSID. It allows assessing the epidemiology of diseases at primary care level including cases without laboratory confirmation. Still, it does not provide the full picture as patients not approaching a physician will be missed. Additionally, it does not cover patients seeking help at emergency departments of hospitals directly.

National guidelines for the management of AG do not exist for Switzerland. Case management by the physician and processing of the stool sample by the laboratory are very heterogeneous. National guidelines could help to harmonise physicians' and laboratories' approaches towards diagnosis and treatment of AG. It is important to consider the different perspectives of patients, physicians, laboratory and public health experts when developing diagnosis and treatment guidelines. Awareness of physicians for the public health aspects of AG should be strengthened while the public health specialist should consider the patient-focused view of physicians.

Estimation of healthcare costs need to be updated and/or refined once new findings are available, either from research studies (such as the upcoming population-based cohort study on AG in Switzerland) or from surveillance systems. Furthermore, indirect healthcare costs and non-healthcare costs due to AG should be explored. Additionally, modelling studies of healthcare and non-healthcare costs should be used to inform development of AG case management guidelines and to evaluate their economic impact.

15.1 Recommendations

The experiences from the different research projects which are part of this thesis can be translated into recommendations for policy makers, authorities and researchers:

For policy makers:

- The purpose and set-up of surveillance systems with their strengths and limitations need to be considered when interpreting surveillance data.
- The (disease-specific) burden of disease below the tip of the iceberg (hence, beyond notification data) and its determinants must be taken into account for planning and prioritising interventions.

- Always include components of operations research when mandating studies on specific infectious diseases in Switzerland to constantly improve the Swiss infectious disease surveillance system.

For health authorities:

- Pilot testing of data collection tools and meticulous documentation of changes therein is good practice for research studies. Pilot testing should also be conducted when notification forms are changed. Similarly, all changes potentially affecting surveillance data (e.g. in data entry, case definition, notification forms, analysis) need to be rigorously documented for accurate interpretation of long-term trends.
- Strengthen personal contact between federal authorities and healthcare personnel "on the ground" (physicians, laboratory experts). This will help improving compliance of reporting as well as understanding of surveillance data. A community of practice among actors of the Swiss surveillance system should be established.
- Restrict information obtained on notification forms to minimum essential and reliable data needed to decide if further action is required (e.g. decision for or against contact tracing). Certain information, e.g. on risk factors and exposures, can more reliably be obtained through complementary research. Before changing notification forms, research studies could be mandated to assess validity of specific information.
- Consider conducting surveys among physicians and clinical laboratories to determine practices in case management on a regular basis, either additional to or in replacement for collecting laboratory statistics (number of tests conducted).

For researchers:

- Triage steps and approaches to case management of AG is likely different in the outpatient and inpatient setting. Additional research studies focussing on the hospital setting – from the emergency (outpatient) department to intensive care – are needed to assess the full (clinical) picture of foodborne diseases at the health care system level in Switzerland.
- Combining authorities' and scientists' research needs is beneficial for both sides: it can help to obtain funding (e.g. mandated research), it can ease implementation of studies by providing access

to existing structures (e.g. *Sentinella*), and it increases the likelihood that findings are taken up by stakeholders. Therefore, seeking close collaboration with health authorities is recommended.

- Explore best practices or ways to collect information on laboratory statistics (number of tests conducted) allowing routine analysis of data, or explore alternative approaches for taking into account changing laboratory practices when interpreting surveillance data.
- Make use of and combine existing networks and data sets considering all surveillance systems (e.g. NNSID, *Sentinella*, Swiss Pediatric Surveillance Unit (SPSU)) and data sources (e.g. population, hospital and mortality statistics) to increase validity of results and effectiveness of surveillance systems.

16 Bibliography

This bibliography contains all references used in the **unpublished** chapters of this thesis (except of those submitted or prepared for submission). Reference lists of published articles (including those submitted) are provided at the end of the corresponding chapter/article.

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Part VI

APPENDICES

Appendix A

List of notifiable observations in Switzerland, as per January 2018

The following table provides an overview of all notifiable observations as defined in appendices 1–4 of the "DHA Ordinance on the reporting of observations on human communicable diseases" of 1st December 2015, as per 01 January 2018 [Das Eidgenössische Departement des Innern, 2015a].

Table A.1: List of notifiable observations for physicians and laboratories with time frame for notification in Switzerland, as per 01 January 2018 [Das Eidgenössische Departement des Innern, 2015a]

Observation	**Time frame for notification**	**Report on clinical findings**	**Supplementary report on clinical findings[a]**	**Report on laboratory finding**	**Statistics on laboratory findings[b]**
Cluster of clinical/laboratory findings	24 hours	x		x	
Unusual clinical/laboratory finding	2 hours	x		x	
AIDS / Human immunodeficiency virus	1 week	x		x	
Anthrax / *Bacillus anthracis*	2 hours	x		x	
Botulism / *Clostridium botulinum*	2 hours	x		x	
Brucellosis / *Brucella* spp.	1 week	x		x	
Campylobacter spp.	24 hours			x	x
Carbapenemase-producing *Enterobacteriaceae*	1 week	x		x	x
Chikungunya fever/virus	24 hours	x		x	
Chlamydia trachomatis	1 week			x	x
Cholera/ *Vibrio cholerae*	24 hours	x		x	
Coxiella burnetii	1 week			x	

