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Update on the burden of Campylobacter in developing countries

James A. Platts-Mills[*,a] and **Margaret Kosek**[b]

[a] Division of Infectious Diseases and International Health, University of Virginia Health System, P.O. Box 801363, Charlottesville, VA 22908

[b] Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, Phone:(410) 955-5932, mkosek@jhu.edu

Abstract

Purpose of review—Recent work has added to the understanding of the burden of *Campylobacter jejuni*, *C. coli*, and non-*jejuni/coli Campylobacter* strains in children living in the developing world.

Recent findings—New diagnostic modalities and carefully-designed field studies are demonstrating that the burden of *Campylobacter* diarrhea in children in the developing world has been greatly underestimated. Furthermore, there is emerging recognition of an association between *Campylobacter* infection and malnutrition. Important progress has been made towards a *Campylobacter jejuni* vaccine. Finally, evidence of antibiotic resistance continues to be an important issue that is accentuated by the realization that the burden of disease is greater than previously recognized.

Summary—Additional research is needed to refine our understanding of the epidemiology of *Campylobacter* infections in developing countries, in particular to improve estimates of the burden of *Campylobacter* diarrhea in endemic settings, to determine the impact of recurrent *Campylobacter* infections on child development, and to describe the prevalence and clinical significance of non-*jejuni/coli Campylobacter* infections. Progressive antibiotic resistance of isolates argues for augmented and expanded control measures of antibiotics in livestock. Continued work in vaccine development is warranted as is the extension of data available on the serotypes related to burden in different areas of the world and the relationship of serotypes to disease severity.

Keywords

Campylobacter; epidemiology; diarrhea; burden; malnutrition

INTRODUCTION

Campylobacter is considered to be the most common cause of bacterial gastroenteritis worldwide and was associated with 7.5 million disability-adjusted life years in the 2010

[*]Corresponding Author Phone: (434) 243-6832, Fax: (434) 924-0075, jp5t@virginia.edu.

Conflicts of interest

There are no conflicts of interest.

Global Burden of Disease Study, more than *Shigella* (7.1 million) and enterotoxigenic *E. coli* (6.9 million)[1]. The epidemiology of *Campylobacter* infection in developed countries is notably different than in the developing world. In the former, *Campylobacter* infections are sporadic, the prevalence of asymptomatic infection is low, and marked seasonality is seen [2]. With the exception of common-source outbreaks, often associated with contaminated dairy products [3], infections are typically linked directly to contaminated food, including poultry [2]. In contrast, in developed countries where *Campylobacter* is often endemic, asymptomatic infections are common and seasonality is less prominent or even absent [4-6]. *Campylobacter* diarrhea is seen in children but rarely in adults [7]. Due to the ubiquitous nature of the pathogen, risk factors are more diffusely associated with exposure to the environment, including contaminated drinking water [8].

While the burden of diarrhea in developed countries has been established by longitudinal surveillance [9,10], accurate estimates of the burden of diarrhea as well as long-term sequelae of *Campylobacter* infection in the developing world remain elusive, in part due to insensitive and inconsistently applied isolation methods; this forms a poor lens through which to study the burden of this common enteropathogen. Studies with improved diagnostics remain limited in number and epidemiologic context, but it is increasingly clear that current estimates significantly underestimate disease burden. Here, we will review developments in diagnostics, studies of both the acute and long-term disease burden, non-*jejuni*/*coli* infections, and new insights on *Campylobacter* immunity and vaccine development. We end by reviewing new data on antibiotic-resistant *Campylobacter* infections.

UPDATE ON *CAMPYLOBACTER* DIAGNOSTICS

Campylobacter species are difficult to isolate in the presence of normal stool flora, thus selective techniques are commonly employed. This most commonly involves the use of antibiotic-containing selective media, which has been the primary diagnostic modality for defining the epidemiology of *Campylobacter jejuni*, the species most commonly implicated in human disease. *C. jejuni* isolation is also facilitated by modified thermal and atmospheric conditions [11]. However, both the culture media and conditions can inhibit isolation of other *Campylobacter* species, and alternative strategies including membrane filtration culture and molecular diagnostics have led to increased detection of a broad range of *Campylobacter* species [12-14]. In South Africa, using filtration culture, *Campylobacter jejuni* isolates represent only about 40% of all *Campylobacter* isolates from children with diarrhea [15]. However, this approach has not been widely adopted.

