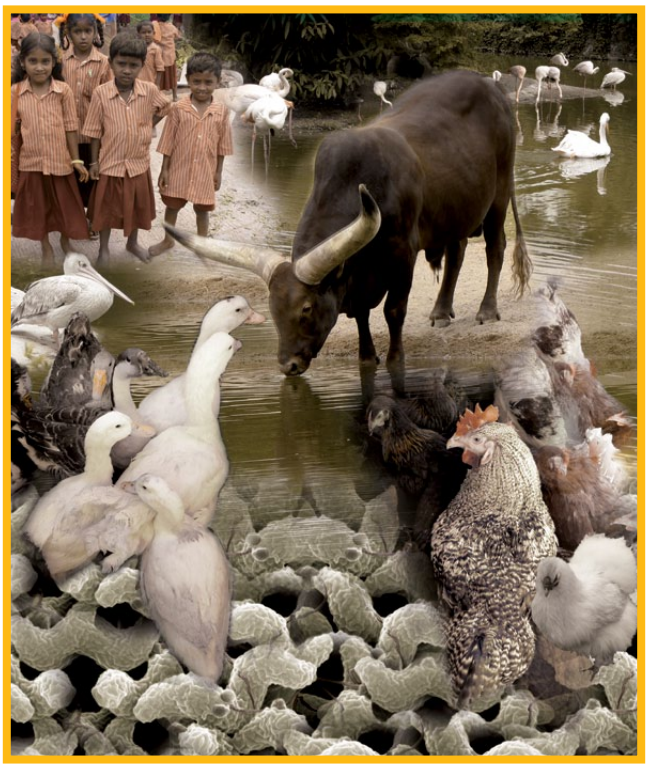
F O O D S A F E T Y

THE GLOBAL VIEW OF
CAMPYLOBACTERIOSIS

REPORT OF AN EXPERT CONSULTATION

UTRECHT, NETHERLANDS, 9-11 JULY 2012



World Health Organization

IN COLLABORATION WITH

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Universiteit Utrecht

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Contents

Acronyms and abbreviations used in this report

AFP	acute flaccid paralysis
AGE	acute gastroenteritis
AGI	acute gastrointestinal illness
CAC	Codex Alimentarius Commission
CD	coeliac disease
CHERG	Children's Health Epidemiology Reference Group
CI	confidence interval
CIDT	culture-independent diagnostic test
CLSI	Clinical and Laboratory Standards Institute
CPS	capsular polysaccharide
DALY	disability-adjusted life year
EHEC	enterohaemorrhagic *Escherichia coli*
EQA	external quality assurance
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agriculture Organization of the United Nations
FD	functional dyspepsia
FERG	Foodborne Disease Epidemiology Reference Group
FGD	functional gastrointestinal disorder
GBD	global burden of disease
GBS	Guillain-Barré syndrome
GEMS	Global Enterics Multi-Center Study
GFN	Global Foodborne Infections Network
GLP	good laboratory practice
GP	general practitioner
HACCP	hazard analysis critical control point
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICD	International Classification of Diseases
IID	infectious intestinal disease
IQC	internal quality control
JEMRA	Joint FAO/WHO Expert Meeting on Microbiological Risk Assessment
LMIC	Low- and Middle-income countries
LOS	lipo-oligosaccharide
LTHO	long-term health outcome
MAL-ED	A Global Network for the Study of Malnutrition and Enteric Diseases
MFS	Miller Fisher syndrome
MLST	multilocus sequence typing
MIC	minimum inhibitory concentration
NRC	national reference centre
OIE	World Organisation for Animal Health
OR	odds ratio
PCR	polymerase chain reaction
PI-FD	post-infectious functional dyspepsia
PS	proportional similarity (index)
PTS	proficiency testing scheme
ReA	reactive arthritis
RR	relative risk
WHO	World Health Organization

Executive summary

On 9–11 July 2012, the World Health Organization (WHO), in collaboration with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), convened an Expert Consultation on The Global View of Campylobacteriosis, in Utrecht, Netherlands. The objectives of the Consultation were:

- to review the progress made in the past 10 years in understanding and controlling Campylobacteriosis, take note of successful approaches and lessons learned, and identify challenges in controlling *Campylobacter* from farm to table and in reducing the human health burden and attributable health consequences;
- to consider cross-cutting areas, such as food- and waterborne *Campylobacter*iosis and antimicrobial resistance, taking into account the context of both high-income countries and low- and middle-income countries (LMIC);
- to suggest how WHO, FAO and OIE could take action to reduce *Campylobacter* in the food chain and the burden of foodborne Campylobacteriosis.

Burden of disease and health impact

Campylobacter is one of the most frequently occurring bacterial agents of gastroenteritis. The true incidence of gastroenteritis due to *Campylobacter* spp. is poorly known, particularly in LMIC; studies in high-income countries have estimated the annual incidence at between 4.4 and 9.3 per 1000 population.

The major sequelae of Campylobacteriosis are Guillain-Barré syndrome (GBS), reactive arthritis (ReA) and irritable bowel syndrome (IBS).

GBS is a severe disease, requiring intensive care in some 20% of cases; case-fatality rates in high-income countries are between 3 and 10%. Globally, approximately one-third of GBS cases have been attributed to *Campylobacter* infection.

While it is difficult to determine the true extent of ReA, because of a lack of clear diagnostic and classification criteria, studies suggest that it occurs in 1–5% of those infected with Campylobacter. It has been estimated that 25% of ReA cases may go on to chronic spondyloarthropathy.

IBS develops in up to 36% of patients with Campylobacteriosis within 1–2 years after infection; the risk appears to be higher among those with more severe acute disease.

Surveillance

Surveillance is important to help identify disease outbreaks, to detect sporadic cases for case–control studies, to provide isolates that can be used in attribution models based on isolate subtyping, and to furnish data that can be used to construct and calibrate risk assessment models. It is also useful for documenting the success of control programmes. While surveillance of enteric diseases, including Campylobacteriosis, is common in high-income countries, it is rarely attempted in other parts of the world. Nevertheless, a well-designed surveillance programme for Campylobacteriosis can provide information

to inform national decision-making by: determining the relative importance of Campylobacteriosis compared with other enteric infections; showing which animals are the primary reservoirs for infection; and helping to identify the most common pathways of transmission. Ideally, such a programme would be cost-effective, and would provide essential epidemiological information for burden of disease studies. Initially, in countries with limited resources, a pilot programme may be useful to gather baseline data on the incidence of the disease and its relative contribution to diarrhoeal illness, seasonal patterns of illness, and risk factors, such as age and urban/rural location and linkages to animal and environmental data.

Source attribution

Source attribution is the estimation of the relative contributions of different sources to the burden of human illness. In relation to Campylobacter, the Consultation proposed that the term "source attribution" should be used as a collective term to cover reservoir attribution, pathway attribution, comparative exposure/risk assessment and risk factor modelling. It developed a general framework showing how these different elements fit together, and reviewed the advantages and disadvantages of the different approaches to source attribution.

Laboratory diagnosis

Campylobacter is difficult to isolate, grow and identify. Only *C. jejuni* can be routinely identified with phenotypic markers, and commercial systems may misidentify non-*jejuni* species. The introduction of new culture-independent diagnostic tests (CIDTs) is starting to allow better monitoring of disease burden and trends in industrialized countries. If the cost of these diagnostic platforms drops sufficiently, and if their sensitivity and specificity are validated in LMIC settings, CIDTs may bring presumptive diagnosis within reach in these countries.

The Consultation stressed the important role of national reference centres (NRCs) in epidemiological surveillance and outbreak prevention. Together with WHO, these centres should reach out to clinical and laboratory partners in the country, providing information, training and coordination, standardizing terminology, nomenclature and diagnostic methods, and applying the appropriate technologies. Good laboratory practice and an effective quality assurance scheme are essential for all diagnostic laboratories.

Antimicrobial resistance

The surveillance of antimicrobial resistance in *Campylobacter* has identified important levels of resistance to tetracyclines and fluoroquinolones in many parts of the world. High level of resistance to fluoroquinolones appears to be associated with the use of these drugs to treat poultry. Patterns of antimicrobial use and selection for resistance in one part of the world affect health in other parts of the world, through international travel and trade. In vitro antimicrobial susceptibility testing is essential to provide guidance to physicians and veterinarians on appropriate treatment of infections and to generate data on the occurrence of acquired resistance in *Campylobacter*.

Control measures

Because of the complex epidemiology of *Campylobacter*, a multi-tiered approach to control is needed, taking into consideration the different reservoirs, pathways, exposures, and risk factors. While the primary target for control measures is the poultry (meat) production chain, other transmission vehicles, such as raw milk and drinking-water, can be controlled through appropriate treatment, e.g. pasteurization of milk and chlorination of water. *Campylobacter* control needs to be adapted to local possibilities, practicalities and preferences. However, the Consultation listed some generally applicable basic principles.

With regard to poultry, the goal of reducing the load of *Campylobacter* to a level with a low probability of causing illness in humans can most likely not be achieved by any single pre-harvest or post-harvest intervention. Success will be most likely through use of multiple stepwise interventions on or in each bird on the farm and in the processing facility. The interventions that have consistently been shown to be effective at pre-harvest are the application of strict biosecurity and good animal husbandry an health measures. Good hygienic practices and the application of control measures based on HACCP principles are also critical for successful post-harvest control, and decontamination of the carcass by physical or chemical means as part of these measures has the greatest chance of success. As for all pathogens control measures need to continue through to the point of consumption with the implementation of appropriate temperature control though distribution, retail and storage and the implementation of good hygienic practices and adequate cooking by the end user.

General conclusions

- Considerable new evidence, data, and analytical tools have emerged in the ten years since the previous WHO consultations on Campylobacter.
- In terms of public health actions, there is already a sufficient evidence base to address the burden of disease from C. *jejuni* and C. coli. The importance of other species in terms of burden of disease is still unclear, but is considered unlikely to eclipse these two species.
- Public health surveillance can provide important basic information to policy-makers about the frequency of infection, who is affected, and the success of specific prevention strategies. Surveillance is the starting point for studies of burden of disease and source attribution.
- There is a need for standardization and validation of laboratory methods.
- Burden of disease studies provide the evidence base that drives the need for control measures across all outcomes of Campylobacteriosis while taking into consideration its underestimation.
- There is considerable potential for the identification of new sequelae from acute infection. However, decision criteria are needed on the level of evidence required to add outcomes to burden estimates. This applies to all sequelae, and may increase burden estimates considerably.
- In order to reduce exposure countries should be encouraged to adopt the recently developed Codex Guidelines for the Control of *Campylobacter* and *Salmonella* in chicken meat which promote a risk based approach to the management of *Campylobacter* in chicken meat traded internationally. Consideration should be given to the development of additional guidance and recommendations for the management of *Campylobacter* in other potential food vehicles that are traded internationally.
- Source attribution studies should adopt a holistic attitude, considering multiple sources and pathways of exposure. Where possible attribution estimates should combine both molecular tying and epidemiological data and include measures of uncertainty.
- Although poultry is the dominant source of infection in many countries, controlling *Campylobacter* in poultry meat will not completely eliminate the disease in humans. Options are available to control other pathways which are based on general hygiene, generic control measures including biosecurity and sanitation.
- Reducing the load of *Campylobacter* in poultry to a level with a low probability of causing illness is unlikely to be achieved by any single pre-harvest or post-harvest intervention. Success will most

likely occur through use of multiple stepwise interventions to lower the load of *Campylobacter* on or in each bird on the farm and in the processing facility.

- The epidemiology of Campylobacteriosis is likely to be different in high-income countries versus LMIC. This will affect control options.

- GFN, as an international training and capacity development network, will play a key role in promoting better and more consistent methodologies and quality assurance for work with *Campylobacter*. Where possible, GFN should link with other international networks, such as FERG, which is promoting capacity development in estimation of burden of foodborne disease.

Recommendations

- The Consultation made a number of recommendations to WHO on actions needed to increase understanding and improve control of *Campylobacter*.

1. Introduction

1.1 Background

Campylobacter is considered to be the most common bacterial cause of human gastroenteritis in the world. An acute infection can have serious long-term consequences, including the peripheral neuropathies, Guillain–Barré syndrome (GBS) and Miller Fisher syndrome (MFS), and functional bowel diseases, such as irritable bowel syndrome (IBS). In many countries, the organism is isolated 3–4 times more frequently from patients with alimentary tract infections than other bacterial enteropathogens (such as *Salmonella* or *Escherichia coli*). In high-income countries, reported cases of Campylobacteriosis often exceed those of salmonellosis. Although scarce, data from low- and middle-income countries (LMIC) suggest that the burden of disease due to *Campylobacter* infection is considerable.

It is often difficult to trace sources of exposure to *Campylobacter* because of the sporadic nature of the infection, and the important role of cross-contamination. Many countries are currently working to prevent foodborne Campylobacteriosis and considerable progress has been made on numerous fronts during the past ten years. Recent scientific advances offer new approaches; for example, whole genome sequencing has led to an improved understanding of pathogenesis. New insights in attribution of infections to their source and recognition of the role of immunity in protecting against *Campylobacter* infection, together with risk assessment studies, have helped to guide management of risk along the farm-to-table continuum. Some countries have invested heavily in reducing Campylobacteriosis transmitted via specific food chains, with some success. Yet, from a global perspective, Campylobacteriosis in humans remains difficult to prevent.

The current meeting provided an opportunity to review the progress made to date, take note of successful approaches and lessons learned, identify challenges in controlling *Campylobacter* from farm to table, and make recommendations to reduce the human health burden.

1.2 International collaboration

The issue of foodborne Campylobacteriosis is well recognized by WHO, the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE). Since *Campylobacter* is a zoonotic hazard, with both food- and waterborne routes of transmission, and in light of the challenges it presents in terms of control, it is clear that – both locally and globally – the infection needs to be addressed in a multidisciplinary manner. Close collaboration is thus essential.

WHO convened two previous meetings on human Campylobacteriosis, in 2000 and 2002. The Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment (JEMRA) have also undertaken a risk assessment for *Campylobacter* spp. in broiler chickens. The present WHO Consultation was organized in collaboration with FAO and OIE, as the three main technical organizations addressing health risks at the human–animal–ecosystems interface. Strengthening cross-sectoral approaches in local, national, regional and international institutions and infrastructure will allow more targeted interventions and improved outcomes.

Just over 10 years ago, shortly after the first WHO meeting on Campylobacteriosis, the issue of *Campylobacter* was raised at one of the committee meetings of the Codex Alimentarius Commission (CAC), leading to a request for an international risk assessment for *Campylobacter* in poultry. This risk assessment (1), which was based on assessments previously undertaken in Canada, Denmark and the

United Kingdom, characterized and assessed the impact of specific mitigation measures for the control of *Campylobacter* in broiler chickens. It also provided a detailed description of a risk assessment approach that could be used by countries. Discussions on this issue continued in CAC for a number of years and, in 2006, the Commission agreed to develop guidelines for the control of *Campylobacter* and *Salmonella* in chicken meat. These were adopted in 2011 (2).

The guidelines describe measures for the control of *Campylobacter* for application at one or more steps in the production-to-consumption continuum. They are presented in three tiers: (1) guidance based on good hygiene practices; (2) hazard-based control measures, based on scientific knowledge of the likely level of a hazard at a step (or series of steps) in the food chain; and (3) risk-based control measures. By their nature, the last-mentioned measures could not be prescriptive. To assist countries in applying these measures, therefore, FAO and WHO developed a Web-based tool which computes the residual risk for a process flow when selected interventions are applied, in comparison with a baseline process flow. This tool is also not intended to be prescriptive, but provides an approach to using the available data in a systematic way to assess the impact of a proposed control measure. The tool is available at http://www.mramodels.org/poultryRMTool, and could be used to test ideas of how *Campylobacter* could be managed in a specific system and to characterize and assess the relative impact of specific mitigation options.

Whatever approach is taken to control *Campylobacter*, some knowledge of *Campylobacter* in the system of concern is critical. While certain countries have the capacity to collect and analyse such data, many others – in particular small and LMIC – struggle to get an overview of their *Campylobacter* problem. Some training activities are available, for example through the WHO-led Global Foodborne Infections Network (GFN), and specific laboratory guidance is available from OIE for testing animals. FAO and WHO are working directly with some LMIC to develop their capacity to collect information on Campylobacter, as well as other pathogens, from relevant points in the food chain. Such projects are also looking at some of the characteristics of the isolates, such as their antimicrobial resistance. The studies are limited in terms of the amount of data they provide, but are valuable for providing baseline data and in highlighting the existence of pathogens such as *Campylobacter* in the food chain, promoting good practices, and raising the awareness of decision-makers. These elements are critical if understanding of *Campylobacter*, particularly in LMIC, is to improve.