Table A.1: (continued)

Observation	**Time frame for notification**	**Report on clinical findings**	**Supplementary report on clinical findings[a]**	**Report on laboratory finding**	**Statistics on laboratory findings[b]**
Creutzfeldt-Jakob disease / Prions	1 week	x	x	x	
Crimean-Congo (haemorrhagic) fever/virus	2 hours	x		x	
Dengue fever/virus	24 hours	x		x	
Diphtheria / *Corynebacterium diphtheriae and other toxin-producing Corynebacteriaceae (C. ulcerans, C. pseudotuberculosis)*	24 hours	x		x	
Ebola (haemorrhagic) fever/virus	2 hours	x		x	
Enterohaemorrhagic *Escherichia coli* (infection)	24 hours	x		x	
Gonorrhoea / *Neisseria gonorrhoeae*	1 week	x		x	x
(Invasive) *Haemophilus influenzae* (disease)	1 week	x		x	

Table A.1: (continued)

Observation	Time frame for notification	Report on clinical findings	Supplementary report on clinical findings[a]	Report on laboratory finding	Statistics on laboratory findings[b]
Hantaviral diseases / Hanta virus	1 week	x		x	
Hepatitis A (virus)	24 hours	x		x	
Hepatitis B (virus)	1 week	x		x	
Hepatitis C (virus)	1 week	x		x	x
Hepatitis E (virus)	24 hours	x		x	x
HIV infection / HI virus	1 week	x		x	x
Influenza A HxNy (new subtype)	2 hours	x		x	
Influenza virus (seasonal, non-pandemic types and subtypes)	1 week			x	
Lassa fever/virus	2 hours	x		x	
Legionellosis / *Legionella* spp.	1 week	x		x	x
Listeriosis / *Listeria monocytogenes*	24 hours	x		x	
Malaria / *Plasmodium* spp.	1 week	x		x	
Marburg fever/virus	2 hours	x		x	
Measles (virus)	24 hours	x	x	x	

Table A.1: (continued)

Observation	Time frame for notification	Report on clinical findings	Supplementary report on clinical findings[a]	Report on laboratory finding	Statistics on laboratory findings[b]
(Invasive) meningococcal disease / *Neisseria meningitidis*	24 hours	x		x	
Middle East respiratory syndrome / MERS coronavirus	2 hours	x		x	
Plague / *Yersinia pestis*	2 hours	x		x	
(Invasive) pneumococcal disease / *Streptococcus pneumoniae*	1 week	x		x	
Poliomyelitis / Poliovirus	24 hours	x		x	
Rabies (virus)	24 hours	x		x	
Rubella (virus)	24 hours	x	x[c]	x	
Salmonella spp.	24 hours			x	x
Severe acute respiratory syndrome / SARS coronavirus	2 hours	x		x	
Shigella spp.	24 hours			x	
Smallpox / *Variola/ Vaccinia* virus	2 hours	x		x	
Syphilis / *Treponema pallidum*	1 week	x		x	

Table A.1: (continued)

Observation	**Time frame for notification**	**Report on clinical findings**	**Supplementary report on clinical findings[a]**	**Report on laboratory finding**	**Statistics on laboratory findings[b]**
Tetanus	1 week	x			
Tick-borne encephalitis (virus)	1 week	x		x	
Trichinellosis / *Trichinella spiralis*	1 week	x		x	
Tuberculosis / *Mycobacterium tuberculosis* complex	variable[d]	x	x	x	
Tularaemia / *Francisella tularensis*	1 week	x		x	x
Typhoid/paratyphoid fever / *Salmonella* Typhi/Paratyphi	24 hours	x		x	
West Nile virus (disease)	1 week	x		x	
Yellow fever (virus)	24 hours	x		x	
Zika fever/virus	24 hours	x		x	x

[a] Notifiable within 1 week

[b] Notifiable once a year until 31st January of the following year

[c] Congenital rubella

[d] Clinical findings: 1 week; laboratory findings: 24 hours

Appendix B

Process of compulsory disease notification in Switzerland

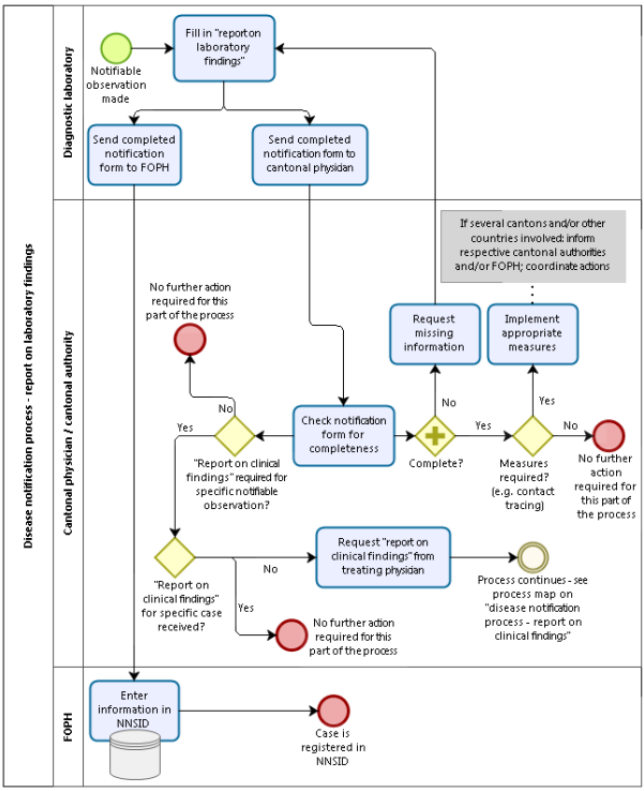

Figure B.1: Process map of disease notification of "report on laboratory findings" in Switzerland