Over the last decade, culture-independent tests have been developed, including enzyme immunoassay (EIA)-based stool antigen tests and nucleic acid-based tests. Early studies suggested that antigen tests had excellent sensitivity and specificity in comparison to culture in children and adults in the developed world [16]. However with routine use in clinical microbiology laboratories, several recent reports have described a high false-positivity rate [17,18]. Ghosh and colleagues performed culture, EIA and PCR for *C. jejuni/coli* on stool specimens from more than 500 children with acute diarrhea presenting to a tertiary care hospital in New Delhi and found culture to have a sensitivity of 37% compared to a gold

standard of either culture positive or both EIA and PCR positive [19]. There is now good evidence that these antigen tests detect non-*jejuni/coli Campylobacter* species, including *C. upsaliensis, C. concisus,* C. troglodytis, C. hyointestinalis subsp. hyointestinalis, C. helveticus and *C. lanienae* [20]. PCR-based tests for detection of *Campylobacter* species directly from stool as well as genus-level assays have begun to be used more widely on clinical specimens, including amplification of 16S ribosomal RNA targets with subsequent sequencing for species identification [14,20,21].

BURDEN OF CAMPYLOBACTER GASTROENTERITIS

Population-based surveillance for *Campylobacter* in the developing world is limited by the frequent asymptomatic detection of *Campylobacter* in stools, which complicates attribution when *Campylobacter* is identified in studies of symptomatic gastroenteritis. Consequently, controlled etiologic studies of diarrhea in these settings have been employed to improve burden estimates. The recently published Global Enteric Multicenter Study (GEMS) of moderate-to-severe diarrhea in children in Asia and Africa was designed to comprehensively identify the pathogen-specific etiology and burden of disease associated with each pathogen [22]. Seven sites in Africa and Asia enrolled cases of moderate-to-severe acute diarrhea and asymptomatic controls matched for age, sex, and village, and in addition to a broad range of other pathogens, *Campylobacter* was detected by culture using selective blood agar plates incubated at 42°C [23]. *C. jejuni* was found to be associated with a significant burden of diarrhea in Mirzapur, Bangladesh (fourth highest in the first year of life behind rotavirus, *Shigella* and *Aeromonas*), Karachi, Pakistan (fifth highest in the first year of life behind rotavirus, *Aeromonas, Shigella* and heat-stable toxin-producing enterotoxigenic *E. coli* and second highest in children ages 2-5 behind *Aeromonas*) and Kolkata, India (third highest in children ages 2-5 behind rotavirus and *Shigella*) but not in four African sites (in the Gambia, Mali, Mozambique, and Kenya). The high burden of *Campylobacter* diarrhea in the oldest age group at some GEMS sites is surprising in light of Calva et al.'s classical evidence from a Mexican birth cohort that the ratio of symptomatic to asymptomatic infections shifted towards more frequent asymptomatic infection by 6 months of age [24].

Studies with culture-independent diagnostic tests have also revealed a substantial burden of disease. The ongoing Study of Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED), designed to assess the impact of malnutrition and recurrent early enteropathogen infections on long-term developmental outcomes in children across eight sites in South America, sub-Saharan Africa, and Asia, has used an EIA for *Campylobacter* detection, chosen for ease of standardization across laboratories [25]. *Campylobacter* has the highest associated burden of diarrhea of all pathogens in children in the first year of life from Loreto, Peru and Venda, South Africa [26]. Two recent analyses of archived specimens using PCR for *C. jejuni/coli* have also revealed a substantial burden of associated diarrhea. In testing of samples from a birth cohort of infants in Bangladesh, *C. jejuni/coli* detection was associated with diarrhea and was estimated to be a probable cause of 11.3% of episodes, second to enteroaggregative *E. coli* [4]. In a large number of samples from hospitalized children with and without diarrhea in Malawi, *Campylobacter jejuni/coli* was detected in 21% of diarrheal episodes

and was strongly associated with diarrhea [27]. Interestingly, *C. coli* represented more than one-third of detections in diarrhea samples.

It is difficult to draw conclusions about the burden of *Campylobacter* infection in settings where the prevalence of asymptomatic infection is high enough to preclude a statistically significant association between detection and disease. It is possible that such settings have reached a force of infection at which the point prevalence of asymptomatic infection would be expected to be as high as or higher than that of symptomatic infection. Such a scenario has been suggested for norovirus, which similarly has a high burden of sporadic disease in the developed world but has been inconsistently associated with diarrhea in children in endemic settings [22,28]. It is also likely that the difference in *Campylobacter* burden estimates between these settings are explained by host factors, infection with less pathogenic *Campylobacter* species (in the case of detection with EIA), and variation in the pathogenicity of circulating serotypes.