The projects also promote engagement with policy-makers and food value chain[1] operators, to ensure that findings are translated into appropriate policy interventions and measures to promote the implementation of practical prevention and control measures during food production, processing and distribution.

WHO, FAO and OIE are also collaborating to address antimicrobial resistance, recognizing the serious nature and extent of the problem. For example, the use of fluoroquinolones, such as enrofloxacin, in food-producing animals has resulted in the development of ciprofloxacin-resistant Campylobacter; such bacteria have spread throughout the world through travel and food trade.

1.3 Objectives and expected outcomes of the meeting

The Expert Consultation had the following objectives:

- to review the progress made since the previous two consultations, take note of successful approaches and lessons learned, and identify challenges in controlling *Campylobacter* from farm to table and in reducing the human health burden and attributable health consequences;

[1] Food Value chain: the process or activities by which value is added to a particular food at different stages of the primary production, processing and distribution chain.

- to consider cross-cutting areas, such as food- and waterborne Campylobacteriosis and antimicrobial resistance, taking into account the context of both high-income and LMIC;
- to suggest how WHO, FAO and OIE could take action to reduce *Campylobacter* in the food chain and the burden of foodborne Campylobacteriosis.

This report captures the main points of the deliberations and proposes future steps, options for reducing the burden of foodborne and waterborne Campylobacteriosis and associated antimicrobial resistance, and appropriate techniques for detection, surveillance, source attribution and control.

1.4 Organization of the Consultation

Four working groups were formed to discuss the following topics and to outline options for the way forward.

Working Group 1. Burden of disease and health impact

Topics discussed included:

- estimation of the human burden of Campylobacteriosis, including the true incidence of gastroenteritis, and geographical and demographic distribution;
- identification and assessment of the major long-term effects of Campylobacteriosis;
- approaches to measuring the burden of Campylobacteriosis and their validity outside their original context;
- the validity of disability weights for acute disease and sequelae, including fatality;
- vaccines for use in humans;
- current trends and clinical relevance of antimicrobial resistance, and sources of resistance.

Working Group 2. Surveillance and antimicrobial resistance

Topics discussed included:

- matching the need for Campylobacteriosis surveillance around the world with the methods used, including integrated surveillance;
- shifts in diagnostic methods, from bacteriology to culture-independent tests;
- antimicrobial resistance surveillance and tracking of trends;
- use of other surveillance systems to improve understanding of Campylobacteriosis, for example global acute flaccid paralysis (AFP) surveillance.

Working Group 3. Source attribution

Topics discussed included:

- how different approaches to understanding sources, pathways, exposures and risk factors can be used to inform decision-making for surveillance;

- "strategy-focused" versus "control-focused" surveillance, and the use of dynamic modelling to assess the impact of interventions;
- sampling of sources in space and time; including the value of sentinel sites; current and future tools.

Working Group 4. Impact of control measures

Topics discussed included:

- intervention methods currently implemented around the world and their effectiveness;
- control measures for non-poultry-related sources;
- control measures for non-food-related *Campylobacter* sources.

Prior to the Consultation, chairs were identified for each of the working groups and were requested to perform a literature review of work in the four areas since 2000. Based on this, background papers were prepared for each working group and provided to the participants prior to the meeting as a basis for discussion.

1.5 Review of progress made since previous consultations

The Expert Meetings on *Campylobacter* of 2000 and 2002 made a great number of recommendations. It subsequently became clear that it was not possible to meet all these recommendations, partly because they were beyond the remit of WHO, and partly because the tasks were simply too large. Some of the recommendations have been responded to by the WHO Global Foodborne Infections Network, the Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment (JEMRA) and the CAC, the WHO Collaborating Centre for Reference and Research on *Campylobacter* in Utrecht, Netherlands and other partners.

In general, there has been considerable progress in *Campylobacter* research since the previous meetings. Besides fundamental research on the bacteria and host-bacterium interactions, progress has been made in applied knowledge. Examples include more precise description of the burden of Campylobacteriosis by the WHO Foodborne Diseases Epidemiology Reference Group and country-specific studies. Considerably more information has also become available on the sequelae of Campylobacteriosis.

Progress has also been made in typing and attribution. In 2000 and 2002, the preferred typing methods were still under debate. Since then, multilocus sequence typing (MLST) has been generally introduced and has proven to be powerful in attribution studies. In New Zealand, this technique has been used to inform and assess interventions. In 2000, the first genome sequence of a *Campylobacter* strain was published. Since then, more sequences have been added and technical advances will allow expansion of this library with many additional strains in the near future. In 2000 and 2002, there was more focus on presence or absence of *Campylobacter* on products. Risk assessment studies have now shifted towards estimation of dose and probability of infection or illness. Consequently, elimination of *Campylobacter* in the final product is not needed, as a simple reduction can lead to a huge reduction in the number of Campylobacteriosis cases in humans.

Although there has been scientific progress in fundamental and applied knowledge, there have been few successful large-scale implementations of measures to prevent disease in humans (except for New Zealand and more modest results in the United States of America (USA)). We still do not know how *Campylobacter* causes disease, or why *C. jejuni/coli* causes disease in humans while few other *Campylobacter* species do.

In 2000, a total of 15 *Campylobacter* species and subspecies had been described; now there are 24 species and subspecies, with an additional 11 proposed new species. One of the needs identified in the 2000 meeting was improved information on the burden of non-*jejuni*, non-*coli* species. The description of a number of additional species has made this assessment even more complex.

1.6 Declaration of interest

All experts and resource advisors invited to participate in the WHO Expert Consultation: The Global View of Campylobacteriosis completed the WHO standard form for declaration of interests prior to the meeting. At the start of the meeting, all participants were asked to confirm their interests, and to provide any additional information, relevant to the subject matter of the meeting. No conflicts of interest were identified.

2 Burden of disease and health impact

2.1 Estimating the true incidence of Campylobacteriosis

The true incidence of gastroenteritis due to *Campylobacter* spp. is poorly known, and several approaches are being used to try to estimate it. Population-based cohort studies, such as the two Infectious Intestinal Disease (IID) studies in the United Kingdom (3, 4) and the Sensor study in the Netherlands (5), estimate the incidence of diarrhoeal illness in the population and the attributable fraction for a number of causative agents by laboratory analysis of stool samples from patients. The Sensor study has been used as a basis for calculation of the burden of campylobacteriosis in terms of disability-adjusted life years (DALYs) in the Netherlands (6). The incidence of campylobacteriosis was estimated to be 9.3 per 1000 person–years in the United Kingdom (for 2008–2009) and 5.8 per 1000 person–years in the Netherlands (for 2009). Only one out of every 9.3 cases in the United Kingdom and one out of 12 in the Netherlands is reported to national surveillance bodies. In the USA, it is estimated that one out of 30.3 cases is reported by FoodNet sites, and that national incidence was 1.3 million cases in 2006 or 4.4 per 1000 (7). These studies also indicate that one out of seven patients with campylobacteriosis in the United Kingdom, and one out of four in the Netherlands, consulted their doctor; this reflects the severe nature of campylobacteriosis. As the faecal samples were tested for a number of pathogens, the incidence of campylobacteriosis can be compared with that of other enteric pathogens. Infections with viral agents occur more commonly in the general population (norovirus incidence is four times higher in the United Kingdom and five times higher in the Netherlands), but *Campylobacter* is one of the most frequently occurring bacterial agents of gastroenteritis. Cohort studies from industrialized countries are rare, because of the high costs, in particular for the collection of faecal samples. New and more cost-effective approaches may be possible using samples from biobanks, e.g. from colon cancer screening programmes.

In LMIC, cohort-based studies are more common than population-based studies, in particular among children under five years of age and in sentinel sites. Reviews of the global incidence of diarrhoeal illness have been published to support WHO's Foodborne Disease (8) and Children's Health (9) Epidemiology Reference Groups. Global estimates of the burden of campylobacteriosis and other diarrhoeal illnesses, as developed by the Global Burden of Disease (GBD) project, have been published. The burden of *Campylobacter* is 7.5 million DALY or 8.4% of the total burden of diarrheal diseases and among identified pathogens ranks fourth after rotavirus (18.7 million DALY) and typhoid fever (12.2 million DALY) and cryptosporidiosis (8.3 million DALY) (10). When considering data from such studies, it needs to be borne in mind that there is enormous variation in study design, data collection and laboratory methods. In addition to culture-based methods, non-culture methods with unknown specificity and sensitivity are increasingly employed. It is recommended that the sensitivity and specificity of methods employed in cohort studies should be better characterized and that efforts are needed to work towards standardization, including internal and external quality control and training. The Global Enterics Multi-Center Study (GEMS[2]) and the MAL-ED study [3] are examples of an attempt to do this. Opportunities to use demographic studies for population-based surveys may be missed because specific questions on diarrhoeal diseases may not be articulated sufficiently in the design phase. It is therefore recommended that epidemiologists and clinical microbiologists participate more actively in such studies.

[2] http://medschool.umaryland.edu/GEMS/; accessed 18 February 2013.
[3] http://mal-ed.fnih.org/ accessed 19 March 2013

Pyramid reconstruction studies are based on the incidence of laboratory-confirmed cases, either reported to national surveillance or resulting from active surveillance and corrected for underdetection and under-reporting, using a variety of data including health-care usage of the population. Such studies have been published in several countries, including the USA (7), Canada (11, 12), and Australia (13); other studies have explored differences between the reported incidence in different countries or regions of a country (14, 15). The data needed to reconstruct the surveillance pyramid include information on health care usage and on laboratory testing. A large number of surveys of the incidence of (self-reported) acute gastroenteritis have been carried out in recent years. Two reviews in 2005 (16, 17) suggested that, in high-income countries, there were 0.6–1.3 cases of acute gastrointestinal illness (AGI) per person per year. Since then, case definitions and study designs have been standardized and studies carried out in different parts of the world, including the Eastern Mediterranean (18), China (19, 20), Latin America (21, 22), New Zealand (23), and Europe (24). The incidence of self-reported acute gastrointestinal illness appears to be similar around the world. In six recently completed telephone surveys across the European Union (EU), self-reported illness rates varied from 1.4 cases per person per year in Denmark (25) to 0.33 per person per year in France (26). By their nature, these studies provide general information on gastroenteritis from all causes, and assumptions need to be made when extrapolating the surveillance pyramid for specific pathogens. Some authors have used bloody stools as a proxy for disease severity (11, 27, 28), but other factors, such as duration of illness and age of the patient, are not taken into account. A study in seven EU countries suggested that the incidence estimates from pyramid reconstruction studies are higher than those from cohort studies (29).

Even though multiplier studies are very useful, they cannot be extrapolated without supporting information. It is, however, not uncommon for pyramid reconstruction studies to use estimates for model parameters based on published data from other countries. Several studies have used the US multipliers for other countries, while others have used components of the multiplier estimate from several countries (30, 31). The results of such extrapolations are questionable if no evidence can be presented that the health care systems in the involved countries lead to similar selection biases. It is recommended that country-specific information is collected as part of multiplier studies. Protocols for such studies are available, for example through the International Collaboration on Enteric Disease "Burden of Illness" Studies.

Relative risks to travellers have been used as a proxy for relative incidence in local residents, as recently published for *Salmonella* spp. and *Campylobacter* spp. in the EU (24). These studies may provide a comparable estimate of the force of infection in different countries, although there are many caveats when interpreting such data. These include underdiagnosis or misdiagnosis of travel-related cases, late appearance of symptoms so that cases cannot always be attributed to a specific country, absence of information on the nature and duration of travel (for example, holiday vs. business) and immunity (in particular against local endemic strains) among the resident population.

2.2 Sequelae

The major recognized sequelae of Campylobacteriosis are Guillain-Barré syndrome, reactive arthritis (ReA), and irritable bowel syndrome. The Miller Fisher syndrome, a GBS variant, is also associated with preceding *Campylobacter* infection. There may be an association with inflammatory bowel disease (IBD), and evidence is increasing that other functional gastrointestinal disorders (FGDs) are linked to gastroenteritis in general (not specifically to Campylobacter). Sequelae contribute significantly to the disease burden of Campylobacteriosis (6).

2.2.1 Guillain-Barré syndrome

The role of *Campylobacter* in triggering an autoimmune response leading to damage of the peripheral nervous system and development of GBS has been extensively studied. *Campylobacter*-induced GBS is now considered a true case of molecular mimicry-mediated disease. There are good data on the

incidence of GBS in Europe and North America (32, 33). The disease has also been well studied in China, where it may occur in outbreaks (34) and in Japan (35), but population-based incidence data are scarce. Seasonal patterns of GBS have been described in Mexico (36) China (37) Argentina (38), Curacao (39) and Japan (40). These seasonal variations may be useful markers for studying the epidemiology of Campylobacter-related GBS.

Data on the worldwide incidence of GBS are limited, in particular regarding some LMIC (Fig. 1). Population-based incidence data for children and adults in Africa and south and east Asia are lacking. Recent work in Bangladesh suggested a higher incidence, and occurrence at younger ages, than in high-income countries (41). A recent Peripheral Nerve Society meeting in Rotterdam (June 25-28 2012) expressed the need for more population-based incidence data from LMIC. The lack of a common definition of GBS hinders data comparability and uniform reporting. Recently, new "Brighton criteria" and guidelines have been developed for a standardised clinical case definition of GBS, and are receiving widespread international support (42).

Globally, approximately one-third of GBS cases have been attributed to precedent *Campylobacter* infection (43), although a higher proportion has been reported for Bangladesh (44). A link between reduced incidence of Campylobacteriosis and reduced incidence of GBS has been reported in New Zealand (45).

The clinical course of GBS has been documented in several clinical studies (46-50). GBS cases that are preceded by *Campylobacter* infection are more severe (47, 51) and have a poorer outcome (47, 49-51). There is increasing evidence of long-term disability due to GBS (52, 53). Treatment includes monitoring, multidisciplinary general care, and specific treatment with either plasmapheresis or intravenous immunoglobulin. Approximately 20% of patients will be admitted to an intensive care unit for respiratory ventilation and to monitor autonomic dysfunction. Access to optimal treatment varies greatly worldwide especially in the least developed countries, where GBS remains a severe and potentially fatal disease. Case-fatality rates vary greatly and are between 3% and 10% in high-income countries. Case-fatality rates in LMIC are assumed to be higher (44). Long-term disabilities due to GBS have not been extensively studied (52, 53) and need to be further researched. New low-cost interventions are needed in both high-income and LMIC.

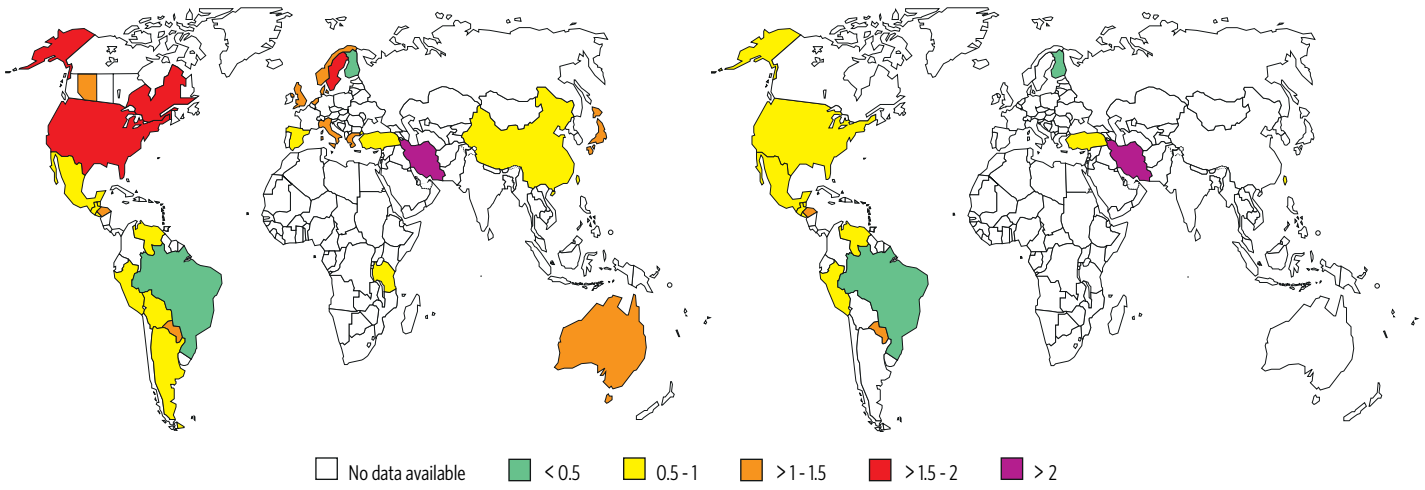


Fig. 1. GBS incidence in the world. Left: all ages; right: children (32).