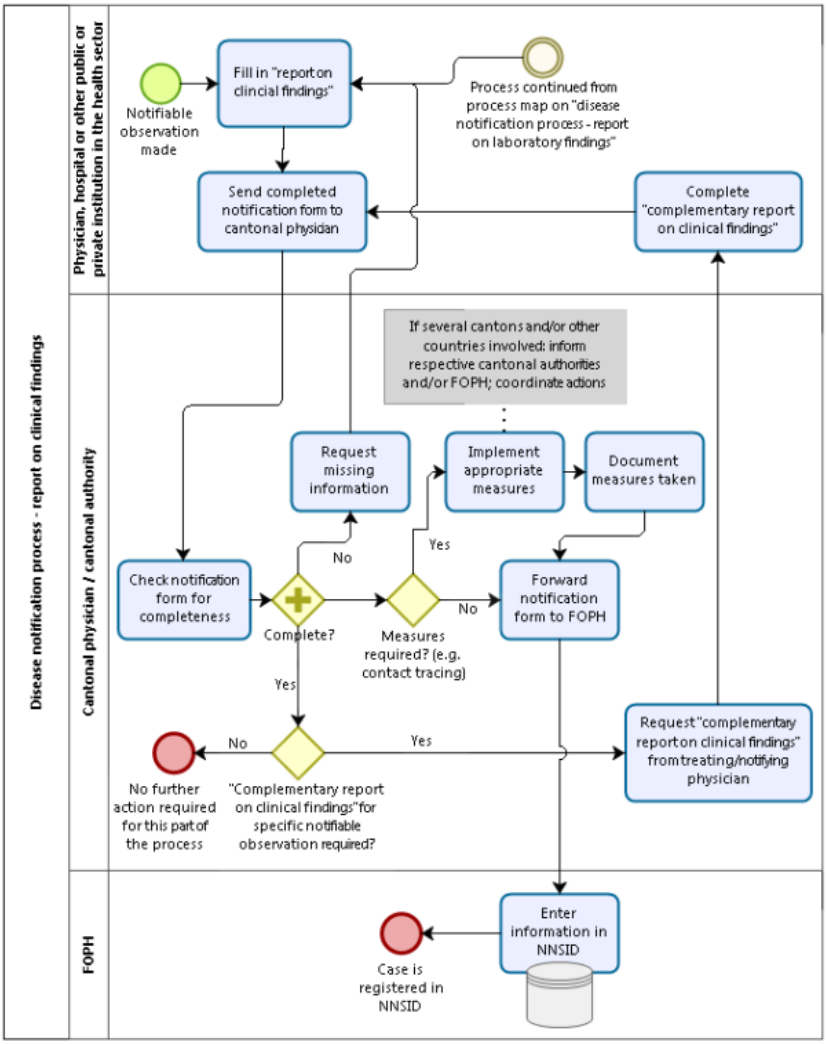

Figure B.2: Process map of disease notification of "report on clinical findings" in Switzerland

Appendix C

The influence of changes in diagnostic approaches on disease surveillance data: Time trend in positivity of EHEC testing in Switzerland, 2007–2016: Supplementary material

Seasonality

The positivity of enterohaemorrhagic *Escherichia coli* testing shows a strong seasonality. The seasonality of the total number of tests and the number of positives was calculated as the average number of tests (positives) of all test years (2007–2016) per calendar month. The number of total tests performed increased by 68% from February with 553 tests until September with 928 tests. The number of positively tested cases follows a similar seasonal pattern with 6 cases detected in February and 16 in August. Positivity peaked in July with 1.9%. The seasonality has been incorporated into the mixed effect logistic regression using sine and cosine functions, in the form of $\sin(d * 2 * \pi/T)$ and $\cos(d * 2 * \pi/T)$, where d is the time period (e.g. January, February) and T is one year, as described by Stolwijk *et al.* [1]. The predicted probabilities for a positive test outcome of the univariable logistic regression are shown in figure C.1.

References

1. Stolwijk AM, Straatman H, Zielhuis GA. Studying seasonality by using sine and cosine functions in regression analysis. *J Epidemiol Community Health* 1999; 53:235–238.