Accurate estimation of the burden of acute diarrheal disease in such settings will likely require novel analytic approaches. These include 1) quantitative PCR-based testing, where the quantity of pathogen detected may help distinguish between high-level infection that is associated with diarrhea and low-level infection of unclear significance [29,30], 2) longitudinal studies with intensive surveillance, molecular typing and force of infection modeling, and 3) incorporation of serologic assays of immunity to better understand and classify asymptomatic infections [31]. Of note, such approaches have been critical for understanding the burden of disease associated with malaria infection in hyperendemic settings [32].

ENDURING CONSEQUENCES OF *CAMPYLOBACTER* INFECTION

Pathogens that have been most clearly associated with physiologic injury extending beyond the acute diarrheal illness include *Cryptosporidium* and *Shigella* in the developing world, and *Campylobacter*, *Shigella* and *Salmonella* in the developed world. Despite the diagnostic limitations, high quality evidence supporting a link with physiologic insults enduring beyond the acute illness is strongest and most consistent across epidemiologic contexts for *Campylobacter* infections.

Guillain-Barré syndrome (GBS)—*C. jejuni* is the pathogen most frequently associated with the development of GBS, specifically the acute motor axonal neuropathy (AMAN) variant [33]. The drive to eradicate poliomyelitis has improved surveillance for acute flaccid paralysis. Several high quality studies have recently shown that GBS is the leading cause of acute flaccid paralysis (AFP) in Bangladesh, with an estimated incidence rate of 3.25 cases/100,000 children under 15 years of age, and *Campylobacter* infection appears to precipitate the majority of cases in this setting [34,35]. Although much attention has been paid to the burden of *Campylobacter* infection and associated GBS in the developed world, it is clear that a substantial burden is present in the developing world as well. Application of molecular diagnostics to stools collected during AFP surveillance may help provide better resolution of this burden.

Inflammatory Bowel Disease and reactive arthritis—Although the associations between *Campylobacter* infection and functional gastrointestinal disorders [36] and to a lesser degree inflammatory bowel disease [37] and celiac disease [38] are described in the United States and Europe, evaluating such relationships is complicated in settings where enteropathogens are ubiquitous. No data from developing world cohorts were considered appropriate for inclusion in a recent review of the associations between Campylobacter and reactive arthritis [39].

Malnutrition—The relationship between *Campylobacter* and malnutrition appears to be bi-directional. The observation has frequently be made that *Campylobacter* infections are more common in malnourished children [5,40], and a recent microbiome study from a malnourished child in India found that the family Campylobacteraceae was 35 times more prevalent than in a well-nourished child [41]. Evidence from gnotobiotic mouse models suggests that shifts in diet and microbiota alter colonization resistance to *Campylobacter jejuni* [42]. These studies suggest that host factors are important and indeed that *Campylobacter* may be a biomarker of enteropathy. However, a single recent longitudinal study has shown that both asymptomatic and symptomatic *Campylobacter jejuni/coli* infections are marginally associated with the acquisition of linear growth over the nine months subsequent to the episode, with more severe disease associated with greater growth deficits, suggesting that infection is not merely a bystander in this context [6]. Validation of this finding in other longitudinal studies with high incidences of *Campylobacter* infection and diarrhea would support the investigation of interventional approaches to improve infant growth in developing world settings.

BURDEN OF NON-JEJUNI/COLI *CAMPYLOBACTER* INFECTIONS

Wider adoption of less-selective isolation techniques as well as culture-independent diagnostics has led to frequent reports of the clinical significance of non-*jejuni/coli Campylobacter* infections. An association with gastroenteritis has been shown for a broad range of species, including *C. concisus* [43], *C. upsaliensis* [44], *C. fetus* [45], *C. ureolyticus* [46], and *C. hyointestinalis* [47]. Lastovica and colleagues have shown that using non-selective culture, *C. concisus* and *C. upsaliensis* can be isolated with a frequency close to that of *C. jejuni* from diarrheal stools from children in South Africa, together representing 47% of all *Campylobacter* detections [48]. Using molecular tests, *C. concisus* was detected more frequently than *C. jejuni* in children with gastroenteritis in Belgium [49] and appears to be associated with milder but more prolonged diarrhea than *C. jejuni* when detected by filtration culture in Denmark [43] and has also been associated with inflammatory bowel disease [50]. There is a pressing need for a more comprehensive assessment of the incidence and pathogenicity of these species in developing countries.