2.2.2 An opportunity at hand? Global surveillance for acute flaccid paralysis

The worldwide poliomyelitis eradication effort includes surveillance in many countries for acute flaccid paralysis. AFP surveillance data have been used in several recent studies to obtain estimates of the population-based incidence of GBS (41) and to validate the new Brighton criteria for GBS (54). The Brighton criteria include standardised clinical case definitions, with four levels of diagnostic certainty (42). For example, Brighton criteria level 3 does not require laboratory testing or electrophysiological tests. The implementation of the Brighton criteria in the current AFP surveillance is likely to result in more reliable population-based GBS incidence data in children under 15 years of age (AFP surveillance does not currently cover adults).

When cases of AFP are reported, a stool sample is collected and analysed for the presence of poliovirus. No other studies are done, but specimens are stored. Surveillance will continue for a decade after polio transmission ceases, providing an opportunity to conduct other studies on the samples, for example to determine the fraction that may be attributable to Campylobacter, and thus the burden of this important sequela worldwide.

In 2011, the annual incidence of non-poliomyelitis AFP among persons less than 15 years old was 5 per 100 000, varying by WHO region from 1 per 100 000 in the Americas to 11.2 in South-East Asia (41). These figures translate to approximately 10 000 cases of non-poliomyelitis AFP per year in under-15-year-olds. The most frequent cause is thought to be GBS. A recent meta-analysis concluded that 31% of GBS cases could be attributed to *Campylobacter* (43). This meta-analysis was based on studies done predominantly in high-income countries and in China and India, while only one study had taken place in a country classified by the United Nations as "least-developed". A more recent study from a least-developed country reported that 57% of GBS cases could be attributed to *Campylobacter* (44). In addition, asymptomatic *Campylobacter* infections should also be considered in outcome trees.

An AFP/GBS surveillance system in LMIC can detect large and unexpected Campylobacter-related events. In 2011, a surge in adult AFP cases of the acute motor axonal neuropathy type in San Luis Rio Colorado, a town in the northwestern state of Sonora in Mexico, was the signal that a large *Campylobacter* outbreak was occurring. The outbreak was simultaneously detected through routine *Campylobacter* surveillance in the nearby US town of Yuma, directly across the border from San Luis (Centers for Disease Control and Prevention, unpublished data). Investigation linked illness to exposure to the water in one part of San Luis, at a time when chlorination was possibly deficient there. In general, connecting AFP surveillance with more routine public health surveillance groups may reveal more such events, and lead to a better understanding of the drivers of Campylobacteriosis, and of ways to prevent it in LMIC.

2.2.3 Reactive arthritis

The reported incidence and prevalence of Campylobacter-associated ReA vary across studies, as a result of differences in case detection, exposure assessment, diagnostic criteria, and study population. However, the available data suggest that reactive arthritis occurs in 1–5% of those infected with Campylobacter. The annual incidence of ReA after *Campylobacter* infection is estimated at 4.3 per 100 000 in high-income countries (55). While the duration of ReA varies, in one prospective cohort study 5% of *Campylobacter* ReA was found to be chronic or relapsing (56). There is evidence that there may be a range of musculoskeletal disorders that could be triggered by *Campylobacter* (and other enteric) infections. For example, in a study in Minnesota and Oregon in the USA, people with culture-confirmed Campylobacter, *Salmonella*, *Shigella*, *Yersinia*, or *E. coli* O157 infection were followed up within 8 weeks of their positive culture (57). Of 6379 patients with culture-confirmed infection, 70% completed screening interviews. Of these, 575 (13%) developed possible ReA, with incidence highest among those infected with Campylobacter.

There are issues related to the basic definitions of ReA, and many would argue that ReA is a concept, not a well-defined disease (58). It is difficult to determine the full extent of a burden that does not have precise diagnostic and classification criteria. Additional follow-up studies of patients with *Campylobacter* infection in ethnically diverse populations would help to clarify the clinical spectrum of illness.

For ReA, the association is established for "severe cases" (59), but there are indications that the risk is lower for general cases (60). Some studies have reported long-term disability due to ReA (61, 62), but this has not been generally acknowledged.

The persistence of reactive arthritis associated with infectious gastroenteritis is less well studied. Hannu et al. (63) estimated that 25% of patients with reactive arthritis may go on to develop chronic spondyloarthropathy, with various manifestations. In a study using the US Department of Defence medical encounter data system, the authors noted that medical visits for reactive arthritis continued in approximately 20–40% of individuals for up to 7 years after infection (64). Further study to describe the diversity of post-*Campylobacter* arthritic disorders, the persistence of reactive arthritic symptoms, and the disability associated with such chronic conditions is warranted to allow better modelling of the disease burden.

2.2.4 Chronic gastrointestinal consequences of *Campylobacter* infection[4]

Post-*Campylobacter* irritable bowel syndrome (IBS)

Infectious gastroenteritis is the best-characterized environmental risk factor for the development of IBS (65, 66). Studies have reported that up to 36% of those with acute Campylobacteriosis develop IBS within 1–2 years (67). Post-*Campylobacter* IBS appears to be of the diarrhoea-predominant phenotype, though changing phenotypes over time have been observed (68-70). There seems to be a positive correlation between IBS risk and severity of acute illness. For example, following a waterborne outbreak of *Campylobacter* and enterohaemorrhagic *E. coli* (EHEC) infections, Marshall et al. reported an increased risk of IBS among those with a longer duration of diarrhoea, dysentery, and abdominal cramps during acute illness (71).

Studies of patients with post-*Campylobacter* IBS have found increased intraepithelial lymphocytes and up-regulated cytokines in their rectal mucosa, indicating persistent immune activation (72-75). Intestinal inflammation and enterochromaffin cell hyperplasia in post-infectious IBS are also accompanied by increased intestinal permeability, which may lead to increased antigenic load and further activation of the immune system (76). Additional evidence suggests that C. *jejuni* can breach the intestinal barrier and may prime the intestine for chronic inflammatory responses in susceptible individuals, which may play a role in triggering IBS after Campylobacteriosis (described further below in relation to inflammatory bowel disease) (77).

Other functional gastrointestinal disorders linked to Campylobacter

There is epidemiological evidence linking infectious diarrhoea with other FGDs, including functional dyspepsia. Mearin et al. (78) *(Salmonella)* and Porter et al. (79) (all causes) have reported an association between invasive infectious diarrhoea and post-infectious functional dyspepsia (PI-FD) (odds ratio (OR) 5.2 and 5.0, respectively). Similarly, Parry et al. reported a 2.9-fold increase in PI-FD following bacterial gastroenteritis (including Campylobacter) compared with unexposed controls (80). A waterborne outbreak of *Campylobacter* and EHEC infections was associated with a similarly increased risk of functional dyspepsia (OR 2.1), particularly among females, smokers, and those with premorbid

[4] Summarized from Riddle MS, Gutierrez RL, Verdu EF, Porter CK. The chronic gastrointestinal consequences associated with Campylobacter. Current gastroenterology reports. 2012;14(5):395-405. Epub 2012.

IBS, anxiety or depression, or more than 7 days of diarrhoea or abdominal cramps during the acute illness (81). An additional study among children also identified a link between acute enteric infection and functional dyspepsia (82). Most recently, Porter et al. reported an increased risk of functional dyspepsia among patients with an ICD-9 medical encounter diagnosis of Campylobacteriosis compared with a non-exposed cohort (83).

While there appears to be some epidemiological evidence for a relationship between *Campylobacter* and other FGDs (for example, functional diarrhoea and functional constipation) and gastro-oesophageal reflux disease (83, 84), more epidemiological, pathological and animal model studies are needed to strengthen understanding of the potentially broad spectrum of post-*Campylobacter* chronic gastrointestinal disorders.

Post-*Campylobacter* inflammatory bowel disease (IBD)

The epidemiological evidence for IBD following acute diarrhoeal infection and *Campylobacter* has grown. Early studies in the 1990s first described the association of acute infection with relapses of IBD (85), and in a case series, Schumacher noted that, in 62% of patients, traveller's diarrhoea requiring treatment was associated with a first attack of IBD (86). *Campylobacter* has been isolated from 10% of presenting or relapsed cases of IBD (87). Such cross-sectional studies are hampered by the inability to assess a temporal relationship, but recent cohort studies have demonstrated a higher risk of IBD following acute *Campylobacter* infection (79, 88-90). A study by Garcia-Rodriguez et al., published in 2006, used the United Kingdom provider clinical database to match 40 000 cases of acute gastroenteritis (AGE) with controls; the risk of IBD was increased in the year after the AGE episode (hazard ratio 2.4), with an incidence of 60 cases per 100 000 person–years in the AGE group (90). Risk was highest after infection with *Campylobacter* or *Salmonella* (89). In 2009, a Danish cohort study followed 13 000 patients with *Salmonella* or *Campylobacter* infection and matched controls, and found an increased risk of IBD among the cases.

Some of the criticism of the data supporting *Campylobacter* as a trigger for IBD concerns the possibility of detection bias. In 2010, Jess et al. tried to test this using Danish laboratory and clinical data to evaluate IBD risk among individuals with positive stool culture compared with those with negative stool culture (91). Rate ratios after a positive *Salmonella* or *Campylobacter* stool culture suggested an increased IBD risk of 9 and 5 times, respectively, while among those with negative stool cultures, the risk was increased over 50-fold. They concluded that, since negative stool cultures were associated with highest risks, the smaller effect seen after positive stool culture implied that detection bias exists and that evidence linking enteric infection and IBD is the result of artefact. In support of the argument, they noted similarities in temporal risk patterns for IBD after pathogen-positive and pathogen-negative stool tests. In response to this article, Riddle et al. suggested that the assumptions behind this interpretation need further consideration (92).

The pathogenesis of post-infectious IBD remains unclear; however, accumulating evidence suggests that IBD involves an inappropriate host response to the gut microbiome (93). Increased intestinal permeability as a mechanism for increased bacterial uptake has also been suggested (90). Bacterial pattern recognition receptors are crucial for maintaining host–microbe homoeostasis and play a key role in innate immunity, by restricting the intestinal microbiota to the mucosal compartment (94, 95).

Post-*Campylobacter* coeliac disease

Coeliac disease is increasingly common, affecting as many as 1% of the population worldwide (96). Reports of infectious diarrhoea as a trigger for coeliac disease are based on attribution of symptom onset by coeliac disease patients (97-99). Recently, a previously healthy subject developed sudden IBS-like symptoms after C. *jejuni* infection (100). Symptoms evolved over a 5-year period to include mild signs of malabsorption and the diagnosis of coeliac disease was confirmed by positive serology and

partial atrophy of the small intestine seen on biopsy. Moreover, symptoms resolved after the patient started a gluten-free diet. Using non-specific ICD-9 codes for infectious gastroenteritis, Riddle et al. found a 3.0-fold increased odds of exposure to pathogens of non-viral etiologies among people with coeliac disease compared with matched controls (101). The odds of exposure were higher when looking at temporal proximity to coeliac disease diagnosis. This work was furthered by Porter et al. using a retrospective cohort study of 739 subjects with known *Campylobacter* infection (83). Despite a limited number of outcomes, a 3.5-fold increase (which was not statistically significant) in the adjusted risk of coeliac disease was found in those with prior *Campylobacter* infection, compared with those with no documented *Campylobacter* infection. Importantly, no association was observed with other bacterial causes of diarrhoea, including non-typhoidal *Salmonella*, *Shigella*, and *Yersinia*.

2.3 Disability weights

A disability weight is a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (equivalent to death). Disability weights are available for most outcomes of Campylobacteriosis, but do not specifically take into account the variable severity and durations of acute disease sequelae, and their validity is not well established. Since the original publication of the Global Burden of Disease study (102), several additional studies have been undertaken. A recent review (Dr. Juanita Haagsma, Erasmus University, pers. comm., March 2013) identified 22 studies published between 1990 and 2011. The authors concluded that "there is considerable variation in methods used to derive disability weights, although most studies used a panel of medical experts that provided the values. Comparisons of disability weights showed that subdivision of a disease into separate health states (stages) and actual values of the disability weights differ markedly across studies". Furthermore, the case definitions used to elicit the disability weights may not match the available epidemiological data, in particular for different levels of the surveillance pyramid. The publication of the Global Burden of Disease 2010 study is anticipated in 2013. One component of the recently published GBD 2010 study is a completely redesigned method to elicit disability weights from the general population, and its application in several countries worldwide. The authors report strong evidence of highly consistent results from elicitation studies in different countries. Disease classes are rather generic. Three different disability weights for diarrhoea (mild-moderate-severe) are provided. There are also three different weights for motor impairments (mild-moderate-severe) that could be used for GBS, and a series of weights for musculoskeletal disorders. It is not clear how specific diseases triggered by *Campylobacter* can be divided over these categories. There is a specific disability weight for IBD (Crohn's disease and ulcerative colitis) but no weight for IBS. Further work on disability weights for health outcomes of Campylobacteriosis is recommended. To support such work, empirical studies on the health-related quality of life of patients with acute Campylobacteriosis and sequelae would be useful.

2.4 Deaths due to Campylobacteriosis

Estimations of fatalities due to *Campylobacter* infection have used a variety of approaches, including surveillance data, outbreaks and registry records (6, 7, 103, 104). Estimates of case-fatality rates range from <0.01% to 8.8%, depending on the population studied (case-definitions, age, co-morbidity) and the methods used, including the period of follow-up. A number of deaths will be related to complications and sequelae, such as GBS, and the estimates therefore depend on completeness and length of follow-up. The lowest case-fatality rate of <0.01% was found in an analysis of surveillance data in Germany (105). This study also reported a mean annual mortality from *Campylobacter* spp. of 0.04 per 100 000 population. Analysis of laboratory surveillance data in the USA showed a case-fatality ratio of 0.1% (7). Similarly, the Foodborne Diseases Active Surveillance Network (FoodNet) in the USA found a case-fatality ratio of 0.1%, defining fatality as death occurring within 7 days of laboratory-confirmation of *Campylobacter* infection (106). Information on occurrence of zoonoses and foodborne outbreaks in 27 Member States of the European Union showed a case-fatality rate of 0.02% (104). However, routine surveillance is usually not suitable for determining disease outcomes.

An envelope for global mortality due to diarrhoeal diseases is available for children under 5 years of age, but does not include specific etiologies (107). A recent study in Kenya showed a much higher case-fatality rate of 8.8% (5/57) among children under 5 years in hospital with a laboratory-confirmed *Campylobacter* infection (108). This figure is of interest, but represents a highly selected population.

In order to assess the causality of Campylobacteriosis and death, Helms et al. compared mortality among patients with laboratory-confirmed *Campylobacter* with that in the general population, adjusted for co-morbidity (103). Mortality within a year of infection was higher among patients than controls (relative risk (RR) 1.9 (confidence interval (CI) 1.6–2.2)). The highest risk of death was seen within 30 days after the infection (RR 5.0 (CI 3.3-7.6)). In absolute numbers, the work by Helms et al. corresponds to a mortality difference of 0.23% in the first 30 days, which is about twice the 7 day estimate from FoodNet.

Mortality depends on several factors, including co-morbidity and timely access to health care. These two factors may be particularly relevant in children, because of dehydration or spread of bacteria to the bloodstream, and may explain why the estimates from Kenya are higher than those from high-income countries. For a global estimate of mortality due to Campylobacteriosis, more information is needed on mortality in LMIC and in all age groups. Mortality may also vary for different subtypes of Campylobacter. The studies described above estimate mortality due to infection with *Campylobacter* spp. in general, and larger studies are needed to assess the mortality due to the specific species or subtypes.

Mortality estimates also depend on the way fatalities due to Campylobacteriosis are defined and the quality and completeness of the data. Some studies counted deaths within 7 days after laboratory confirmation of infection, others counted deaths within a year. An important limitation of the case-fatality rate is that it cannot be adjusted for other possible causes of death within the chosen period of time. The Kenyan study, for example, showed that malnutrition on admission and oral candidiasis (which can be associated with human immunodeficiency virus (HIV) infection) were independent risk factors for death. Excess mortality estimates would be more appropriate to use in burden of disease estimates, but are not available for most countries.

Although the different estimates may be difficult to compare, it can be concluded that mortality from *Campylobacter* infection in high-income countries is low; however, it should not be ignored. Furthermore, there is evidence to suggest that infection with resistant *Campylobacter* strains increases the risk of death (109). Unpublished data from Denmark confirm this association, but there is still controversy about the magnitude of the public health impact of resistance in *Campylobacter* (109). It is therefore important to estimate the mortality in different populations, to study the causes of excess mortality, and to take these findings into account in burden of disease estimates.