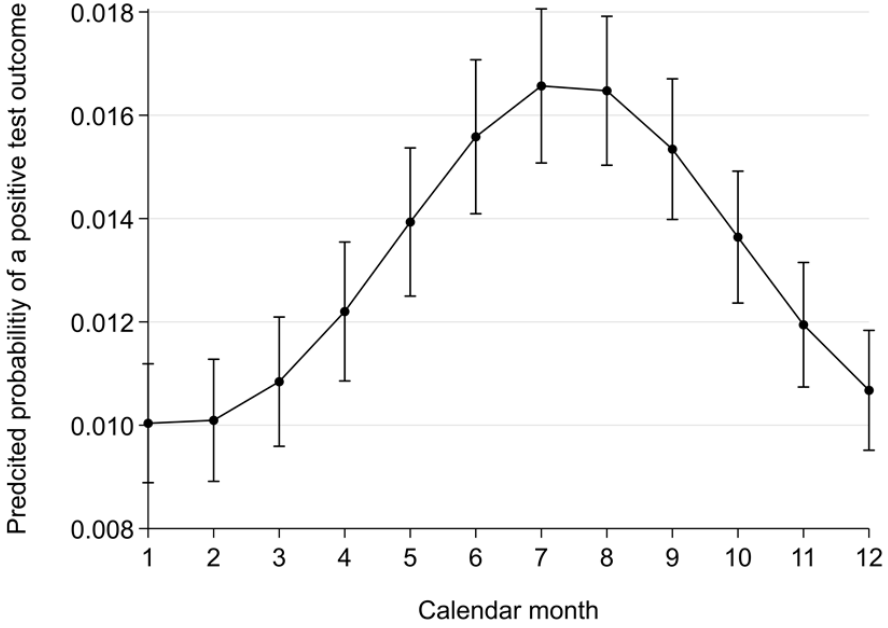

Figure C.1: Predicted probability per calendar month for a positive test outcome of an enterohaemorrhagic *Escherichia coli* infection for the univariable model using sine and cosine functions, 2007–2016, Switzerland

Appendix D

Notification form: Statistic of reports on laboratory findings 2017

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG
Direktionsbereich Öffentliche Gesundheit

2018

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!

Statistik zum laboranalytischen Befund 2017
Blatt 1

Vertraulich

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

☐ *Campylobacter spp.* ☐ *Chlamydia trachomatis* ☐ Carbapenemase bildende *Enterobacteriaceae* ☐ Hepatitis-C-Virus[3]
☐ Hepatitis-E-Virus ☐ *Legionella spp.* ☐ *Neisseria gonorrhoeae* ☐ *Salmonella spp.* ☐ Zika-Virus

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

Methode[4]

		C	G	S IgM	S IgG	A	M	T	Andere[5]
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

[1] Aktuelle Formulare abrufbar unter www.bag.admin.ch/infreporting
[2] Bei Serologie: nur Ig total; Serologien zur Bestätigung (z. B. immunoblot) sind unter „Andere" aufzuführen.
[3] C = Kultur/Isolat; G = Genomsequenz (DNA/RNA); S = Serologische Antikörpernachweise; A = Antigen-Nachweis; M = Mikroskopie; T = Toxin-Nachweis
[4] Andere Methode, welche: _____

Schweizerische Eidgenossenschaft
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Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG
Direktionsbereich Öffentliche Gesundheit

2018

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: 058 483 87 77). Besten Dank![a]

Statistik zum laboranalytischen Befund 2017
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 www.bag.admin.ch/infreporting
[b] ohne Tests im Rahmen der Blutspende
[c] in einem Bestätigungslabor (gemäss HIV-Testkonzept)

Appendix E

The burden of gastroenteritis in Switzerland (BUGS) study: a research proposal for a one-year, prospective cohort study: Additional file 1

Sample size calculation for the burden of gastroenteritis in Switzerland (BUGS) study based on different parameter assumptions, including derivation of underlying formulas

Comparison between two distinct groups (exposed and unexposed)

Power calculations were based on Hayes and Bennett [1], with adjustment for the situation of unequal group sizes.

Let

λ = average event rate among exposed persons (expressed as number of events per person year)
$d\lambda$ = hypothesized difference in average event rate between exposed and unexposed persons
λ_1 = average event rate among exposed persons
λ_0 = average event rate among exposed persons

q = proportion of exposed person

Then,

$\lambda_1 = \lambda + (1-q) \times d\lambda$ and $\lambda_0 = \lambda - q \times d\lambda$.

The corresponding weekly event rates are $\lambda'_1 = \frac{\lambda_1}{52}$, $\lambda'_0 = \frac{\lambda_0}{52}$.

Let y = average number of weeks of observation per subject.

Then, formula (2) of Hayes and Bennett [1] was adapted and slightly simplified to provide the minimal total number N of subjects required as

$$N = (1.96 + z_{1-\beta})^2 \times \left[\left(\frac{\lambda'_1}{q} + \frac{\lambda'_0}{1-q} \right) / y + CV^2 \times \left(\frac{\lambda'^2_1}{q} + \frac{\lambda'^2_0}{1-q} \right) \right] / \left(\lambda'_1 - \lambda'_0 \right)^2$$

where β denotes the accepted type II-error probability. In case of $q = 0.5$, N equals $2 \times (c-1)$, where c = number of clusters per group according to formula (2) of Hayes and Bennett [1].