Using an EIA, *Campylobacter* has been the most frequently detected pathogen in the MAL-ED study in children 0-2 years of age. We have shown that about one-third of EIA detections in the Bangladesh, Peru and Tanzania cohorts represented non-*jejuni/coli* species, the majority of which were identified as *C. hyointestinalis* subsp. *lawsonii* or *C. troglodytis* [20]. The former is of porcine origin and was the most frequently identified species in Peru and Tanzania. *C. troglodytis* was most frequently identified in Bangladesh and is similar to

an uncultured species identified 16S rRNA-based sequencing of stool from infants in Bangladesh [51]. The clinical significance of infections with these species is not known. An association between non-*jejuni/coli Campylobacter* infections and malnutrition has not been described. Accurate estimates of the relative prevalence and importance of non-*jejuni/coli Campylobacter* species will require broader use of less selective diagnostic modalities.

PROSPECTS FOR CONTROL OF *CAMPYLOBACTER JEJUNI INFECTION*

Control of exposure to *Campylobacter* in the developing world will be challenging, as contamination of food and water is common. Specific interventions, such as corralling chickens, have not been demonstrated to have a significant public health impact [52]. Despite the challenge of developing a vaccine for *C. jejuni*, there has been some recent progress. Studies in the late 1980s showed homologous protection using *C. jejuni* 81-176 [53], however this strain contains GM2 and GM3 ganglioside mimics, implicated in the pathogenesis of Guillain-Barré syndrome. In order to avoid this safety concern, a strain lacking ganglioside mimics was described (CG 8421)[54] but recently demonstrated a lack of homologous protection in a human challenge model [55]. In parallel work, the development of a capsular conjugate vaccine, which in principal could both be more immunogenic and avoid the subsequent risk of Guillain-Barré syndrome [56,57], has been shown to confer protection in non-human primates.

Although classically *C. jejuni* was typed by Lior or Penner typing strategies, the demonstration that the capsule was the serodeterminant of the Penner scheme and that the capsule structure play an important role in facilitating colonization [58] has led to epidemiologic studies to define the prevalence of diverse capsular types in regions of the world which are important for guiding development of a multivalent vaccine [59]. Additional studies such as these are warranted, because despite the disappointing results in the recent study with strain CG8421, prior human challenge studies support homologous protection, as does the epidemiology of infections in children in endemic areas. The development of multiplex PCR-based capsular typing [60] should help close these knowledge gaps.

ANTIBIOTIC RESISTANCE

Increasingly, the progressive spread of antibiotic-resistant *Campylobacter* strains is a concern, in particular in Southeast Asia and South America. Resistance against fluoroquinolones has increased substantially over the last decade [61,62] and macrolide resistance has been increasingly described [63-65]. Although treatment of Campylobacter enteritis for the general population beyond the immunosuppressed or pregnant remains somewhat controversial, severe disease is not uncommon in undernourished children in the developing world, and the diminishing number of susceptible oral therapies is concerning. In the US and Europe, restricting the use of the fluoroquinolone enrofloxacin (Baytril) in poultry was a major regulatory step meant to limit the expansion of fluoroquinolones-resistant strains. However, nearly a decade later, fluoroquinolone resistance persists in the United States [66]. A recent analysis of feather meal used as animal feed strongly suggests that ongoing antimicrobial exposure may explain this [67]. Fluoroquinolone use in animals, particularly poultry for prophylaxis or growth promotion, is not regulated in most countries

in the developing world, and increasingly affordable generics are allowing for expanded use, an issue that will need to be dealt with on an international scale.

CONCLUSION

Though progress has been made, the global burden of *Campylobacter* infection remains poorly understood. Advances in diagnostics as well as comprehensive and well-standardized prospective studies are helping to refine estimates of the acute and long-term burden of disease associated with a broad range of *Campylobacter* species. Better and more consistently applied assays are necessary for an improved understanding of the epidemiology of different Campylobacter species and to guide vaccine development. Antimicrobial resistance is of increasing concern and serves to underline the importance of control strategies as well as the regulation of antibiotic use.