2.5 Serosurveillance

Serosurveillance has recently been developed for *Salmonella* spp. (110, 111). Serosurveillance data provide comparative data on (asymptomatic) infection independent of surveillance systems; however, they are considered to reflect exposure rather than disease incidence. For *Salmonella*, "seroincidence" is well correlated with the force of infection as measured by the "Swedish travellers" approach (112), as well as with the occurrence of *Salmonella* in pigs and chickens, as measured by the European "baseline" surveys carried out by the European Food Safety Authority. It has also been shown in Denmark that the emergence of *Salmonella* in the human population (as seen in the official bacteriological surveillance) was mirrored by an increase in seroincidence. Seroincidence is, however, much higher than the incidence of notified infections. This is because many infections are not diagnosed, and seroincidence studies measure all infections, including asymptomatic ones. Seroincidence can be applied to measure the force of infection and monitor effects of interventions, but does not readily measure burden of illness (113).

Serosurveillance has also been proposed for *Campylobacter* spp. (114). Data from the Netherlands suggest a very high seroincidence (up to 1 infection per person per year) for *Campylobacter* spp. (115). Recent unpublished studies indicate that there is no clear relation between *Campylobacter* seroincidence and national estimates of the force of infection (for example, by the Swedish travellers approach or prevalence of *Campylobacter* in broiler chickens). Hence, at present serosurveillance of *Campylobacter* is not an obvious tool to monitor the effects of interventions to improve food safety. It is possible, for example, that environmental exposures (potentially at low doses) or exposures from non- *jejuni*, non-*coli* strains contribute to the high seroincidence data.

The relationship between seroincidence and disease incidence is at present poorly understood, but is unlikely to be linear because of the impact of acquired immunity (116). The colonization/disease ratio may further be affected by strain and host characteristics, as well as exposure dose. It should also be noted that correlates of protection are poorly understood.

In summary, seroepidemiology is a useful tool to compare *Salmonella* rates between countries and over time. For Campylobacter, seroepidemiology can be used to study epidemiology and dynamics, but not as a surveillance tool. Immunity to *Campylobacter* is crucial for understanding disease to infection ratio, for quantifying the burden of illness, and for understanding risk factors and the impact of interventions. In the future, it will be of interest to link analytical studies of risk factors with serology or other measures of past exposure.

2.6 Vaccine development

WHO recognizes that there is considerable potential value in *Campylobacter* vaccines for humans and animals. In humans, this potential relates to the prevention not just of acute infection but also of sequelae, which may lead to a greater reduction in the burden of disease. Vaccines are unlikely to be used in a prophylactic role for the general public, but may have value for high-risk groups, such as travellers or military troops. However, considerable research is required before this potential can be realized.

In the past few years, momentum has been building in both the public and private sectors around efforts to develop new diarrhoeal disease interventions, including vaccines against rotavirus, cholera, typhoid, enterotoxigenic *E. coli* and *Shigella*. Currently, there are no approved vaccines or drugs that prevent *Campylobacter*-associated traveller's diarrhoea. Antibiotics can treat illness, but cannot prevent it effectively and may have the unintended consequence of contributing to increased antimicrobial resistance.

Vaccine strategies against *C. jejuni* are limited by incomplete understanding of its pathogenesis and by the strong association of this pathogen with GBS. Most strains of *C. jejuni* produce lipo-oligosaccharide (LOS) molecules that are decorated with sialic acid (Neu5Ac) moieties, such that they mimic human gangliosides in structure. Antibodies directed against these molecular mimics can cross-react with human peripheral nerves, resulting in GBS. This association between *C. jejuni* and GBS precludes many whole cell vaccine approaches, and most recent studies have focused on recombinant subunit protein antigens. However, the recent discovery that (unlike other enteric pathogens) *C. jejuni* expresses a capsular polysaccharide (CPS) has fuelled the development of a CPS-conjugate vaccine similar to those that have been licensed for other mucosal pathogens. Although few details of molecular pathogenesis are known, invasion of intestinal epithelial cells appears to be a critical step, and the CPS has been shown to play a role in invasion. Thus, antibodies against CPS may elicit a protective immune response. Moreover, unlike LOS cores, there is no evidence of any ganglioside mimicry in CPS that could induce autoimmune reactions. There is little reason to think that vaccination would prevent future GBS.

One recurring problem associated with capsular vaccines is their poor immunogenicity in infants, a population to which many of these vaccines are directed. This is because most pure polysaccharide

antigens are T-cell-independent, and are capable of stimulating only mature B cells. However, conjugation of polysaccharides to proteins converts the immunological response to a T-cell-dependent one, leading to the development of immunological memory, in both children and adults (117). Responses in infants to vaccines against type B *Haemophilus influenzae* groups A, B and C, *Neisseria meningitidis*, and *Streptococcus pneumoniae* type 6A and serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F have all improved following conjugation to carrier proteins inducing predominantly serological responses, though some indications of secretory IgA responses have also been observed (118, 119). Additionally, a conjugate vaccine directed against the O-polysaccharide of *Shigella* species, another cause of bacterial diarrhoea, has been shown to be effective in adults (120, 121) and elicits both serum IgG and IgA antibodies.

2.7 Data gaps and recommendations

2.7.1 Data gaps

- data needed to support causal associations between *Campylobacter* and long-term health outcomes (LTHOs), particularly the functional gastrointestinal disorders and inflammatory bowel diseases.
- minimum criteria for causality with the purpose of considering LTHOs in cost-of-illness and other economic analyses.
- studies to explore the range of musculoskeletal and gastrointestinal sequelae that may be attributed to *Campylobacter* infection.
- studies on duration of LTHOs and their impact on health and quality of life in different populations.
- incidence and impact of LTHOs in populations in LMIC.
- information on LTHOs and the cognitive and physical impacts of *Campylobacter* among children in LMIC is lacking (although studies from GEMS and MAL-ED may be revealing).

2.7.2 Recommendations to WHO

Incidence of *Campylobacter* enteritis

WHO should:

- encourage collaboration between laboratories and countries, building on the Global Foodborne Infections Network, including consideration of performance characteristics and quality assurance of diagnostic methods;
- encourage rising economies to invest in public health laboratory infrastructure to provide enhanced capacities for diagnosis and laboratory testing;
- promote the participation of epidemiologists and microbiologists in the design of demographic studies;
- discourage countries from using data from other countries to develop multipliers for extrapolating from reported to true incidence; encourage them to base such estimates on their own studies and case selection in the health care system;
- develop implementable guidelines on how to perform such studies.

GBS

WHO should:

- promote population-based studies on the incidence and triggering agents of GBS, particularly in Africa and Asia, using common standardised case definitions;
- encourage follow-up studies on disability, long-term outcomes and mortality associated with GBS;
- increase awareness of GBS and promote lower-cost case management;
- promote the validation of assays for serological studies of GBS;
- evaluate the use of AFP surveillance as a means of public health monitoring for paralytic diseases other than poliomyelitis.
- explore the feasibility of conducting studies of AFP specimens to determine the fraction related to Campylobacter-associated GBS.

ReA

WHO should:

- promote studies to estimate the risk of ReA following Campylobacter-associated gastroenteritis in ethnically diverse populations;
- promote the validation of assays for serological studies of ReA;
- promote studies on long-term disability caused by ReA.

Functional and chronic gastrointestinal disorders

WHO should:

- promote studies on the incidence of, and disability caused by, functional gastrointestinal disorders, inflammatory bowel disease and coeliac disease following *Campylobacter* enteritis.

Disability weights

WHO should:

- promote empirical studies on quality of life in unselected populations of patients with *Campylobacter* enteritis and sequelae.

Mortality

WHO should:

- evaluate different approaches to estimate mortality due to *Campylobacter* and promote studies using the most appropriate methods.

Serosurveillance and immunity

WHO should:

- promote research on the impact of acquired immunity on the dynamics of Campylobacteriosis, including its impact on risk assessment and epidemiological studies;
- promote the further development and use of serosurveillance as an independent tool to measure exposure to *Campylobacter* in a population.

Vaccines

WHO should:

- consider the potential use of vaccines against *Campylobacter* in high-risk populations.

3. Surveillance and antimicrobial resistance

3.1 *Campylobacter* surveillance

Public health surveillance is the systematic collection, analysis and interpretation of data on specific diseases in a defined population, to guide public health decisions (122). For infectious diseases, the data come largely from the clinical health care system, sometimes strengthened by further study of the microbes themselves. Surveillance can define the magnitude of a health problem, driving policies that will reduce or prevent it. Surveillance can identify an increase in the number of reported cases above the expected baseline, triggering an investigation into the possible outbreak so that the source can be identified and controlled. Surveillance can also provide a platform for more detailed studies to improve management and prevention, such as attribution of infections to particular reservoirs. Finally, surveillance can track trends over time, measuring the impact of control and prevention efforts.

In high-income countries, surveillance is most often conducted through reporting of laboratory-diagnosed infections in a population, and thus depends critically on the routine diagnostic practices in the health care system. Laboratory diagnosis for enteric infections is routine in most industrialized countries, and largely absent in LMIC.

Additional information can be collected to strengthen surveillance data. Estimation of the public health burden of *Campylobacter* in a population requires information about the severity of illness, such as the number days of school or work lost, whether or not the patient was admitted to hospital, and whether or not the patient died. To estimate the number of illnesses that went undiagnosed, using a pyramid model, data is needed on the health-care-seeking behaviour of people with diarrhoeal illness, and on the frequency with which *Campylobacter* diagnostic tests are performed. Monitoring of trends over time requires regular data collection and consideration of changes in diagnostic practices.

Monitoring of trends in resistance requires standardized testing of a systematic sample of isolates. For some enteric pathogens, such as *Salmonella*, Shiga toxin-producing *E. coli* and Listeria, surveillance conducted to detect outbreaks is far more sensitive if it includes subtyping, as an increase in a specific subtype signals a possible outbreak Defining a practical and effective subtyping system for that purpose has proved elusive for Campylobacter, and subtyping is rarely done routinely. However, once a *Campylobacter* outbreak has been detected, subtyping can be useful in refining the case definition used in the investigation, and in matching isolates from suspect foods and animal reservoirs with those from the affected persons.

3.1.1 *Campylobacter* surveillance in high income countries

The incidence of *Campylobacter* infections has been measured in many high-income countries. In the USA, this has been done through active surveillance (FoodNet programme) and the measurement of annual incidence of laboratory-confirmed infection (refer to Section 2.1) (123). Substantial regional differences may reflect differences in the degree of contamination of poultry, and are not accounted for by differences in risky behaviour, health-care-seeking or laboratory practices. In 27 European countries, the collective annual incidence of laboratory-confirmed *Campylobacter* infection in 2010 was 48.6 per 100 000 (124, 125). European rates have increased in the past 5 years. There are substantial differences between countries, some of which are probably related to differences in the health care system, and some to completeness of surveillance reporting, and also differences between related authorities within the same country,. Some country to country variation may also reflect

true frequency differences. (4, 126). Collecting systematic reports of investigated common source outbreaks of campylobacteriosis is another kind of surveillance that can help define the spectrum of food, water and other exposures and risk factors that are important in transmission (127).

Studies of sources of infection depend on surveillance to help identify outbreaks, to detect sporadic cases for case–control studies, to provide isolates that can be used in attribution models based on isolate subtyping, and to furnish data that can be used to construct and calibrate risk assessment models. Iceland offers one dramatic instance. After chicken began to be sold fresh and unfrozen at the end of the 1990s, the incidence of *Campylobacter* infections surged to a peak of 426 culture-confirmed cases in 1999 (156 per 100 000 population) (128). A new "test and freeze" control strategy was introduced, using freezing to reduce *Campylobacter* counts in poultry from farms documented to have Campylobacter. After this and other measures were implemented, the incidence dropped dramatically, so that by 2008 it was only 30 per 100 000, or 15 per 100 000 after excluding travel-associated cases (129). Substantial reduction was also seen in New Zealand, where systematic changes in poultry industry sanitation brought down the annual rate from 400 to 160 per 100 000 in 2009 (130). In the USA, incidence declined 30% from the baseline period of 1996-1998 (131) after the introduction of new poultry and meat inspection, and enhanced prevention measures based on the hazard analysis critical control point (HACCP) approach (similar to those introduced later in New Zealand), but has remained unchanged for the past decade (123, 131).

Travel-related Campylobacteriosis is an important subset of all cases; in the USA, 13% of *Campylobacter* infections are associated with international travel, and *Campylobacter* is the most frequently reported travel-associated infection (132). In Scandinavia, the proportion of travel-related cases is higher, and systematic reporting of such infections has provided proxy surveillance information for parts of the world where diagnostic testing or reporting of the infection is less frequent (133, 134).

3.1.2 *Campylobacter* surveillance in low- and middle-income countries

In many LMIC, laboratory diagnosis of enteric disease is rarely attempted and surveillance data on *Campylobacter* are scant. The available data indicate that the pathogen is particularly likely to be associated with illness in young children, and may be frequently found in stools from healthy people (135). In a recent study in rural Kenya, 5% of children less than 5 years old admitted to hospital with diarrhoeal illness had stools yielding *Campylobacter* (108). In older children and adults, the frequency among healthy controls was similar to that among people with diarrhoea, which may reflect high levels of immunity (135). However this was not uniform (135). In recent years, the GEMS project has provided systematic data from seven study sites in Asia and Africa on the frequency of many pathogens in people with and without diarrhoea (136). Preliminary analysis indicates that, in Asian sites, *Campylobacter* is among the five most frequent causes of diarrhoeal illness in children, even after accounting for its frequency among controls. In African sites, carriage in healthy people is so frequent that it is difficult to attribute a major fraction of diarrhoeal illness to *Campylobacter* (Levine, unpublished information, 2012). If high levels of maternal antibody can mask the clinical burden of *Campylobacter* in the first months of life, during which time high exposure and colonization rates produce some active immunity, then there may be less opportunity for it to cause overt illness, since high exposure rates will continue to boost immunity. In studies in South African clinics using non-selective media and a hydrogen-enriched microaerobic atmosphere, a variety of non-*jejuni*, non-*coli* species were identified among children, many of whom had HIV infection. The clinical significance of these infections and their frequency in other locations and different populations remains unclear (137).

In LMIC, the potential value of surveillance is complicated by the scarcity of microbiological laboratories, the lack of supplies and equipment, and the challenge of coordinating the monitoring effort across sectors. The WHO GFN is a collaborative training effort to increase capacity in LMIC for diagnosis and surveillance of foodborne pathogens, including *Campylobacter* (138).

3.1.3 Integrated surveillance and attribution of infections to sources and reservoirs

A well designed surveillance programme for Campylobacteriosis can provide information to inform national decision-making by: determining the relative importance of Campylobacteriosis compared with other enteric infections; showing which animals are the primary reservoirs for infection; and helping to identify the most common pathways of transmission (pathway attribution). Ideally, such a programme would be cost-effective, with the scale of data collection informed by statistical considerations. This "strategy-focused" surveillance (139) would also provide essential epidemiological information for burden of disease studies.

In high-income countries with established Campylobacteriosis surveillance systems, efforts should be directed at monitoring the impact of interventions and improving efficiency, by taking into account sample size and statistical power. Case–control studies to identify risk factors can be helpful. One approach is to add standard questions to an existing surveillance system of other enteric pathogens, to act as controls. When combined with microbial typing data and attribution models, these could help to identify risk factors for cases associated with particular reservoirs, such as poultry or ruminants (140).

With sufficient resources to obtain information close to real-time – such as the identification of clusters in space and time and rapid typing of isolates from cases – such a surveillance programme could also be used for "control-focused" surveillance (139). In this way, outbreaks associated with specific food premises or environmental contamination events could be identified quickly and control measures taken locally (139).

Surveillance of Campylobacteriosis can be carried out at national level, with relevant data recorded in all regions, including case notifications and microbial subtyping data on isolates from both cases and animal reservoirs (to allow attribution of human cases to animal reservoirs). Alternatively, well-resourced sentinel sites that are broadly representative of the whole country could be monitored. In New Zealand, a hybrid approach combines national reporting of notified cases and case-related epidemiological information, with sentinel site surveillance for source attribution (130).

3.2 Issues in laboratory diagnosis and identification

Surveillance depends on laboratory diagnosis, and variation in diagnostic methods can affect the results of surveillance (141). *Campylobacter* is difficult to isolate, grow and identify. Public health reference laboratories can play a key role in standardizing, validating and disseminating methods for clinical diagnosis, and in supporting periodic or sentinel targeted surveillance studies.