Table E.1: Sample size calculation for the burden of gastroenteritis in Switzerland (BUGS) study for a comparison of the mean number of events per person and year between two distinct groups (exposed and unexposed) based on different parameter assumptions

Parameters specified / assumptions						**Comparison of mean number of events per person and year between two distinct groups (exposed and unexposed)**
Mean number of events per person and year	Difference in mean number of events per person and year between exposed and unexposed	Power	Proportion exposed	ICC	Average number of weeks observed	Calculated sample size needed
1	0.3	0.9	0.2	0.2	40	1'162 (n_1= 929, n_2= 233)
0.75	0.3	0.9	0.2	0.2	40	909 (n_1= 727, n_2= 182)
0.75	0.3	0.9	0.2	0.2	26	1'384 (n_1=1'107, n_2= 277)
0.75	0.3	0.9	0.2	0.2	52	705 (n_1= 564, n_2= 141)
0.75	0.2	0.9	0.2	0.2	40	1'908 (n_1=1'526, n_2= 382)
0.75	0.2	0.8	0.2	0.2	40	1'425 (n_1=1'140, n_2= 285)
0.75	0.1	0.8	0.2	0.2	40	**5'295 (n_1=4'236, n_2=1'059)**
0.75	0.2	0.9	0.2	0.5	40	2'172 (n_1=1'737, n_2= 435)
0.75	0.2	0.9	0.2	0.5	26	**3'172 (n_1=2'537, n_2= 635)**
0.75	0.2	0.8	0.2	0.5	26	2'369 (n_1=1'895, n_2= 474)
0.75	0.3	0.9	0.1	0.2	40	1'722 (n_1=1'549, n_2= 173)
0.75	0.2	0.9	0.1	0.2	40	**3'552 (n_1=3'196, n_2= 356)**
0.75	0.2	0.8	0.1	0.2	40	2'653 (n_1=2'387, n_2= 266)
0.5	0.3	0.9	0.2	0.2	26	1'008 (n_1= 806, n_2= 202)

Table E.1: (continued)

Parameters specified / assumptions						**Comparison of mean number of events per person and year between two distinct groups (exposed and unexposed)**
Mean number of events per person and year	Difference in mean number of events per person and year between exposed and unexposed	Power	Proportion exposed	ICC	Average number of weeks observed	Calculated sample size needed
0.5	0.3	0.9	0.2	0.2	40	660 (n_1= 528, n_2= 132)
0.5	0.3	0.8	0.2	0.2	26	753 (n_1= 602, n_2= 151)
0.5	0.3	0.9	0.2	0.5	40	733 (n_1= 586, n_2= 147)
0.5	0.2	0.9	0.2	0.5	40	1'484 (n_1=1'187, n_2= 297)
0.5	0.1	0.9	0.2	0.5	40	**5'299 (n_1=4'239, n_2=1'060)**
0.5	0.1	0.8	0.2	0.2	40	**3'634 (n_1=2'907, n_2= 727)**

ICC = intraclass correlation coefficient
bold: Calculated minimal sample size exceeds envisaged cohort size of 3'000 individuals

Within-subject comparison between two distinct periods (high and low risk period): Longitudinal comparison of rates

Let $X_{ij}^{(1)}$ = number of events in subject i during unit interval j (e.g. week j) in low risk period
Let $X_{ij}^{(2)}$ = number of events in subject i during unit interval j (e.g. week j) in high risk period

Assumptions:

(1) $X_{ij}^{(1)} = Pois\left(\lambda_1 + d\lambda_{i0} + d\lambda_{i1}\right),\ j = 1, \ldots, m_1$

(2) $X_{ij}^{(2)} = Pois\left(\lambda_2 + d\lambda_{i0} + d\lambda_{i2} + d\lambda_{i3}\right),\ j = m_1 + 1, \ldots, m_1 + m_2$

where λ_1 and λ_2 denote the average rates in the low and high risk period, respectively,
$d\lambda_{i0}$ denotes a subject-specific random effect with $E\left(d\lambda_{i0}\right) = 0$ across both periods,
$d\lambda_{i1}$ and $d\lambda_{i2}$ denote subject-specific random period effects with $E\left(d\lambda_{i1}\right) = E\left(d\lambda_{i2}\right) = 0$ and $E\left(d\lambda_{i1}^2\right) = E\left(d\lambda_{i2}^2\right)$,
and $d\lambda_{i3}$ denotes an additional subject-specific random effect in the high risk period with $E\left(d\lambda_{i3}\right) = 0$.
All random effects are assumed to be mutually independent.

We define:

$$U_i = \frac{1}{m_2} \sum_{j=m_1+1}^{m_1+m_2} X_{ij}^{(2)} - \frac{1}{m_1} \sum_{j=1}^{m_1} X_{ij}^{(1)}$$

The variance of U_i conditional on fixed values of the random effects then becomes:

$$Var\left(U_i | random\ effects\right) = \frac{1}{m_2}\left(\lambda_2 + d\lambda_{i0} + d\lambda_{i2} + d\lambda_{i3}\right) + \frac{1}{m_1}\left(\lambda_1 + d\lambda_{i0} + d\lambda_{i1}\right)$$

giving

$$E\left[Var\left(U_i | random\ effects\right)\right] = \frac{1}{m_2}\lambda_2 + \frac{1}{m_1}\lambda_1 \tag{E.1}$$