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REFERENCES AND RECOMMENDED READING

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012380:2197–2223.
2. Nichols GL, Richardson JF, Sheppard SK, et al. Campylobacter epidemiology: a descriptive study reviewing 1 million cases in England and Wales between 1989 and 2011. BMJ Open. 20122
3. Taylor EV, Herman KM, Ailes EC, et al. Common source outbreaks of Campylobacter infection in the USA, 1997-2008. Epidemiol Infect. 2013141:987–996.
4. Taniuchi M, Sobuz SU, Begum S, et al. Etiology of diarrhea in Bangladeshi infants in the first year of life analyzed using molecular methods. J Infect Dis. 2013; 208:1794–1802. [PubMed: 24041797]
5. Rao MR, Naficy AB, Savarino SJ, et al. Pathogenicity and Convalescent Excretion of Campylobacter in Rural Egyptian Children. American Journal of Epidemiology. 2001; 154:166–173. [PubMed: 11447051]
6**. Lee G, Pan W, Penataro Yori P, et al. Symptomatic and asymptomatic Campylobacter infections associated with reduced growth in Peruvian children. PLoS Negl Trop Dis. 2013; 7:e2036. [PubMed: 23383356] [This cohort study provides the most direct available evidence that *Campylobacter* infections lead to malnutrition and stunting. It provides an analytic approach that could be applied in other cohort studies.]
7. Coker AO, Isokpehi RD, Thomas BN, et al. Human campylobacteriosis in developing countries. Emerg Infect Dis. 2002; 8:237–244. [PubMed: 11927019]
8. Lengerh A, Moges F, Unakal C, Anagaw B. Prevalence, associated risk factors and antimicrobial susceptibility pattern of Campylobacter species among under five diarrheic children at Gondar University Hospital, Northwest Ethiopia. BMC Pediatr. 2013; 13:82. [PubMed: 23694714]
9. Crim SM, Iwamoto M, Huang JY, et al. Incidence and trends of infection with pathogens transmitted commonly through food - foodborne diseases active surveillance network, 10 u.s. Sites, 2006-2013. MMWR Morb Mortal Wkly Rep. 201463:328–332.
10. Jore S, Viljugrein H, Brun E, et al. Trends in Campylobacter incidence in broilers and humans in six European countries, 1997-2007. Prev Vet Med. 201093:33–41.
11. M'Ikanatha N M, Dettinger LA, Perry A, et al. Culturing stool specimens for Campylobacter spp., Pennsylvania, USA. Emerg Infect Dis. 2012; 18:484–487. [PubMed: 22377086]
12. Lastovica AJ, Le Roux E. Efficient isolation of Campylobacter upsaliensis from stools. J Clin Microbiol. 2001; 39:4222–4223. [PubMed: 11712518]

13. Man SM. The clinical importance of emerging Campylobacter species. Nat Rev Gastroenterol Hepatol. 2011; 8:669–685. [PubMed: 22025030]

14. Bullman S, O'Leary J, Corcoran D, et al. Molecular-based detection of non-culturable and emerging campylobacteria in patients presenting with gastroenteritis. Epidemiol Infect. 2012; 140:684–688. [PubMed: 21676357]

15. Lastovica AJ. Emerging Campylobacter spp.: The tip of the iceberg. Clinical Microbiology Newsletter. 2006; 28:49–56.

16. Granato PA, Chen L, Holiday I, et al. Comparison of premier CAMPY enzyme immunoassay (EIA), ProSpecT Campylobacter EIA, and ImmunoCard STAT! CAMPY tests with culture for laboratory diagnosis of Campylobacter enteric infections. J Clin Microbiol. 2010; 48:4022–4027. [PubMed: 20810765]

17. Giltner CL, Saeki S, Bobenchik AM, Humphries RM. Rapid Detection of Campylobacter Antigen by Enzyme Immunoassay Leads to Increased Positivity Rates. Journal of Clinical Microbiology. 2013; 51:618–620. [PubMed: 23175262]

18. Bessede E, Delcamp A, Sifre E, et al. New methods for detection of campylobacters in stool samples in comparison to culture. J Clin Microbiol. 2011; 49:941–944. [PubMed: 21209172]

19. Ghosh R, Uppal B, Aggarwal P, et al. A comparative study of conventional and molecular techniques in diagnosis of campylobacter gastroenteritis in children. Ann Clin Lab Sci. 2014; 44:42–48. [PubMed: 24695473]

20**. Platts-Mills JA, Liu J, Gratz J, et al. Detection of campylobacter in stool and determination of significance by culture, enzyme immunoassay, and PCR in developing countries. J Clin Microbiol. 2014; 52:1074–1080. [PubMed: 24452175] [This analysis of diarrheal and non-diarrheal surveillance samples from infants in three developing countries with culture, EIA and PCR demonstrates the poor sensitivity of culture and provides both direct and indirect evidence that antigen-based tests detect a number of non-*jejuni/coli Campylobacter* species.]