3.2.1 Isolation and identification in the clinical setting

Culture and isolation

Most *Campylobacter* spp. require a microaerobic atmosphere containing about 5% oxygen, 10% carbon dioxide, and 85% nitrogen. Some species of Campylobacter, such as C. sputorum, C. concisus, C. mucosalis, C. curvus, C. rectus and C. hyointestinalis, may require hydrogen for primary isolation. Commercial gas packs do not yield sufficient hydrogen for the isolation of these species. The conventional method for isolating the common enteric *Campylobacter* species (*C. jejuni* and C. coli) from faeces is primary plating on selective media and incubation at 42 °C in a microaerobic atmosphere. There is a distinct advantage in incubation at 42 °C rather than 37 °C for the isolation of these species (142).

Selective media that suppress competitive flora and enhance recovery of *Campylobacter* are blood-based, or blood-free charcoal-based, and contain one or more antibiotics, mainly cefoperazone.

Not all media in common use have been fully validated in clinical diagnostic laboratory settings. An increase in antimicrobial-resistant competitive flora may impair selectivity (143). The newly introduced Campylobacter-selective chromogenic medium, CASA, could reduce the laboratory workload (144).

Some less common *Campylobacter* species, the role of which in the disease process is not fully understood, are inhibited by conventional selective agents, standard microaerobic gas mixture, and/or incubation at 42 °C. To determine the presence of such organisms, stool filtration and culture on a non-selective medium with incubation in a hydrogen-enriched atmosphere at 37 °C has been successfully used (137).

Identification

The conventional identification scheme for *Campylobacter* and related microorganisms is based on classical phenotypic characteristics, such as morphological appearance, biochemical reactions, and growth temperature and tolerance tests. The various *Campylobacter* species isolated from humans are not easy to identify. Only *C. jejuni* can be routinely identified with phenotypic markers; others require a polyphasic approach, using a combination of phenotypic and molecular markers. In many clinical laboratories, the identification of *Campylobacter* spp. is only performed to the genus level. Commercial manual or automatic systems for bacterial identification are routinely used in many clinical laboratories, but may misidentify non-*jejuni Campylobacter* species, and depend on access to, and maintenance of dynamic reference databases (145-147). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) offers a new and attractive means of identifying *Campylobacter* species that may prove relevant to public health and food safety, though it does not provide information on bacterial resistance, and lacks a computerized "expert system" to advise the microbiologist on other supplementary tests (145). Alternative identification methods, such as molecular assays using either species-specific or multiplex reactions based on ribosomal 16S gene sequences, rpo B and other species-specific gene sequences, and microarray-based identification tests, have been developed for use in public health reference laboratories (148-150).

3.2.2 Role of national reference centres in low- and middle-income countries

In LMIC, national reference centres (NRCs) appointed by the Ministries of Health support the microbiological surveillance of specific infectious diseases. Similar to national reference laboratories in high-income countries, NRCs are primarily responsible for: (1) maintaining technical expertise in laboratory methods for microbiology or pathology of infectious agents, so that they can provide consultation and laboratory testing services for diagnosis, identification and subtyping of infectious agents isolated by medical laboratories; (2) contributing to epidemiological surveillance (for example, by monitoring trends in the frequency and characteristics of specific infections, and their resistance to antimicrobial agents) and supporting epidemiological and clinical trials relating to their field of expertise; and (3) reporting unusual events, such as outbreaks, and emergence or resurgence of infectious agents, to the Ministry of Health (151).

In collaboration with WHO, the NRCs also reach out to clinical and laboratory partners in the country, providing information, standardizing terminology, nomenclature and diagnostic methods, and applying the appropriate technologies. They provide in-country training and coordination to other institutions, and may participate in collaborative research and promote the application of the results of such research.

3.2.3 Good laboratory practice and quality assurance

Good laboratory practice (GLP) defines a framework, or set of principles for quality management, within which laboratory studies are planned, performed, monitored, recorded reported and archived. This framework provided documented evidence that laboratory results are accurate, reliable and reproducible

and that results are submitted to relevant stakeholders, such as clinicians, public health practitioners, animal health practitioners and allied personnel. They help ensure that the data submitted can be relied upon when making risk or safety assessments. Internationally accepted standards for GLP are published by the International Organization for Standardization (ISO) (152). These and other guidelines (153, 154) highlight the importance of quality management in laboratory testing. Strict adherence to quality requirements will produce high quality, reliable data, reduce the occurrence of laboratory errors, and lead to continuous improvement in laboratory processes and services. While the principles discussed below were developed for general laboratory management, the points made are pertinent for identification of Campylobacter.

Quality assurance can be addressed through a systematic four-point plan (155).

Proficiency testing.

1. **Proficiency testing schemes** (PTSs) are essential for laboratories to monitor the reliability of their analyses and to identify critical points in their procedures. They provide external evidence of a laboratory's technical competence. Documentation of receipt of blinded PTS samples, testing methods and review of the results of the tests in comparison to what was expected for the samples being tested shows whether the results are within the acceptance limits, and if not, corrective actions are proposed. PTSs can also be used to verify that standard operating procedures (SOPs) are followed. Few proficiency testing schemes are available for Campylobacter. National laboratories may wish to participate in the GFN external quality assurance (EQA) programme, which includes *Campylobacter* (138). An alternative, which may supplement existing EQA, is to implement an isolate exchange programme with other clinical, public health and reference laboratories.

2. **Internal quality controls.** A quality control plan should be established, specifying when, how and which internal quality control (IQC) checks are to be performed, acceptance and rejection criteria for IQC, the review plan for the documented IQC results, and follow up with corrective action as appropriate (152). Documentation and review of the IQC results and of corrective actions taken when necessary indicate whether quality assurance objectives are being fulfilled. Documentation of use of laboratory consumables and reagents, laboratory equipment, internal quality control records and recording of results are crucial in developing an audit trail for traceability of a specimen. Documentation of the examination procedure in the form of an internationally accepted SOP helps ensure that laboratory personnel perform the procedure correctly and that consistent results are produced (153, 154). There should be appropriate documentation, including relevant training records, that laboratory staff are competent to perform the work with which they are entrusted, or are acting under supervision.

3. **Maintenance and calibration of laboratory equipment.** Operational laboratory equipment is crucial to producing quality results. All equipment should be regularly maintained and serviced according to the manufacturer's instructions. Measuring equipment usually needs to be calibrated to ensure accuracy in accordance with the manufacturer's recommendations. Equipment should be validated before being used in the laboratory. The accuracy of laboratory equipment should be verified and documented before use. There should be a file for each piece of equipment, documenting its history (153).

4. **Reagent supply management.** Inventory management ensures that adequate supplies of reagents and consumables are available. Laboratory reagents and consumables should be inspected on delivery for damage, correctness of items ordered and expiry date. The reagents and consumables should be stored at the correct temperatures (as specified by the manufacturer). The identity and expiry date of reagents should be verified . Reagents must pass QC before use. The lot number

of reagents used in examination procedures should be recorded on a worksheet or automated equipment to ensure that they can be traced (153).

Accreditation

International standardization schemes can help countries to initiate an in-country accreditation scheme by providing a framework and guidelines for developing such schemes (152-155). These schemes are based on internal and external review of laboratory quality assurance and practice, to check that GLP is implemented to an internationally acceptable level. Techniques may include document review, vertical audits of laboratory tests, participation in quality assessment or proficiency testing schemes, and review of staff competence.

Isolate exchange programmes

In isolate exchange programmes, participating laboratories exchange unknown clinical isolates to evaluate the competency and methods for organism identification in each laboratory. The sending laboratory prepares the set of isolates or simulated specimens, the identity of which must be unknown to the receiving laboratory. The receiving laboratory processes the isolate or specimens as it would normally, to test the quality assurance criteria listed above. The receiving laboratory can then document progress in dealing with such isolates or specimens. These programmes are most easily implemented between laboratories that are geographically close and in the same country, in order to decrease transport costs and avoid the need to transport materials across borders. Laboratories may alternate in sending and receiving PTS isolates.

3.2.4 Culture-independent diagnostic tests

The introduction of new culture-independent diagnostic tests (CIDTs) is starting to allow better monitoring of disease burden and trends. In the industrialized world, a variety of rapid enzyme immunoassays or DNA-based diagnostic tools are being developed and adopted for direct detection of *Campylobacter* in stool. These tests vary greatly in sensitivity and specificity, and do not yield isolates for further identification or characterization (156, 157). While the tests are easy to use, give same-day results and avoid some of the challenges of culture, their adoption can lead to public health quandaries about which diagnoses to accept as confirmed, which to use as a basis for further public health action, how to account for the impact of changing sensitivity on trends, and how to ensure the availability of isolates for subtyping and resistance monitoring (158). The sensitivity and specificity of the new assays need to be compared with those of standard microbiological methods in realistic clinical settings. Also, surveillance will need to monitor the diagnostic methods in use, in order to interpret observed differences. At least a subset of specimens yielding a positive signal will also need to be cultured, to provide information on subtypes and antimicrobial resistance. The USA has developed guidelines for clinical and public health laboratory practice for Shiga-toxin-producing *E. coli*, which strongly encourage reflex culturing of samples that are positive by CIDT (159, 160). Similar guidelines are being developed for Campylobacter.

While current *Campylobacter* CIDTs do not differentiate between *C. jejuni* and C. coli, and do not identify the other species at all, the development of better gene-based species-specific diagnostic assays will offer an opportunity to identify more of the *Campylobacter* species that are missed by routine clinical laboratory methods. The use of multiplex platforms is likely to increase the number of polyclonal detections, which will make diagnostic interpretation more complex. In the USA, a limited set of species-specific DNA probes is beginning to be used in state reference laboratories to identify common species (148). If the cost of the diagnostic platforms drops sufficiently, and if their sensitivity and specificity are validated in developing world settings, CIDTs may bring presumptive diagnosis within reach in LMIC.

3.2.5 Harmonizing methods for food and water

The isolation of *Campylobacter* from food and environmental samples requires more complex methods. Enrichment cultures are essential and are often preceded by pre-incubation at 37 °C to repair bacteria that have been sublethally damaged by exposure to heat or cold (161). Variations in the enrichment method used and in the timing of the addition of antibiotics can affect the results. International developed standards exist for isolation of *Campylobacter* spp. in food and water (162). ISO has published four standards covering detection and enumeration of *Campylobacter* spp. in food, feed and water. ISO standard 10272-1:2006 (163) part 1 describes a method that can be used in a variety of matrices (a so-called "horizontal method") for the detection of *Campylobacter* spp. in food and animal feed. Part 2 of the standard describes the enumeration method and part 3 describes a horizontal method for semi-quantitative determination of *Campylobacter* spp. Similarly, ISO standard 17995:2005 (164) describes a method for detection and enumeration of thermophilic *Campylobacter* species in water, which is also applicable to qualitative analysis (presence/absence) of *Campylobacter* species.

A revision of ISO standard 10272-1:2006 was begun in 2009 (165). The new standard will be divided into three parts. Part A will focus on detection of *Campylobacter* in foods with a low background count of non-Campylobacters or with stressed Campylobacters; part B will cover detection in foods with a high background level of non-Campylobacters; and part C will cover detection by direct plating in samples with a high *Campylobacter* spp. load, for example in faeces or poultry caecal contents. The aim is to improve the enrichment and confirmation steps, as well as the conditions for microaerophilic incubation. It should be noted that *Campylobacter* spp. have hardly ever been detected in feed.

Non-culture methods based on the polymerase chain reaction (PCR) are increasingly being used to diagnose Campylobacteriosis in humans, as well as to detect *Campylobacter* spp. in food and animal samples. At least one Real-Time PCR Assay has been validated by rigorous comparison against the regional standard EN ISO 10272-1:2006 for the detection of *C. jejuni*, C. coli, and C. lari in poultry faeces of cloacal swabs (166) .

In addition, the Nordic Committee on Food Analysis (NMKL) has published a standard method for the detection and enumeration of thermotolerant *Campylobacter* in food. The ISO and NMKL methods have been compared; the NMKL method No 119 is considered equivalent with the ISO method 10272-1:2006 for *Campylobacter* (167). The EU legislation on microbiological criteria in food (168) specifies ISO standards as the official methods for testing for several pathogens, such as *Salmonella* spp. and Listeria monocytogenes; so far, however, *Campylobacter* spp. have not been included in the criteria.

There is a need for simplified methods, particularly for use in countries with limited laboratory capacity. These methods should ideally be validated against internationally accepted standard methods through interlaboratory collaborative studies, though this is not always possible. On the other hand, standardization alone is not sufficient to ensure that results are valid and reliable. Several factors may influence the results, from sampling to performance of individual laboratory technicians, and thus broader guidance is needed. OIE has provided detailed guidance on collection, transportation and analysis of samples from live animals (169). The proposed ISO 10272-1C, now under development, will also cover investigation of animal faeces.

Harmonization of qualitative and quantitative analysis methods for *Campylobacter* in food, feed, water and animals at the global level is needed. GFN, FAO and OIE can play key roles in leading this process to ensure that laboratory methods throughout the world provide valid and reliable results. The ISO standards and corresponding NMKL methods should be used to validate new methods. Ideally, any new method or modification of an existing standard method should be validated against the international standard, or at least tested in several laboratories through EQA schemes.

3.3 Surveillance of antimicrobial resistance

The surveillance of antimicrobial resistance in *Campylobacter* has identified important levels of resistance to tetracyclines and fluoroquinolones in many parts of the world. In the USA, in 2010, 1% of *C. jejuni* isolates from humans were resistant to erythromycin, 43% to tetracycline, and 22% to ciprofloxacin (170). For *C. jejuni* from broiler chicken meat, the comparable figures were 1% for erythromycin, 36% for tetracycline, and 22% for ciprofloxacin (171). In the EU in 2010, 2% of *C. jejuni* in humans were resistant to erythromycin, 21% to tetracycline, and 52% to fluoroquinolones; for broiler chicken meat the figures were 2%, 22% and 50%, respectively (104). In both the USA and the EU, resistance is generally higher in *C. coli* than in *C. jejuni* (104). One cause of the high level of resistance to fluoroquinolones appears to be the use of these drugs to treat poultry (172). In the USA, fluoroquinolone resistance in *Campylobacter* isolated from humans was linked to consumption of poultry, as well as to foreign travel; approval of fluoroquinolone use in poultry was withdrawn in 2005 (173). In Australia, where such use was never approved, fluoroquinolone resistance in domestically acquired *Campylobacter* infections is rare (172).

Patterns of antimicrobial use and selection for resistance in one part of the world affect health in other parts of the world, through international travel and trade. It has been observed that fluoroquinolone-resistant infections are often associated with travel to developed or developing countries (174-176). More systematic collection of such information may offer a way of monitoring resistance patterns in parts of the world where local surveillance is limited or lacking. It is difficult to conduct systematic case–control studies among returning travellers, but comparison of strains from returning travellers with those from meat, poultry or other food products imported from the same countries may be useful. This information is of particular value when combined with detailed data on antimicrobial use in humans and animals. Resistance prevalence data are the starting-point for assessing the risk associated with antimicrobial resistance (177).

3.3.1 Harmonizing methods for determining antimicrobial resistance

In vitro antimicrobial susceptibility testing is essential to provide guidance to physicians and veterinarians on appropriate treatment of infections and to generate data on the occurrence of acquired resistance among bacteria. Several testing methods based on agar dilution, disc diffusion, Etest, and broth microdilution have been used to determine the susceptibility of *Campylobacter* to antimicrobial agents. Each method has advantages and disadvantages.

In the USA, agar and microbroth dilution are the principal recognized methods for susceptibility testing of *Campylobacter* (178, 179). Both methods are reproducible and can provide minimum inhibitory concentration (MIC) values, which are critical for antimicrobial resistance monitoring programmes. However, these methods are relatively expensive and require specialized equipment and training.

Disc diffusion testing is relatively simple, flexible, convenient and inexpensive. However, because of its poor reproducibility and variations in inhibition zone sizes, the Clinical and Laboratory Standards Institute (CLSI) in the USA has recommended disc diffusion testing only as a screening method for strains resistant to ciprofloxacin and erythromycin (178). In this method, growth of the organism up to the edge (no zone of inhibition) of a 5 ×g ciprofloxacin disc or a 15 ×g erythromycin disc is considered to indicate resistance. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has proposed a disc diffusion method with quality control limits for ciprofloxacin, erythromycin and tetracycline (180).

Another widely used method is the Etest. This technique is also convenient, and has the advantage of providing MIC values over a wide range. A number of studies have examined the correlation between the Etest and agar dilution for susceptibility testing of Campylobacter, and have found that the MICs varied greatly depending on the antimicrobial agent tested. The overall agreement of MICs (+$\log_2$ dilution)

between the two methods ranged from 62% to 83% (181, 182). While MICs do not always agree, the E-test does correlate with dilution methods for identifying strains with acquired resistance (181).