Moreover,

$$E\left(U_1 | random\ effects\right) = \left(\lambda_2 + d\lambda_{i0} + d\lambda_{i2} + d\lambda_{i3}\right) - \left(\lambda_1 + d\lambda_{i0} + d\lambda_{i1}\right) = \left(\lambda_2 - \lambda 1\right) + \left(d\lambda_{i2} - d\lambda_{i1}\right) + d\lambda_{i3}$$

implying that

$$E\left[E\left(U_i|random\ effects\right)^2\right] = \left(\lambda_2 - \lambda_1\right)^2 + Var\left(d\lambda_{i2}\right) + Var\left(d\lambda_{i1}\right) + Var\left(d\lambda_{i3}\right)$$

and

$$Var\left[E\left(U_i|random\ effects\right)\right] = Var\left(d\lambda_{i2}\right) + Var\left(d\lambda_{i1}\right) + Var\left(d\lambda_{i3}\right) \tag{E.2}$$

For the variance of U_i, which is the sum of E.1 and E.2, we thus obtain

$$Var\left(U_i\right) = \frac{1}{m_2}\lambda_2 + \frac{1}{m_1}\lambda_1 + 2 \times Var\left(d\lambda_{i1}\right) + Var\left(d\lambda_{i3}\right) \tag{E.3}$$

If we assume that $Var\left(d\lambda_{i1}\right) = Var\left(d\lambda_{i2}\right) = Var\left(d\lambda_{i0}\right)$ and relate $Var\left(d\lambda_{i0}\right)$ to λ_1 through

$$Var\left(d\lambda_{i0}\right) = \left(\lambda_1 \times CV_1\right)^2$$

where CV_1 is the coefficient of variation of $\lambda_1 + d\lambda_{i0}$, and $Var\left(d\lambda_{i3}\right)$ to $|\lambda_2 - \lambda_1|$ through

$$Var\left(d\lambda_{i3}\right) = \left(|\lambda_2 - \lambda_1| \times CV_2\right)^2$$

where CV_2 is the coefficient of variation of $|\lambda_2 - \lambda_1| + d\lambda_{i3}$, then we finally obtain

$$Var\left(U_i\right) = \frac{1}{m_2}\lambda_2 + \frac{1}{m_1}\lambda_1 + 2 \times \left(\lambda_1 \times CV_1\right)^2 + \left(|\lambda_2 - \lambda_1| \times CV_2\right)^2 \tag{E.4}$$

In our power calculations we chose $CV_1 = CV_2 = 0.25$. If all random effects were normally distributed, this would imply that $d\lambda_{i1}, d\lambda_{i2} \in \left(-0.5 \times \lambda_1, 0.5 \times \lambda_1\right)$ and $d\lambda_{i3} \in \left(-0.5 \times |\lambda_2 - \lambda_1|, 0.5 \times |\lambda_2 - \lambda_1|\right)$, each with a probability of 95%.

Table E.2: Sample size and power calculation for the burden of gastroenteritis in Switzerland (BUGS) study for a comparison of the mean number of events per person and year between two distinct periods (high and low risk period) based on different parameter assumptions

Parameters specified / assumptions						**Comparison of mean number of events per person and year between two distinct periods**
Mean number of events per person and year	Difference in mean number of events per person and year between high and low risk period	Power	Proportion observed weeks at high risk	Individual coefficient of variation	Average number of weeks observed	Calculated sample size needed
1	0.3	0.9	0.2	0.25	40	1'133
0.75	0.3	0.9	0.2	0.25	40	890
0.75	0.3	0.9	0.2	0.25	26	1'365
0.75	0.3	0.9	0.2	0.25	52	687
0.75	0.2	0.9	0.2	0.25	40	1'875
0.75	0.2	0.8	0.2	0.25	40	1'400
0.75	0.1	0.8	0.2	0.25	40	**5'219**
0.75	0.2	0.9	0.2	0.5	40	1'926
0.75	0.2	0.9	0.2	0.5	26	2'926
0.75	0.2	0.8	0.2	0.5	26	2'186
0.75	0.3	0.9	0.1	0.25	40	1'678
0.75	0.2	0.9	0.1	0.25	40	**3'472**
0.75	0.2	0.8	0.1	0.25	40	2'593
0.5	0.3	0.9	0.2	0.25	26	996

Table E.2: (continued)

Parameters specified / assumptions						**Comparison of mean number of events per person and year between two distinct periods**
Mean number of events per person and year	Difference in mean number of events per person and year between high and low risk period	Power	Proportion observed weeks at high risk	Individual coefficient of variation	Average number of weeks observed	Calculated sample size needed
0.5	0.3	0.9	0.2	0.25	40	649
0.5	0.3	0.8	0.2	0.25	26	744
0.5	0.3	0.9	0.2	0.5	40	659
0.5	0.2	0.9	0.2	0.5	40	1'354
0.5	0.1	0.9	0.2	0.5	40	**4'905**
0.5	0.1	0.8	0.2	0.25	40	**3'595**

bold: Calculated minimal sample size exceeds envisaged cohort size of 3'000 individuals

References

1. Hayes RJ, Bennett S: Simple sample size calculation for cluster-randomized trials. *Int J Epidemiol* 1999, 28:319–326.