21. de Boer RF, Ott A, Guren P, et al. Detection of Campylobacter species and Arcobacter butzleri in stool samples by use of real-time multiplex PCR. J Clin Microbiol. 2013; 51:253–259. [PubMed: 23152553]

22**. Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet. 2013; 382:209–222. [PubMed: 23680352] [A case-control study of moderate-to-severe diarrhea in 7 sites in Africa and Asia, using traditional selective culture for isolation of *C. jejuni/coli* and demonstrating a substantial burden of disease in some sites. Interestingly, *C. jejuni* was associated with a higher attributable fraction of diarrhea in children 2-5 years of age than in younger children.]

23. Panchalingam S, Antonio M, Hossain A, et al. Diagnostic microbiologic methods in the GEMS-1 case/control study. Clin Infect Dis. 2012; 55(Suppl 4):S294–302. [PubMed: 23169941]

24. Calva JJ, Ruiz-Palacios GM, Lopez-Vidal AB, et al. Cohort study of intestinal infection with campylobacter in Mexican children. Lancet. 1988; 1:503–506. [PubMed: 2893920]

25. Houpt ER, Gratz J, Kosek M, et al. Microbiologic Methods Utilized in the MAL-ED Cohort Study. Clin Infect Dis. 2014 In Press.

26. Platts-Mills J MB, McGrath M, Miller M, Gratz J, Kosek M, Havt A, Samie A, Zaidi A, Kang G, Haque R, Bodhidatta L, Houpt E. Association between enteropathogens, diarrhea and growth in the MAL-ED cohort. 62nd Annual Meeting of the American Society of Tropical Medicine and Hygiene. 2013

27*. Mason J, Iturriza-Gomara M, O'Brien SJ, et al. Campylobacter infection in children in Malawi is common and is frequently associated with enteric virus co-infections. PLoS One. 2013; 8:e59663. [PubMed: 23555739] [One of only a few studies to use PCR-based testing for *Campylobacter* in developing countries, this study documents a surprisingly high rate of *Campylobacter* detection in diarrheal stools from Malawi using PCR and notes that viral co-infections are common, especially in infants.]

28. Lopman B, Kang G. Editorial commentary: in praise of birth cohorts: norovirus infection, disease, and immunity. Clin Infect Dis. 2014; 58:492–494. [PubMed: 24300039]

29. Platts-Mills JA, Gratz J, Mduma E, et al. Association between stool enteropathogen quantity and disease in Tanzanian children using TaqMan array cards: a nested case-control study. Am J Trop Med Hyg. 2014; 90:133–138. [PubMed: 24189366]

30. Platts-Mills JA, Liu J, Houpt ER. New concepts in diagnostics for infectious diarrhea. Mucosal Immunol. 2013; 6:876–885. [PubMed: 23881355]

31. Havelaar AH, van Pelt W, Ang CW, et al. Immunity to Campylobacter: its role in risk assessment and epidemiology. Crit Rev Microbiol. 2009; 35:1–22. [PubMed: 19514906]

32. Mueller I, Schoepflin S, Smith TA, et al. Force of infection is key to understanding the epidemiology of Plasmodium falciparum malaria in Papua New Guinean children. Proc Natl Acad Sci U S A. 2012; 109:10030–10035. [PubMed: 22665809]

33**. Kuwabara S, Yuki N. Axonal Guillain-Barre syndrome: concepts and controversies. Lancet Neurol. 2013; 12:1180–1188. [PubMed: 24229616] [A systematic review of acute motor axonal neuropathy, the most common subtype of Guillain-Barré syndrome seen in Asia and Central and South America. Describes the role of *Campylobacter jejuni* and outlines the need for epidemiologic studies to improve burden estimates.]

34. Islam Z, Jacobs BC, Islam MB, et al. High incidence of Guillain-Barre syndrome in children, Bangladesh. Emerg Infect Dis. 2011; 17:1317–1318. [PubMed: 21762603]

35. Islam Z, Gilbert M, Mohammad QD, et al. Guillain-Barre syndrome-related Campylobacter jejuni in Bangladesh: ganglioside mimicry and cross-reactive antibodies. PLoS One. 2012; 7:e43976. [PubMed: 22952833]

36. Porter CK, Choi D, Cash B, et al. Pathogen-specific risk of chronic gastrointestinal disorders following bacterial causes of foodborne illness. BMC Gastroenterol. 2013; 13:46. [PubMed: 23510245]