Because *Campylobacter* is a slow-growing organism, and requires microaerobic conditions and supplemented growth medium, variations in the media used and in the incubation conditions, e.g. atmosphere, temperature and time of incubation, could affect the results of antimicrobial susceptibility tests. Quality control is therefore important in the testing procedure, and should include the use of quality control strains with defined susceptibility. CLSI and EUCAST have made recommendations on testing methods and quality control procedures, using *C. jejuni* ATCC33560 as the quality control organism.

Currently, there are no validated clinical breakpoints for any antimicrobial agents for Campylobacter. It is important to differentiate MIC interpretative criteria used for clinical purposes (clinical breakpoints) from those recommended for monitoring programmes (epidemiological cut-off values or microbiological breakpoints). The former are based on extensive data sets comprised of population MICs, pharmacological properties and the outcome of clinical trials. In the case of Campylobacter, for which there are insufficient outcome data, CLSI has recommended population MIC distributions as the basis for tentative resistance breakpoints for ciprofloxacin (MIC U 4 mg/l), erythromycin (MIC U 32 mg/l), doxycycline (MIC U 8 mg/l), and tetracycline (MIC U 16mg/l) (178).The CLSI approach sets cut-off values based on the MIC distributions of resistant populations, with a view to guiding therapy. These values are highly correlated with the presence of known resistance determinants.

The epidemiological cut-off values used by EUCAST define the susceptible population with a view to harmonized surveillance reporting of non-wild-type organisms (183). This approach identifies strains with acquired traits that confer decreased susceptibility, which may encompass strains that are still responsive to antimicrobial therapy (i.e. not clinically resistant). Both approaches should be considered with caution as guides to antimicrobial therapy until supporting clinical outcome data are available.

The choice of testing methods for individual laboratories will depend on the objective of the testing (guide for clinical therapy vs. monitoring of resistance in surveillance programme) and laboratory capacity. The reproducibility, relative ease of performance, cost, flexibility in the selection of drugs for testing, and perceived accuracy of the results should be taken into consideration. Real-life comparison of standard methods is needed, including those that can be done with limited laboratory resources, in order to make practical recommendations for LMIC.

3.4 Data gaps and recommendations

3.4.1 Data gaps

- few data are available on the incidence and clinical importance of *Campylobacter jejuni* or *C. coli* infection in many LMIC.
- few data are available on the sources of resistant infections in many countries.
- clinical response data are lacking with which to validate the resistance breakpoints that have been proposed.
- little is known about test performance and clinical utility of the rapid antigen detection methods and other CIDTs in a variety of settings.
- few data are available with which to assess the public health or clinical importance of non-*jejuni/coli* species of Campylobacter.

3.4.2 Recommendations to WHO

- develop guidelines for studying the incidence of Campylobacteriosis in different regions of the world, taking into consideration the availability of data in LMIC;
- encourage routine national surveillance of *Campylobacter* infections to determine incidence of diagnosed infections, prevalence of resistance, and to gather reports of outbreak investigations
- when systematic national control strategies are planned, encourage their linkage to the appropriate surveillance systems and analyses, so that the impact can be documented and measured by reduction of positive flocks, decrease in positive carcasses and retail products, as well as reduction in human illness
- encourage more systematic description of *Campylobacter* infections in international travellers, including monitoring resistance and MLST subtyping, to provide geographically representative initial information for those countries that do not as yet have surveillance.
- encourage limiting standard surveillance to *C. jejuni* and *C. coli* infections, and surveillance of resistance to tetracycline, erythromycin and ciprofloxacin;
- encourage incorporating information on the diagnostic test used as part of routine surveillance data collection, in order to monitor changing diagnostic practices;
- support the use of CIDT tests for *Campylobacter* diagnosis in countries;
- support work to assess the sensitivity and specificity of CIDTs to detect *Campylobacter* in stools in different clinical and geographical settings;
- ensure correct conditions and media for isolating and typing *Campylobacter* which are crucial for the reliability and interpretation of results;
- foster formal validation of standard culture media in different geographical settings;
- foster development and field-testing of a diagnostic culture protocol and method for determining antimicrobial resistance, in settings with limited resources, and evaluate CIDT approaches at the same time.
- promote and provide training in the implementation of a quality management system in laboratories in resource-poor settings;
- continue to foster research on the diagnosis of non-*jejuni*, non-*coli Campylobacter* species and to define their public health importance;
- make available updated ISO culture protocols or equivalent for food and environmental specimens as they become available.
- work with FAO and OIE to promote the harmonization of qualitative and quantitative analysis methods for *Campylobacter* in food, feed, water and animals at the global level.

4. Source attribution

Source attribution (sometimes called food attribution) is the estimation of the relative contributions of different sources to the burden of human illness; it is used to inform policies for prevention and control. Until now, the term source has been used to mean any point along the transmission pathway, such as the animal reservoir or amplifying host (for example, cattle or chickens), the transmission pathway (for example, food, water or direct contact) and even specific food products. A number of approaches can be used for source attribution, including microbial subtyping, outbreak summary data, epidemiological studies, comparative exposure assessment, and structured expert opinion (184). These approaches can be broadly divided into epidemiological and microbiological approaches (184-187). Pires et al. (187) listed a number of approaches to source attribution, with key references and a summary of their advantages and disadvantages. They highlighted the importance of the "point of attribution", defined as the location in the food chain addressed by a particular approach. In other, similar frameworks describing the relationship between environmental factors and disease, the terms "proximal determinants" and "distal determinants" have also been used to describe the location of points of attribution along a transmission pathway (188).

4.1 A general framework

The term source attribution should be used as a collective term to cover reservoir attribution, pathway attribution, comparative exposure/risk assessment and risk factor modelling, as outlined in Fig. 2.

- **Reservoirs.** These are animal reservoirs or "amplifying hosts". They can be grouped or subdivided into epidemiologically meaningful categories, depending on the question being addressed. For example, cattle and sheep may be grouped as ruminants if it is not important to distinguish between them, or if it is not possible to determine their independent contributions. Alternatively, poultry may be subdivided according to the supplier, if it is possible and important to determine their independent contributions. Reservoir attribution models provide estimates of the relative contribution of the amplifying hosts to the burden of human disease for the purpose of targeting interventions. In reservoir attribution modelling, it may also be convenient to use a non-animal source to capture the contribution from an unmeasured host or group of hosts; an example is the use of environmental water to capture the contribution from wildlife hosts (189, 190).

- **Pathways.** These may be considered the primary routes by which *Campylobacter* shed by amplifying hosts reach and infect humans. Again these can either be grouped or subdivided according to the question being addressed. The most meaningful categories for informing policy (e.g. for allocating resources or identifying the authority responsible for control) are likely to be food, environment, water (which may be considered part of the environmental pathway) and direct contact. A range of techniques have been used to estimate the contribution of different pathways to human infection: top-down approaches, which subdivide the contribution of amplifying hosts into food and environmental pathways; or bottom-up approaches, which combine the contributions from different exposures and risk factors.

- **Exposures.** Primary pathways can be subdivided into a number of secondary exposures. For example, the food pathways can be divided into meat and milk, while environmental contamination of surface water may affect drinking-water and recreational water. The relative contributions of the exposures can be determined using comparative exposure or risk assessment models

- **Risk factors.** In population-based epidemiological studies, such as case–control studies, variables are measured that describe specific determinants of risk (such as the consumption of a specific food product), the magnitude of risk associated with these factors is estimated, and statistical tests of association are conducted. These are represented as a further subdivision of pathways and exposures. For example, cattle (source) may contaminate the food chain (pathway) resulting in hazard in the milk supply (exposure), which manifests itself as an increased risk associated with the consumption of raw, unpasteurized milk (risk factor). This cascade is analogous to the point of attribution defined above (186, 187).

Fig. 2 illustrates how different elements of source attribution fit within a wider framework, incorporating multiple data sources and modelling approaches. The framework may need to be modified depending on the setting: for example, municipal drinking-water supplies may need to be considered in a separate pathway to bottled water supplies if different authorities are responsible for regulation and control. Although this framework is designed for Campylobacteriosis, it can also be applied to other zoonotic pathogens with minor modifications.

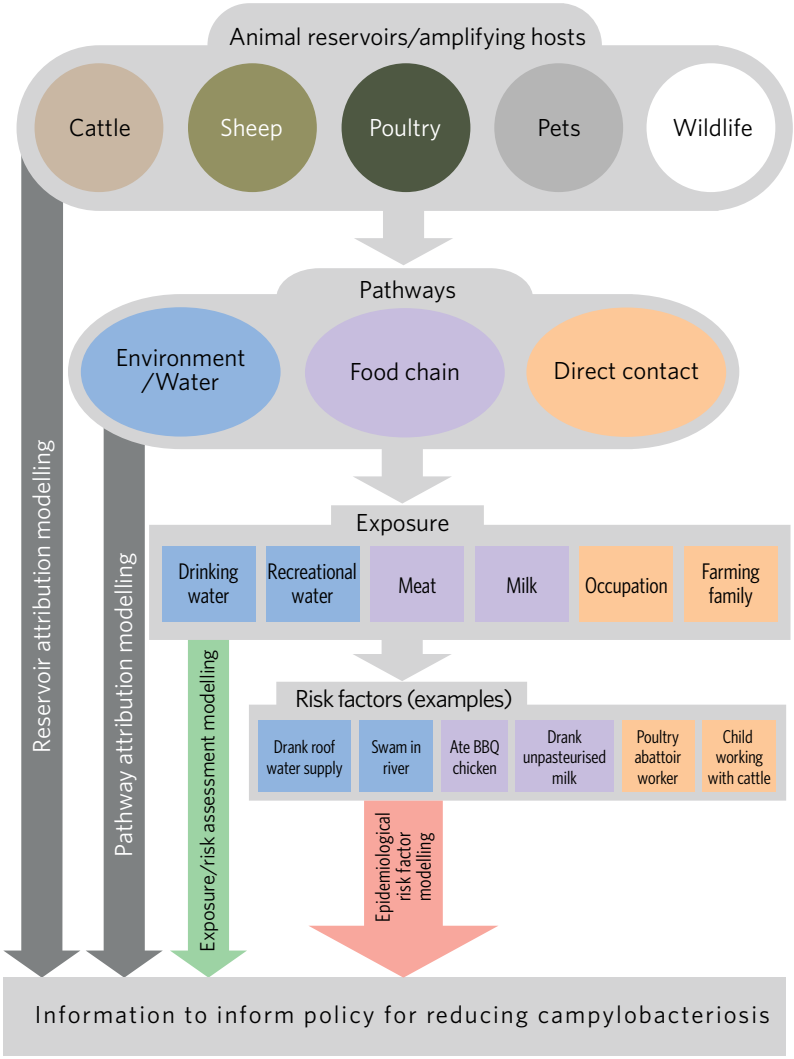


Fig. 2. Framework showing sources of information and modelling approaches for the transmission of zoonotic diseases, such as Campylobacteriosis. Note: the terms reservoir, pathway, exposure and risk factor are used here for illustrative purposes, to show how various levels of data disaggregation and refinement can be incorporated into different models for informing decision-making.

Other factors may need to be considered when examining likely sources of Campylobacteriosis. For example, the framework does not consider person-to-person spread, infections acquired during overseas travel, the impact of imported food products, or the potentially complex transmission cycles that could occur between animal hosts, either directly or indirectly via the environment. Person-to-person spread could be included by considering humans as a spillover host (191) infected from an animal reservoir, with direct contact as the pathway. Similarly, imported food could be considered part of the food pathway, with the reservoir located outside the country. In order to keep the framework relatively simple, complex feedback loops representing transmission between reservoirs are omitted, although it should be recognized that these may be important when considering possible interventions (188). Some reservoirs may be repeatedly infected by other reservoirs, effectively acting as an intermediate host in a direct contact pathway (i.e. not a true maintenance host). For example, pets may be repeatedly infected from food animals, but not be primary amplifying hosts. Likewise, human infections associated with pet ownership may be the result of direct contact with pet food contaminated by food animals, rather than the pet itself (192).

4.2 Advantages and disadvantages of different approaches to source attribution

Each of the techniques currently in use for source attribution has advantages and disadvantages, some of which are described below using a framework developed by the European Food Safety Authority (184). This outline should be considered alongside other reviews providing similar summaries (185-187).

4.2.1 Epidemiological observations and studies

The most common type of epidemiological study used to calculate population attributable risks is the case–control study (193). This compares the characteristics of cases of disease with those of a sample without disease, representative of the population from which the cases arose (the controls). The variables measured may be primary risk factors, or potential confounding variables that need to be controlled for. The analysis usually leads to the calculation of an odds ratio or relative risk, which is adjusted for confounding factors; these can be combined with information on the prevalence of the risk factor in the population under investigation to calculate the proportion of cases that could be attributed to the risk factor. This is the population attributable risk, and can be expressed as a percentage or a fraction. Such studies can be done rapidly, and can provide valuable insight into the role of risk factors. Information can then be aggregated to provide estimates of the relative contribution of different exposures, pathways and potential sources. They can also assess changes in human behaviour, and detect emerging problems.

However, such studies have a number of disadvantages. They are prone to reporting bias, particularly inaccurate recall of risk factors by cases and controls. Importantly for diseases such as Campylobacteriosis, they are also inefficient when there is a high rate of exposure to the pathogen in the population. In this situation, a large proportion of controls are likely to be immune to the disease. This will tend to bias estimates of odds ratios towards the null value (1.0) and reduce the power of the study to detect significant risk factors.

Other types of population-based studies have used surveillance data and other information to attribute reservoirs and pathways (184-187). They include studies of surveillance data on sporadic cases and outbreaks (see below), cohort studies, and the impact of serendipitous events such as the decrease in *Campylobacter* infections that occurred when no poultry meat was available for a period of time due to the dioxin feed contamination in Belgium and the avian influenza epidemic in the Netherlands, which resulted in reduced exposure due to culling of poultry flocks (194, 195). All of these approaches can provide valuable insights into the disease using existing data, and can be both cost-effective and efficient. However, the lack of data, or poor quality of the available data, and the time taken to produce what are often highly retrospective estimates can limit the usefulness of these methods.

4.2.2 Analysis of outbreak data

Although generally considered as a separate category in reviews, the compilation and analysis of outbreak data is in essence another use of epidemiological data. Outbreaks are commonly defined as two or more epidemiologically linked cases, often identified as part of a national surveillance programme or as a result of local public health activities. The evidence that cases are part of an outbreak will include epidemiological information on where and when they occur (they are often clustered) and indications of a common exposure or risk factor. The latter is particularly important for reservoir and pathway attribution. Information obtained during the investigation of outbreaks will often identify specific events arising from contamination of food or the environment, such as undercooked poultry served to nursing home residents, or a batch of contaminated unpasteurized milk. It may be difficult to aggregate information at varying levels of resolution to identify the precise source of contamination, and this could lead to misclassification as a result, for example, of exposure to multiple food ingredients. Large and diffuse outbreaks may be due to the widespread dissemination of contaminated food products, including imported food. Although the vast majority of campylobacteriosis cases are considered to be sporadic (i.e. are not known to be epidemiologically linked), outbreaks do occur frequently and can provide valuable information to be considered together with other approaches. However, this assumes that outbreak and sporadic cases have a similar epidemiology. This may not always be the case. For example, at least in terms of the US, the most frequent food vehicle reported in outbreaks of campylobacteriosis is raw unpasteurized milk, while for sporadic cases, eating poultry is the greatest risk factor. The relative contribution of animal reservoirs and raw milk accounts for only a small fraction of sporadic cases (127, 196). Estimates derived from outbreak data may be combined with estimates of under-reporting to determine the total burden of outbreak-associated disease attributable to each pathway and exposure (197).

4.2.3 Comparative risk and exposure assessment modelling

This approach is termed comparative exposure assessment in the review article by Pires et al. (187), and uses Monte-Carlo modelling to determine the relative importance of different exposures, by simulating the prevalence and numbers of pathogens along transmission routes to the point of human exposure (198, 199). In the context of attribution, this could be considered a simplified version of a food chain quantitative microbial risk assessment, which models the propagation of pathogens along specific food pathways (for example, the modular process risk model (200). This approach typically uses information from a number of published studies, expert opinion and small-scale experiments to determine the relative exposure for each pathway. When combined with a dose–response model, the exposure assessment becomes a risk assessment, estimating the relative or absolute number of cases arising from each source. This method has the advantages that specific exposures and pathways are considered, and the impact of potential mitigation measures can be assessed. Its disadvantages include the lack of good data to inform the model, and the uncertainty associated with dose–response, both of which result in a lack of precision in risk estimates.