Appendix F

Selected media articles

F.1 Selected media reactions on studies presented in this thesis

Durchfall kostet Gesundheitswesen jährlich 50 Millionen Franken

Zwischen 300 und 700 000 Patienten gehen in der Schweiz pro Jahr wegen Durchfall zum Arzt. (Symbolfoto: Shutterstock)

Krankheit Magen-Darm-Erkrankungen belasten das Schweizer Gesundheitswesen mit jährlich rund 50 Millionen Franken. Dies zeigen Schätzungen im Rahmen einer Studie des Schweizerischen Tropen- und Public-Health-Instituts (Swiss TPH).

Pro Jahr suchen in der Schweiz rund 300 000 bis 700 000 Patientinnen und Patienten aufgrund einer akuten Durchfallerkrankung einen Arzt auf, wie es in einer Medienmitteilung vom Freitag heisst. Je nach Schweregrad der Erkrankung koste eine Behandlung zwischen gut 30 bis 5800 Franken. Wie das Swiss TPH in Basel in ihrer in der Fachzeitschrift «Epidemiology & Infection» publizierten Studie errechnet hat, haben im Jahr 2012 Magen-Darm-Erkrankungen Kosten zwischen 40 und 50 Millionen Franken verursacht. Berücksichtigt worden seien dabei Ausgaben für Arztbesuche, Spitalaufenthalte, Labordiagnosen und Medikamente.

Fondue Chinoise und Grillfleisch

Nicht in die Studien eingeflossen seien indes volkswirtschaftliche Kosten wie etwa Arbeitsausfälle. Die Gesamtkosten von Durchfall als «Volkskrankheit» dürften gemäss den Studienautoren demnach beträchtlich höher liegen. Durchfall führe im Weiteren jährlich zu mehr Arztkonsultationen als die Grippe während der Grippesaison. Etwa ein Viertel der in der Studie geschätzten Kosten geht auf Infektionen mit dem Durchfall-Erreger Campylobacter zurück, wie es weiter heisst. Dies seien in der Schweiz die am häufigsten gemeldeten über Lebensmittel übertragenen Infektionen. Jährlich werden landesweit bis zu 8500 Erkrankungen diagnostiziert.

Ein erhöhtes Risiko zeigt sich gemäss früheren Untersuchungen des Swiss TPH bei Verzehr von Pouletfleisch etwa bei Fondue Chinoise. Während der Grillsaison sei die Ansteckungsgefahr ebenfalls deutlich erhöht. Das Risiko könne mit Hygienemassnahmen aufseiten der Fleischproduzenten und der Konsumenten gesenkt werden. In der Regel verlaufe eine Campylobacter-Erkrankung mild. In einigen Fällen könne sie jedoch zu mehrtägigen Spitalaufenthalten mit hohen Kostenfolgen führen. Die Ursachen der meisten anderen Magen-Darm-Erkrankungen sind gemäss Mitteilung unbekannt. (sda)

Figure F.1: Newspaper article in response to publication on healthcare costs of acute gastroenteritis and campylobacteriosis; Source: Volksblatt Liechtenstein, 13.08.2016, page 32

Sanità **La diarrea costa e c'è poca prevenzione**

I problemi gastrointestinali provocano in Svizzera costi elevati. È quanto emerge da uno studio effettuato dall'Istituto tropicale e di sanità pubblica svizzero (Swiss TPH) di Basilea e dall'Ufficio federale della sanità pubblica (UFSP). I risultati della ricerca verranno pubblicati sulla rivista specialistica «Infection».

Più nel dettaglio, ogni anno in Svizzera 175.000 pazienti si recano dal medico per un problema acuto di dissenteria, si legge in un comunicato. In nove casi su dieci queste persone si assentano in seguito dal lavoro per quattro giorni.

Il team di ricercatori ha analizzato i dati presenti nel sistema Sentinella relativi al 2014. «È sorprendente che in casi acuti di problemi gastrointestinali venga effettuata così poca prevenzione», afferma l'autrice Claudia Schmutz, citata nella nota. Lo studio mostra che la diarrea provoca lo stesso numero di consultazioni mediche dell'influenza nella stagione di maggiore incidenza.

In molti casi, secondo gli autori, non è chiaro quali siano gli agenti patogeni che causano tale malattia. Infatti solo nel 10% delle visite il medico effettua un esame delle feci. La maggior parte di questi malanni sono ricondotti a infezioni da Campylobacter, legate alle derrate alimentari.

Per i malati è spesso poco importante se il problema gastrointestinale sia provocato da un germe virale o batterico. Secondo Schmutz, questa informazione ha tuttavia un valore indispensabile per la costituzione di misure di prevenzione a livello nazionale.

Un'altra scoperta ha sorpreso i ricercatori: il maggior numero di consultazioni mediche per problemi gastrointestinali è stato riscontrato in gennaio e febbraio. Gli autori dello studio si aspettavano un aumento dei casi in estate, tradizionalmente la stagione delle grigliate.