37. Mukhopadhya I, Hansen R, El-Omar EM, Hold GL. IBD-what role do Proteobacteria play? Nat Rev Gastroenterol Hepatol. 2012; 9:219–230. [PubMed: 22349170]

38. Riddle MS, Murray JA, Cash BD, et al. Pathogen-specific risk of celiac disease following bacterial causes of foodborne illness: a retrospective cohort study. Dig Dis Sci. 2013; 58:3242–3245. [PubMed: 23812827]

39. Ajene AN, Fischer Walker CL, Black RE. Enteric pathogens and reactive arthritis: a systematic review of Campylobacter, salmonella and Shigella-associated reactive arthritis. J Health Popul Nutr. 2013; 31:299–307. [PubMed: 24288942]

40. da Silva Quetz J, Lima IF, Havt A, et al. Campylobacter jejuni and Campylobacter coli in children from communities in Northeastern Brazil: molecular detection and relation to nutritional status. Diagn Microbiol Infect Dis. 2010; 67:220–227. [PubMed: 20542202]

41. Gupta SS, Mohammed MH, Ghosh TS, et al. Metagenome of the gut of a malnourished child. Gut Pathog. 2011; 3:7. [PubMed: 21599906]

42*. Masanta WO, Heimesaat MM, Bereswill S, et al. Modification of intestinal microbiota and its consequences for innate immune response in the pathogenesis of campylobacteriosis. Clin Dev Immunol. 2013; 2013:526860. [PubMed: 24324507] [A review of evidence from recent work using gnotobiotic mouse models elucidating the relationship between nutrition, shifts in the intestinal microbiota, establishment of *C. jejuni* infection, and associated immune responses. This work provides a potential mechanism for the association between malnutrition and *Campylobacter* infection.]

43*. Nielsen HL, Engberg J, Ejlertsen T, Nielsen H. Clinical manifestations of Campylobacter concisus infection in children. Pediatr Infect Dis J. 2013; 32:1194–1198. [PubMed: 23743545] [This study compares diarrheal cases in which *C. jejuni/coli* or *C. concisus* was isolated and shows the latter to be associated with mild to moderate, prolonged diarrhea. Long-term gastrointestinal complaints were common with both infections.]

44. Labarca JA, Sturgeon J, Borenstein L, et al. Campylobacter upsaliensis: Another pathogen for consideration in the United States. Clin Infect Dis. 2002; 34:E59–60. [PubMed: 12015708]

45. Wagenaar JA, van Bergen MA, Blaser MJ, et al. Campylobacter fetus Infections in Humans: Exposure and Disease. Clin Infect Dis. 2014; 58:1579–1586. [PubMed: 24550377]

46. O'Donovan D, Corcoran GD, Lucey B, Sleator RD. Campylobacter ureolyticus: A portrait of the pathogen. Virulence. 2014; 5:498–506. [PubMed: 24717836]

47. Edmonds P, Patton CM, Griffin PM, et al. Campylobacter hyointestinalis associated with human gastrointestinal disease in the United States. J Clin Microbiol. 1987; 25:685–691. [PubMed: 3571477]

48. Lastovica AJ, le Roux E. Efficient isolation of campylobacteria from stools. J Clin Microbiol. 2000; 38:2798–2799. [PubMed: 10979752]

49. Vandenberg O, Cornelius AJ, Souayah H, et al. The role of Epsilonproteobacteria in children with gastroenteritis. Pediatr Infect Dis J. 2013; 32:1140–1142. [PubMed: 23624432]

50. Kaakoush NO, Mitchell HM. Campylobacter concisus - A new player in intestinal disease. Front Cell Infect Microbiol. 2012; 2

51. Lin A, Bik EM, Costello EK, et al. Distinct distal gut microbiome diversity and composition in healthy children from Bangladesh and the United States. PLoS One. 2013; 8:e53838. [PubMed: 23349750]

52. Oberhelman RA, Gilman RH, Sheen P, et al. An intervention-control study of corralling of free-ranging chickens to control Campylobacter infections among children in a Peruvian periurban shantytown. Am J Trop Med Hyg. 2006; 74:1054–1059. [PubMed: 16760519]

53. Black RE, Levine MM, Clements ML, et al. Experimental Campylobacter jejuni infection in humans. J Infect Dis. 1988; 157:472–479. [PubMed: 3343522]

54. Poly F, Read TD, Chen YH, et al. Characterization of two Campylobacter jejuni strains for use in volunteer experimental-infection studies. Infect Immun. 2008; 76:5655–5667. [PubMed: 18809665]

55*. Kirkpatrick BD, Lyon CE, Porter CK, et al. Lack of homologous protection against Campylobacter jejuni CG8421 in a human challenge model. Clin Infect Dis. 2013; 57:1106–1113. [PubMed: 23840001] [This study reports that infection with CG8421, a strain of *C. jejuni* which lacks ganglioside mimicry, does not protect against re-challenge with the same strain after a 3 month interval, although immunogenicity was demonstrated with both mucosal and serum antibodies in the majority of subjects.]