4.2.4 Source attribution modelling based on microbial subtyping

This approach compares the distribution of microbial subtypes, such as MLST genotypes (201), in human cases with those isolated from a range of sources, to determine the contribution of each source to the burden of disease. The advantages of this approach include its ability to determine the primary animal reservoirs, and the contribution of subsets of these to the burden of human disease. Recent advances in reservoir attribution models specifically designed for microbial subtyping data have greatly improved the quality of the results (190, 202). The data generated by molecular subtyping are also of considerable value for understanding the epidemiology of the disease, and therefore refining understanding of the relative contribution of reservoirs, pathways, exposures and risk factors. In particular, they provide a means of monitoring changes in reservoir attribution and epidemiology over time (dynamic reservoir attribution modelling), which is of particular value for assessing the

impact of interventions (130, 203, 204). The disadvantages include the costs of sampling, isolation and genotyping of isolates which, if not already integrated in existing surveillance programmes, may be prohibitive, and the lack of genetic discrimination between the *Campylobacter* populations found in hosts, such as cattle and sheep.

4.2.5 Expert elicitation

The formal gathering of structured expert opinion has been used for source attribution, both as a stand-alone qualitative exercise and as a way of estimating parameters for model-based approaches. There have been a number of recent developments in the field, including the introduction of quantitative methods. Techniques for reducing bias in expert estimates have been developed for other risk assessments, and are likely to be deployed for source attribution in the future. A more thorough review of these approaches is given elsewhere (184).

Given the limitations of individual methods, a comparative modelling approach is advisable; this may use multiple tools and address different points. An example is the study by Lake et al. (205) in New Zealand, which used multiple tools for source and pathway attribution, exposure assessment and risk factor analysis.

4.2.4 Modelling methods for data on microbial subtypes

A number of statistical tools and models are available for analysis of data on microbial subtypes.

- **Proportional similarity (PS) index.** The PS index is an objective and simple estimate of the area of intersection between two frequency distributions (206). In this way, it assesses the similarity between the frequency distributions of subtypes for each reservoir and that among human cases. The PS index ranges from 1 (identical distribution) to 0 (no common subtypes). Confidence intervals can be estimated (189, 207).

- **Dutch model.** This method compares the number of reported human cases caused by a particular subtype with the relative occurrence of that subtype in each reservoir. This method is easy to apply and the method of Garrett et al (207) can be extended to provide bootstrap confidence intervals (189).

- **Modified Hald model.** The Hald model is a Bayesian risk assessment model, originally developed to quantify the contribution of different food sources to cases of salmonellosis in humans in Denmark; this has now been modified and applied to Campylobacteriosis (189). The original model compares the number of human cases caused by different types with their prevalence in different food sources, weighted by the amount of food consumed. This is a development of the Dutch model described above, and requires a heterogeneous distribution of some types among animal and food sources. However, by using a Bayesian approach, the Hald model can explicitly include and quantify the uncertainty surrounding each of the parameters. The modified Hald model overcomes some of the problems of the original model associated with overparameterization and incorporates uncertainty in the prevalence matrix (202). It also includes environmental pathways of Campylobacteriosis. Other modifications of this model have been developed and applied to salmonellosis (208) and listeriosis (209).

- **Island model.** This population genetics approach is fundamentally different from the Dutch and Hald models. It is a model of gene flow derived from population genetics (210). The technique (190) reconstructs the genealogical history of the isolates, based on their allelic profiles, and estimates mutation and recombination rates, as well as the migration rates from each reservoir into the human "island". These migration rates are then used to estimate the relative contribution

from each reservoir. This technique has one major advantage over the other methods, in that it can assign human cases that have no identified subtype in any of the animal or environmental reservoirs.

- **Dynamic attribution model.** This model describes how reservoir attribution changes over time, and can be used for ongoing surveillance and for assessing the impact of interventions (203, 204, 211). Current models are based on the Hald model, providing outputs with estimates of uncertainty (Bayesian credible intervals). There are a number of ways that this might be improved; a recent publication from Finland proposed a refinement of the dynamic Hald model that, although only applied at the species level in the paper, could be extended and applied to more refined subtyping data (212).

Sampling issues for reservoir attribution studies

Although there is evidence that microbial subtypes are more strongly associated with particular hosts than with geographical location (213), there are still strong differences in the distribution of host-associated genotypes between countries, and these can change over time (214). This underlines the need to consider concurrent sampling of reservoirs in different places. Other important considerations include: which reservoirs to sample; whether and how to sample the environment as a proxy for unsampled hosts; and which microbiological and genotyping tools to use. Within-country variation may also be a consideration when deciding whether to adopt a whole-country approach or to use sentinel sites (189). Currently there are few guidelines regarding sample sizes for reservoir attribution studies, or the impact of genotype distributions between similar hosts (for example, cattle and sheep) on the uncertainty surrounding reservoir attribution estimates (215, 216).

New tools for source attribution modelling

Improved models, better genotyping tools and the integration of different approaches, e.g. epidemiological and evolutionary modelling, in a single framework will improve the range of techniques available for source attribution in the future. There is scope for applying source attribution modelling, such as the island model, to determine a probabilistic reservoir assignment for each genotype, and using these as outcomes in epidemiological studies. For example, extending case–case comparisons of poultry- and ruminant-associated cases of Campylobacteriosis (217, 218) to include information on non-diseased controls (192) is likely to identify more subtle associations and improve source attribution modelling.

Molecular subtyping tools may be improved with the addition of whole genome sequence data from high through-put sequencing platforms, particularly when combined with improved bioinformatics and web-based database tools that input short read sequence data. These have already led to the development of extended and generic multilocus typing schemes (219, 220). Whole genome sequencing will be used to understand the evolution of epidemiologically important strains of *C. jejuni* and, with advanced phenotyping technologies, identify potential new markers for host association. This may help to improve the discrimination of reservoirs of human infection, such as between cattle and sheep, and result in more precise attribution estimates. The identification of genetic markers for resistance to stress, such as pH, temperature, oxidative stress, and freeze–thaw, could also help to determine the sources and transmission pathways associated with strains isolated from humans, further refining attribution studies.

Extending the application of source attribution modelling

Source attribution models can be extended to consider the source of particular subsets of human cases, such as those with infections resistant to antimicrobials and those associated with particular sequelae, such as GBS. For example, antimicrobial resistance test results could be used alongside the genotype of individual isolates in reservoir attribution models.

Methods based on microbial subtyping could be used to model the relative contribution of reservoirs contaminating particular pathways, such as surface water supplies to water treatment plants. Similarly, molecular epidemiological techniques using similar modelling approaches could be used to understand transmission cycles in primary production (for example the determinants of new infections being introduced into poultry flocks and the factors that result in dissemination and persistence). This will require new epidemiological studies at the farm level that include genotyping of isolates.

There is also a need to extend the application of source attribution to LMIC. Annex 2 describes a possible pilot programme for countries with limited resources.

4.3 Data gaps and recommendations

4.3.1 Data gaps

- few data are available for source attribution of Campylobacteriosis in LMIC.
- there is a need to acquire more comprehensive typing data from multiple sources sampled in different geographical locations over time. These data would help to determine how *Campylobacter* populations are structured in space and time, the potential biases introduced by not sampling reservoirs contemporaneously in the same geographical location, and inform sample size calculations.
- there is a need for more rapid, less expensive typing tools that are suitable for source attribution.

4.3.2 Recommendations for WHO

- foster a limited number of pilot integrated surveillance projects in LMIC, to increase capacity in national reference centres, and to provide a "snapshot" of information for preliminary assessment of resistance and source attribution. Annex 2 outlines the design of pilot programme for LMIC;
- promote the application of the general framework for source attribution, including reservoir and pathway attribution, exposure assessment and risk factor analysis;
- encourage the development and application of new and refined approaches to source attribution. This includes new models, and the integration of molecular subtyping and epidemiological data to determine risk factors for infection acquired from particular reservoirs and pathways;
- extend source attribution models to consider the source of particular subsets of human cases, such as those with infections resistant to antimicrobials and those associated with particular sequelae, such as GBS.
- extend the application of source attribution tools and apply them to the identification of sources of *Campylobacter* in poultry flocks, as well as the contribution of poultry and other reservoirs to the *Campylobacter* burden. Similar approaches can be applied to determine the reservoirs contributing to contamination of surface water.
- promote the use of information from observational studies to design and implement intervention studies, ideally randomized control trials, and use source attribution models to aid the evaluation of interventions;

5. Impact of control measures

Because of the complex epidemiology of *Campylobacter*, a multi-tiered approach to control is needed, taking into consideration the different reservoirs, pathways, exposures, and risk factors (see section 3.2). While poultry is a major reservoir of *Campylobacter* and the primary target for control measures, other transmission vehicles, such as raw milk and drinking-water also need to be considered together with appropriate measures, e.g. pasteurization of milk, chlorination of water.

Control of *Campylobacter* needs to be multi tiered and goal orientated and provide flexibility to producers and processors to meet such a goal. Such an approach is promoted in the recently adopted Codex guidelines (2) which emphasizes a three tiered approach which first focuses on hygiene measures, then hazard specific measures and finally risk-based measures. *Campylobacter* control needs to be adapted to local possibilities, practicalities and preferences. Some basic principles, however, are generally applicable.

- Begin as close as possible to the primary source.
  - Pre-harvest control (prevention of colonization) (see below) will prevent the amplification of *Campylobacter* and will limit transmission through pathways other than the poultry meat food chain.
  - If poultry flocks are positive for *Campylobacter* or positive and negative flocks are transported and or harvested together the meat is likely to be contaminated with Campylobacter, and there will also need to be a focus on post-harvest control measures.
  - If the *Campylobacter* load on the poultry farm is high, decontamination in the abattoir/processing facility could be efficient as an interim measure, while other more cost-efficient albeit slower-acting measures such as biosecurity and good husbandry and health practices, are implemented.

- Where possible, use generic control measures, i.e. measures that have an impact on multiple pathogens and transmission routes. An example is the application of biosecurity and good husbandry and hygiene measures which could reduce *Salmonella* as well as Campylobacter.

- Set performance targets for reduction or presence of *Campylobacter* in the primary source of human infection. These should apply to both domestic and imported products at the appropriate point of the food chain. The targets should take into account the local situation, e.g. climate and farming practices. Nevertheless the degree of reduction of infection or carriage by reservoirs and of contamination of products should be risk-based, for the type of food product.

- Track the efficacy of implemented control measures through their effect for example on prevalence of *Campylobacter* contaminated product on the market or on human illness i.e. linking to human disease surveillance system. Targets may be set based on envisaged reductions in human disease (see section 3).

- Perform a systematic review at regular intervals, e.g. every five years, of the interventions and control measures being used, to evaluate their efficacy and impact on risk reduction (for example, the FAO/WHO Web-based risk management tool for the control of *Campylobacter* and *Salmonella* in chicken meat [5] may be used to assess the impact of specific interventions compared to the baseline scenario).

5 http://www.mramodels.org/poultryRMTool/ accessed 2 July 2012.

- Support control programmes by appropriate policies, strategies and regulatory frameworks as well as promotion of good practices and appropriate economic incentives for producers and processors.
- Antimicrobials should not be used for pre-harvest control of *Campylobacter* due to the risk of selection for antimicrobial resistant strains but improved biosecurity, husbandry and hygienic practices and other methods of control should be promoted.
- The use of source attribution allows the impact of the control programme on particular reservoirs and pathways to be monitored, independent of the actual numbers of human cases of Campylobacteriosis.

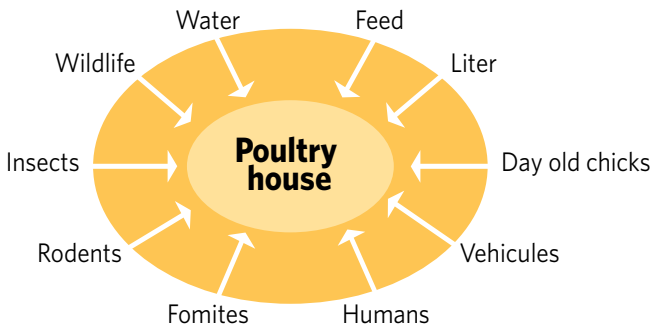
5.1 Control measures in poultry

All types of poultry can become colonized with *Campylobacter* (221). Vertical transmission of *Campylobacter* from parents to progeny through eggs is an extremely rare event if it happens at all (222). Broilers, therefore will be free of *Campylobacter* on the day of hatching, which means that each broiler cycle starts with a *Campylobacter* negative flock. Once *Campylobacter* is introduced into a flock, there is rapid spread so that colonization occurs in virtually all the animals in the flock (up to 108 campylobacters per gram caecal content). These counts remain almost at the same level until slaughter age (42 days in conventional production systems). Colonization of the gut with *Campylobacter* does not lead to any clinical signs nor a reduction in life span of poultry. Strong seasonality has been observed in the colonization rate and incidence of positive flocks may vary depending on geographic region and climatic conditions. Broilers may become colonized with *C. jejuni* and *C. coli*. However, at about 6 weeks the majority of strains isolated from broilers is C. jejuni. In older animals there is a shift towards *C. coli* (223, 224).

There have been many published reports of interventions with the potential to control *Campylobacter* in chickens on the farm (pre-harvest) and in the slaughter/processing facility (post-harvest). However, in commercial poultry settings few of these interventions have been demonstrated to be as effective in lowering either the number of positive carcasses or the number of *Campylobacter* (load) on each carcass as in the research laboratory. This may be because *Campylobacter* is easily spread within the processing plant environment from previous positive birds entering the facility or the actual load on each bird is so high that the interventions in the processing plant environment are unable to be effective (225) in reducing the contamination load. In addition, the benefit of an intervention on the farm may be lost if there are not concurrent interventions in the transport from the farm to the processing facility to reduce cross-contamination (226, 227).

5.1.1 Pre-harvest interventions

There are considerable differences in poultry production around the world, e.g. in style of housing (indoor vs. outdoor access), equipment used for feed and water, type of bedding material (whether it is new or reused between flocks), climate, method of ventilation, and breed of birds. These differences will have an impact on the effectiveness of particular interventions and will determine which interventions should



be given more emphasis, in order to bring about the greatest reduction in risk. Fig. 3 shows the various inputs to a poultry facility that can be potential sources of *Campylobacter* infection. While *Campylobacter* control is a global issue, each country will need to formulate its own approaches to control.

Figure 3: Potential sources of *Campylobacter* infection for poultry

The only intervention that has consistently been shown to be effective in preventing the introduction of *Campylobacter* is the application of strict biosecurity measures (228, 229). Biosecurity includes but is not limited to: (1) Access control – to minimize access by unauthorized personnel, birds, rodents etc; (2) insect control (e.g. flies and beetles) (230-233); (3) farm worker control (i.e. hygiene barriers that require footwear changes before entering poultry house) (234); (4) drinking-water sanitation (i.e. chlorination or organic acids) (234); (5) bedding material/floor litter source, change between flocks, treatment (type, reuse, etc.) (235, 236); (6) wildlife and rodent control (237); (7) cleaning and disinfecting equipment used for thinning/depopulation (226); (8) fomite control (disinfect equipment used between farms or houses, etc.) (238); and (9) cleaning and disinfection of entire house and equipment between flocks (233). Other specific pre-harvest interventions that have been successful in research settings but have not yet been shown to be effective in commercial settings as a single therapy include: bacteriocins, bacteriophages, competitive exclusion, organic and inorganic acids in feed or drinking-water, essential oils in the drinking water prior to processing, vaccination (traditional/recombinant) and breeding for genetic resistance.

Success in reducing *Campylobacter* pre-harvest is most likely from a combination of interventions coupled with enhanced biosecurity. The combination of interventions that will be most successful will probably depend on farming practices, climate and housing style.

5.1.2 Post-harvest interventions

For the purposes of this discussion, the post-harvest period includes catching the birds for harvest, transport to the abattoir and time spent in the abattoir or processing facility (239). Withdrawal of feed and water prior to harvest has a significant impact on the amount of *Campylobacter* in the crop and faecal material. Interventions in the withdrawal water or feed will reduce the *Campylobacter* load in the transport and the processing facility and is, therefore, considered part of post-harvest control. For example, use of organic acids and other chemicals in this withdrawal period, for example in the final drinking-water may reduce the load of live *Campylobacter* in the crop (240). A reduction of *Campylobacter* in the crop leads to less *Campylobacter* that can be a source for cross contamination in the processing facility/abattoir (240).

As with pre-harvest control measures, good hygiene is critical for successful post-harvest control (241-243). Appropriate measures include cleaning, disinfection and drying of transport modules, crates and coops, correct loading densities, sanitation of surfaces or liquids (scalder, chiller, etc.) that come in contact with each carcass to reduce cross-contamination, and use of specific food safety approaches e.g. application of good hygienic practices and HACCP. Some specific interventions may appear logical, but may not be readily implementable. Scheduled slaughter and logistic slaughter are currently impractical because there are currently no tests available to give results in a fast enough time to alter the order of flocks slaughtered (i.e. processing positive flocks at the end of the day).