Figure F.2: Newspaper article in response to publication on acute gastroenteritis in Swiss primary care, *Sentinella*; Source: Corriere del Ticino, 05.08.2017, page 5

Grosser Ausfall wegen Durchfall

BERN | Magen-Darm-Erkrankungen führen hierzulande zu beträchtlichen Erwerbsausfällen und verursachen hohe volkswirtschaftliche Kosten. Zu diesem Schluss kommt eine Studie des Schweizerischen Tropen- und Public Health-Instituts (Swiss TPH) und des Bundesamtes für Gesundheit (BAG). Jedes Jahr suchen 175 000 Menschen hierzulande hausärztliche Hilfe wegen einer akuten Durchfallerkrankung. | **sda**

Figure F.3: Newspaper article in response to publication on acute gastroenteritis in Swiss primary care, *Sentinella*; Source: Walliser Bote, 05.08.2017, page 19

Wissen im Comic Akuter Durchfall belastet die Volkswirtschaft

Magen-Darm-Erkrankungen verursachen in der Schweiz hohe volkswirtschaftliche Kosten. Das haben Forscher des Schweizerischen Tropen- und Public-Health-Instituts berechnet. Demnach suchen 175 000 Personen jährlich deswegen ärztliche Hilfe. Das seien ähnlich viele wie wegen Grippe. Erwerbstätige, die wegen Durchfall einen Arzt aufsuchen, werden im Durchschnitt vier Tage krankgeschrieben. Illustration: Felix Schaad

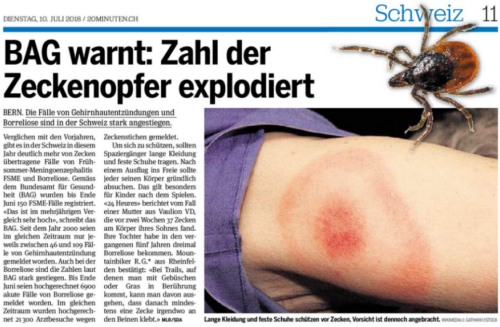
Figure F.4: Newspaper article in response to publication on acute gastroenteritis in Swiss primary care, *Sentinella*; Source: Tages-Anzeiger, 26.08.2017, page 58

F.2 Selected media reactions on surveillance data

Viele Junge liegen mit Grippe im Bett

BERN. Die Grippewelle bleibt hartnäckig und hält an, in einigen Regionen nimmt die Zahl der Neuerkrankungen gar zu. Daniel Koch vom Bundesamt für Gesundheit zeigt sich in einem SRF-Interview überrascht. Die Hartnäckigkeit dieser Grippewelle führt Koch auf das Virus selbst zurück. «Dieses sogenannte Yamagata-Virus hatte wahrscheinlich noch nie einen ähnlichen Verwandten in der Bevölkerung. Das heisst, dass die Jüngeren keinen Immunschutz dagegen haben und viele deshalb sehr lange zum Teil sehr heftig erkranken.» Glück im Unglück sei, dass die Grippe für junge Menschen nur selten gravierende Folgen habe. Koch geht nicht davon aus, dass die Grippewelle nochmals stark anzieht. «Momentan liegen aber weiterhin sehr viele Leute mit Grippe im Bett und können noch andere anstecken.» Er rät daher, weiterhin vorsichtig zu sein. SEP

Figure F.5: Newspaper article in response to interview aired on Swiss TV, based on weekly situation report on influenza-like illnesses published in the "BAG Bulletin"; Source: 20 Minuten (issue region Basel), 09.03.2018, page 9



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BAG warnt: Zahl der Zeckenopfer explodiert

BERN. Die Fälle von Gehirnhautentzündungen und Borreliose sind in der Schweiz stark angestiegen.

Verglichen mit den Vorjahren, gibt es in der Schweiz in diesem Jahr deutlich mehr von Zecken übertragene Fälle von Frühsommer-Meningoenzephalitis FSME und Borreliose. Gemäss dem Bundesamt für Gesundheit (BAG) wurden bis Ende Juni 170 FSME-Fälle registriert. «Das ist im mehrjährigen Vergleich sehr hoch», schreibt das BAG. Seit dem Jahr 2000 seien im gleichen Zeitraum nur jeweils zwischen 46 und 109 Fälle von Gehirnhautentzündung gemeldet worden. Auch bei der Borreliose sind die Zahlen laut BAG stark gestiegen. Bis Ende Juni seien hochgerechnet 6500 akute Fälle von Borreliose gemeldet worden. Im gleichen Zeitraum wurden hochgerechnet 21 300 Arztbesuche wegen Zeckenstichen gemeldet.

Um sich zu schützen, sollten Spaziergänger lange Kleidung und feste Schuhe tragen. Nach einem Ausflug ins Freie sollte jeder seinen Körper gründlich absuchen. Das gilt besonders für Kinder nach dem Spielen. «24 Heures» berichtet vom Fall einer Mutter aus Vaulion VD, die vor zwei Wochen 37 Zecken am Körper ihres Sohnes fand. Ihre Tochter habe in den vergangenen fünf Jahren dreimal Borreliose bekommen. Mountainbiker R. G.* aus Rheinfelden bestätigt: «Bei Trails, auf denen man mit Gebüschen oder Gras in Berührung kommt, kann man davon ausgehen, dass danach mindestens eine Zecke irgendwo an den Beinen klebt.» MLA/SDA

Lange Kleidung und feste Schuhe schützen vor Zecken, Vorsicht ist dennoch angebracht. WANDERLI GATHWIHTOOK

Figure F.6: Newspaper article in response to weekly situation report on tick-borne diseases published in the "BAG Bulletin"; Source: 20 Minuten (issue region Basel), 10.07.2018, page 11