Decontamination of the carcass by physical or chemical means has the greatest chance of success of all the proposed post-harvest interventions (244, 245). Methods include large volumes of water to wash carcasses, counter-current flow of water in scalders and water chillers, freezing of carcasses, heat (steam) treatment of carcasses and irradiation. Chemical decontamination products include chlorine compounds, organic acids, ozone, peracetic acid, peracetic acid with hydrogen peroxide, and trisodium

phosphate, as well as some "natural" methods such as bacteriophages and bacteriocins. However, some of these methods are associated with negative cultural, political or consumer attitudes.

The goal of reducing the load of *Campylobacter* to a level with a low probability of causing illness (246) can most likely not be achieved by any single pre-harvest or post-harvest intervention. Success will most likely occur through use of multiple stepwise interventions to lower the load of *Campylobacter* on or in each bird on the farm and in the processing facility.

When poultry meat entering the market is likely to be contaminated with *Campylobacter* then it is critical that measures for its control extend to the distributors, retailers and end users. As with any raw product basic good hygiene practices during food preparation are necessary to prevent contamination and cross-contamination of food during storage, preparation and handing. Such practices include hand washing before and after handling food and between handling raw and cooked or ready-to-eat food; keeping raw meat separate from cooked or ready-to-eat foods; avoiding using the same utensils to prepare raw meats and other foods (e.g. chopping boards and other surfaces, knives, and plates, for instance) and washing and disinfecting all surfaces and utensils that have been in contact with raw meat. As *Campylobacter* is sensitive to cooking temperatures, cooking the food to 70oC will minimize the risk.

5.2 Control measures in the environment

Campylobacter is widespread in the environment. Contamination occurs through animal faeces and sewage discharge (247). Survival of *Campylobacter* in the environment depends strongly on the conditions, with humidity playing an important role. In particular in LMIC, *Campylobacter* infection is often endemic because of poor sanitation and close contact with animals and environmental sources (248, 249). In these countries, untreated drinking-water is an important risk factor in *Campylobacter* transmission. The effect of water treatment in reducing *Campylobacter* in humans has been shown in Peru (250) and Bolivia (251).

There is evidence that poor basic sanitation conditions are related to higher rates of isolation of *Campylobacter* from dogs (252), hens (253), cows (254) and young children (255).

While *Campylobacter* does not multiply in the environment, it plays a role in transmission of the bacteria to humans and animals. If the quantitative role of this environmental reservoir can be estimated, more targeted and effective interventions can be developed.

5.3 Data gaps and recommendations

5.3.1 Data gaps

- limited data available on the efficacy and the impact of potential interventions in a range of different field conditions and particularly those in LMICs.
- limited information on the contribution of different potential routes of infection of *Campylobacter* into poultry flocks and on transmission within and between flocks particularly in production settings in LMICs
- limited understanding of antibiotic resistance of *Campylobacter* strains isolated from humans, birds, animals and the environment.
- on the effect of adverse environmental factors (temperature fluctuations, changes in osmolarity, atmospheric oxygen concentrations, nutrient deprivation and natural ultraviolet radiation) on the survival and transmissibility of Campylobacter.

- Limited data availability on the interactions of *Campylobacter* with environmental protozoa and the possible effect on *Campylobacter* survival and transmissibility (256, 257).

5.3.2 Recommendations to WHO

WHO should work with relevant international partners such a FAO and OIE in implementing the following recommendations:

- support countries in the implementation of the Codex guidelines for the control of *Campylobacter* and *Salmonella* in chicken meat.
- Support CODEX in the development of any further international guidance or recommendations that are needed to support reduced human exposure to *Campylobacter* via foods traded internationally.
- Facilitate wider accessibility to existing systematic reviews of interventions and control measures and facilitate new work in this area as needed including the provision of further guidance and data to support the application of the FAO/WHO Web-based Risk Management Tool for the control of *Campylobacter* and *Salmonella* in chicken meat.
- promote the use of information from observational studies to design and implement intervention studies, ideally randomized control trials as a means of addressing some of the data gaps on the efficacy of interventions in practical settings.
- raise awareness among producers and processors that more rigorous biosecurity, good animal health and husbandry practices are needed to control Campylobacter;
- provide guidance and support on improving slaughter and processing hygiene to reduce the level of contamination of end products from infected flocks.
- disseminate existing recommendations on proper food handling, hygiene and safe drinking-water, for example the WHO Five Keys Programme (258).

6. Lessons learned: New Zealand

From 2006 to 2008, the rate of Campylobacterosis cases reported to the notifiable disease surveillance system in New Zealand dropped dramatically from 383.5 per 100 000 to 156.8 per 100 000. This was a result of efforts to control *Campylobacter* in the poultry supply, notably by the regulator, the Ministry for Primary Industries (MPI, formerly the New Zealand Food Safety Authority), and the industry (130).

Extensive research over the preceding decade had investigated the reasons for New Zealand's high reported rate of Campylobacteriosis compared with other high-income countries. Evidence from case–control studies and literature reviews had gradually accumulated to indicate that the most important transmission vehicle was poultry meat (259)

The key study supporting this conclusion was a sentinel site investigation, funded by the MPI and carried out by Massey University. This study combined MLST of isolates from human cases and potential sources with detailed risk factor information from individual cases, to assemble a series of reports on attribution (204, 260, 261). As a result of these studies, the poultry industry was convinced that chicken was the most significant foodborne source of the disease (262).

Foodborne Campylobacteriosis was also found to have the greatest burden of disease of all the potentially foodborne enteric illnesses (30). This made it a priority for the MPI, which established a performance target of a 50% reduction in reported annual incidence of foodborne Campylobacteriosis by 2013.

Proceeding from this scientific basis, the MPI published its first *Campylobacter* Risk Management Strategy in 2006, covering the years 2007–2010. The strategy has since been updated for 2008–2011 and 2010–2013.[6]

The Strategy for 2010–2013 has the following objectives:

1. to estimate the proportion of foodborne cases attributable to poultry and other sources;

2. to determine the relative contributions of different interventions throughout the food chain in reducing risks to human health;

3. to continue to make well-informed risk management decisions on appropriate control measures and their implementation;

4. to assess the effectiveness of risk management decisions by using a monitoring and review programme;

5. to coordinate and prioritize research activities.

6. In response, the New Zealand poultry industry initiated a programme of risk management measures that were designed in collaboration with the MPI and implemented through a collaborative effort by the various companies involved in broiler production and processing. Exchange of technical and processing information was fostered by the Poultry Industry Association of New Zealand, which brought together the expertise of member companies.

6 http://www.foodsafety.govt.nz/science-risk/programmes/hazard-risk-management/Campylobacter.htm; accessed 2 July 2012.

Specific measures were taken along the entire poultry food chain, although the most effective controls were in the processing plants. These have been described elsewhere but, broadly, attention to detail during primary processing (new equipment for evisceration or spray washing, improved evisceration settings, optimized pH and chlorine settings for spray washes and immersion chillers) reduced the prevalence and numbers of *Campylobacter* in chickens (130, 262).

A key factor in the management of *Campylobacter* in poultry was the introduction of a detailed monitoring programme, in which samples taken from the processing plant were analysed and the results collated by the National Microbiological Database (NMD), which is administered by the MPI. The programme included presence/absence testing of caeca from dead birds at the start of primary processing, and enumeration of rinsates of carcasses sampled at the end of primary processing, i.e. post-immersion chiller. *Campylobacter* sampling and testing of poultry commenced in April 2007, and after establishment of a baseline, *Campylobacter* Performance Targets (CPT) were introduced in April 2008. The CPT were specified in terms of the numbers of *Campylobacter* on carcasses exiting the immersion chiller, as well as requiring a plant-specific *Campylobacter* management plan. If a plant fails to meet CPT, the regulator can require the implementation of a graduated sequence of responses to address the problem, ending if necessary with plant closure. From April 2008 to December 2011, some plants were required to freeze all products until compliance was achieved, but no plant was required to stop production.

The decline in the reported rate of Campylobacteriosis over the period 2006––2008 has been linked to the interventions in the poultry food chain because of the following considerations (130):

- consistency of the reduced rate across regions and age groups;
- the temporal association between the interventions and the reduction rate;
- source attribution analysis indicating a decline of 74% in the proportion of cases from poultry-associated MLST types (Manawatu study);
- a concurrent reduction in number of hospitalizations for Campylobacteriosis; and
- evidence of a concurrent reduction in the number of hospitalizations for Guillain-Barré syndrome associated with Campylobacteriosis (45).

As part of her investigation into the reasons for the reported decline, Dr Ann Sears interviewed key informants from industry, the regulator and researchers. The following factors were identified as influencing the success (263).

- *Campylobacter* in poultry was recognized as an industry-wide issue, reinforced by accumulation of attribution studies (especially MLST studies).
- There was discussion of the issue in the public media (prompted partly by public health researchers advocating for interventions like freezing the entire poultry supply).
- A good working relationship was developed between regulators and industry; mandated targets also encouraged action by industry.
- The focus of the CPT on results rather than specific interventions was appreciated by industry.
- Because CPT were specified as targets and not as changes by processors (for example, log reduction on carcasses),good performers had less work to do than poor performers.

- No single intervention was most effective; rather, the key was attention to detail in primary processing (for example, evisceration, spin chiller and spray washes), and new equipment for some processors

- A high level of industry intercompany collaboration was achieved, and communication was facilitated via an industry-wide forum.

The number of notified cases of Campylobacteriosis has been relatively static since 2008 (151.9 per 100 000 in 2011). Poultry remains an important exposure pathway (estimated as responsible for approximately 50% of cases in 2009–2010 in the Manawatu study (261)). Subtypes associated with ruminants (cattle and sheep) were found in approximately 32% of cases in the Manawatu study in the same period. Some research has been conducted into other pathways of exposure.

Environmental exposures may explain the relatively high notification rate in rural populations in the Manawatu study, and in young children in rural areas across New Zealand (205, 264). Analyses of risk factors from notified cases are hampered because data are not provided for all cases. However, analyses suggest that infections acquired during overseas travel contribute 5–10% of notified cases (205). Infections acquired from occupational exposures were estimated to have been responsible for approximately 6% of the notifications in 2008. Exposure modelling suggests that red meat exposures have a minor role (estimated as contributing 1–2% of notified cases in 2008), which raises the question of how people are acquiring infection from ruminant-associated types of Campylobacter. Infections acquired from drinking-water and recreational activity involving freshwater are difficult to estimate. The water supplies serving the majority of the New Zealand population are monitored and are of high quality. The size of the population that uses small supplies is not well characterized, and information about the quality of this water is scarce (205). The MLST types of *Campylobacter* found in surface waters in the Manawatu study were dominated by water-bird associated types, which occur rarely in human cases (264).

The following lessons can be learned from the New Zealand experience.

- Cooperation between regulators and industry can be effective, once industry is convinced that their product is responsible for a significant part of the problem, and risk management activity will reduce the burden of disease.

- Legal power to mandate control actions is still essential.

- Advances in molecular typing provide important new tools.

- Advocacy by public health professionals can promote action.

- Human health surveillance and food monitoring are both necessary to establish baselines and provide measures of effectiveness.

- Coordinated research activity by the regulator can provide a mandate for action (including burden of disease measures).

- Providing targets rather than prescriptive measures allows flexibility in actions by industry.

- Radical new measures may not be necessary – attention to detail at multiple points along the food chain can be effective.

7. General conclusions

- Considerable new evidence, data, and analytical tools have emerged in the ten years since the previous WHO consultations on Campylobacter.
- In terms of public health actions, there is already a sufficient evidence base to address the burden of disease from *C. jejuni* and C. coli. The importance of other species in terms of burden of disease is still unclear, but is considered unlikely to eclipse these two species.
- Public health surveillance can provide important basic information to policy-makers about the frequency of infection, who is affected, and the success of specific prevention strategies. Surveillance is the starting point for studies of burden of disease and source attribution.
- There is a need for standardization and validation of laboratory methods.
- Burden of disease studies provide the evidence base that drives the need for control measures across all outcomes of Campylobacteriosis while taking into consideration its underestimation.
- There is considerable potential for the identification of new sequelae from acute infection. However, decision criteria are needed on the level of evidence required to add outcomes to burden estimates. This applies to all sequelae, and may increase burden estimates considerably.
- In order to reduce exposure countries should be encouraged to adopt the recently developed Codex Guidelines for the Control of *Campylobacter* and *Salmonella* in chicken meat which promote a risk based approach to the management of *Campylobacter* in chicken meat traded internationally. Consideration should be given to the development of additional guidance and recommendations for the management of *Campylobacter* in other potential food vehicles that are traded internationally.
- Source attribution studies should adopt a holistic attitude, considering multiple sources and pathways of exposure, molecular and epidemiological data.
- Although poultry is the dominant source of infection in many countries, controlling *Campylobacter* in poultry meat will not completely eliminate the disease in humans. Options are available to control other pathways which are based on general hygiene, generic control measures including biosecurity and sanitation.
- Reducing the load of *Campylobacter* in poultry to a level with a low probability of causing illness is unlikely to be achieved by any single pre-harvest or post-harvest intervention. Success will most likely occur through use of multiple stepwise interventions to lower the load of *Campylobacter* on or in each bird on the farm and in the processing facility.
- The epidemiology of *Campylobacter* is likely to be different in high-income countries compared with LMIC, and between different production systems and value chain structures. This will influence the choice and application of control options.
- GFN, as an international training and capacity development network, will play a key role in promoting better and more consistent methodologies and quality assurance for work with Campylobacter. Where possible, GFN should link with other international networks, such as FERG, which is promoting capacity development in estimation of burden of foodborne disease.

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Annex 2. A possible pilot programme for countries with limited resources

LMIC should focus on determining whether Campylobacteriosis is a priority that requires public health investment and, if so, which reservoirs and pathways should be targeted for prevention and control. If no surveillance system for Campylobacteriosis exists, it may be useful and cost-effective to start a pilot programme to gather baseline data on the incidence of the disease and its relative contribution to diarrhoeal illness, seasonal patterns of illness, and risk factors, such as age and urban/rural location. The addition of poultry sampling would provide some data on the hazard arising from the poultry supply. Microbial subtyping would allow preliminary reservoir attribution and identification of potential pathways, particularly if MLST is feasible. The data from such a pilot study could indicate whether investment in the control of Campylobacteriosis is warranted, whether further surveillance is necessary, and what form it should take. It would also help to identify potential interventions aimed at reducing human exposure. One suggested approach is outlined below:

- Select a sentinel region that is reasonably representative of the population.

- Take stool samples from all patients with gastroenteritis over a specified period, ideally a full calendar year, and submit for *Campylobacter* culture using a recommended protocol. Store presumptive isolates, for example in glycerol at –80 °C. Collect epidemiological information on cases using a standardized questionnaire with 10–12 key questions, including exposure to poultry, untreated water, and unpasteurized milk. This will allow basic incidence data to be collected to determine the relative importance of *Campylobacter* as a cause of diarrhoeal illness, as well as describing seasonal trends, age distribution, the distribution of cases between urban and rural populations, and the frequency of exposures of possible importance.

- Identify the sources of poultry consumed in the region. Take carcase rinse samples from all the major suppliers, conducting a series of repeated cross-sectional studies (for example, 3–4 over a 12-month period). Culture the samples for *Campylobacter* spp. using the same methods as for the human specimens. The aim is to get 100–150 isolates for typing so, depending on the initial prevalence, subsequent sample sizes can be adjusted accordingly. Store isolates as described above. (Note that the reason for just selecting poultry is that recent evidence suggests that the population structure of poultry C. jejuni varies more, both spatially and temporally, than that of isolates from other reservoirs (213-215).

- If the isolation of *Campylobacter* spp. from patients with diarrhoea, combined with a preliminary assessment of burden of disease, supports the need for further public health investment, a subset of 150 randomly selected human isolates could be speciated and typed (ideally using MLST to ensure comparison with the large international database, PubMLST) (215). Similarly 100–150 isolates from poultry would need to be typed using the same method for attribution studies (215, 216). Ideally, other sources, such as ruminants and wildlife from the same region should be sampled, but for a preliminary analysis it may be sufficient to use isolates from international datasets for comparison. However, once the distribution of strain types in human cases has been determined, a decision whether to sample from other sources can be taken, and these can be carried out as one-off cross-sectional studies. Determining antimicrobial resistance in the same collection against a standard panel of agents would add information of use for development of clinical guidelines as well as for source attribution.

- The distribution of microbial subtypes in human cases and reservoirs could be used for preliminary reservoir attribution studies, using the proportional similarity index, Dutch, Hald, dynamic and assymmetric island model approaches (see section 4.2.4).

THE GLOBAL VIEW OF
CAMPYLOBACTERIOSIS

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