56. Monteiro MA, Baqar S, Hall ER, et al. Capsule polysaccharide conjugate vaccine against diarrheal disease caused by Campylobacter jejuni. Infect Immun. 2009; 77:1128–1136. [PubMed: 19114545]

57*. Maue AC, Poly F, Guerry P. A capsule conjugate vaccine approach to prevent diarrheal disease caused by Campylobacter jejuni. Hum Vaccin Immunother. 2014; 10 [Mar 14 Epub ahead of print. A comprehensive review of the current state of *Campylobacter* vaccine development, focusing on the capsular conjugate vaccine approach.]

58**. Maue AC, Mohawk KL, Giles DK, et al. The polysaccharide capsule of Campylobacter jejuni modulates the host immune response. Infect Immun. 2013; 81:665–672. [PubMed: 23250948] [This study establishes the role of the capsular polysaccharide in facilitating colonization in a mouse model through modulation of the immune response, likely through IL-17. This may in part explain prolonged asymptomatic shedding after *Campylobacter* infection, which is not seen with other bacterial enteropathogens.]

59. Pike BL, Guerry P, Poly F. Global Distribution of Penner Serotypes: A Systematic Review. PLoS One. 2013; 8:e67375. [PubMed: 23826280]

60. Poly F, Serichatalergs O, Schulman M, et al. Discrimination of major capsular types of Campylobacter jejuni by multiplex PCR. J Clin Microbiol. 2011; 49:1750–1757. [PubMed: 21411576]

61. Ahmed D, Hoque A, Elahi MS, et al. Bacterial aetiology of diarrhoeal diseases and antimicrobial resistance in Dhaka, Bangladesh, 2005-2008. Epidemiol Infect. 2012140:1678–1684.

62. Mukherjee P, Ramamurthy T, Bhattacharya MK, et al. Campylobacter jejuni in hospitalized patients with diarrhea, Kolkata, India. Emerg Infect Dis. 2013; 19:1155–1156. [PubMed: 23763834]

63. Ghosh R, Uppal B, Aggarwal P, et al. Increasing antimicrobial resistance of campylobacter jejuni isolated from paediatric diarrhea cases in a tertiary care hospital of new delhi, India. J Clin Diagn Res. 2013; 7:247–249. [PubMed: 23543776]

64. Pollett S, Rocha C, Zerpa R, et al. Campylobacter antimicrobial resistance in Peru: a ten-year observational study. BMC Infect Dis. 2012; 12:193. [PubMed: 22898609]

65**. Mukherjee P, Ramamurthy T, Mitra U, Mukhopadhyay AK. Emergence of high-level azithromycin resistance in Campylobacter jejuni isolated from Paediatric Diarrhoea cases in Kolkata, India. Antimicrob Agents Chemother. 2014 [April 28 Epub ahead of print. Campylobacter resistance to quinolones emerged rapidly and is now being followed by the emergence of resistance to macrolides. This recent studies details the characterization of mutations associated with high levels of resistance to Azithromycin in India.]

66. United States Food and Drug Adminstration. [May 8, 2014] 2011 retail meat report: national antimicrobial resistance monitoring system. Available at: http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM334834.pdf.

67**. Love DC, Halden RU, Davis MF, Nachman KE. Feather meal: a previously unrecognized route for reentry into the food supply of multiple pharmaceuticals and personal care products (PPCPs). Environ Sci Technol. 2012; 46:3795–3802. [PubMed: 22435972] [This study demonstrates high rates of banned quinolones in poultry feathers. These feathers contain not only trace, but inhibitory levels of antimicrobials, that can them re-enter the food chain when they are used as fertilizer and/or animal feed. The study was done after the FDA ban on enrofloxacin use in poultry, suggesting that the ban in its current state does not appear to effectively eliminate exposure of poultry to the drugs with predictable adverse consequences in the development and maintenance of antibiotic resistant Campylobacter.]

KEY POINTS

- Adoption of less-selective culture and culture-independent diagnostic tests suggests that both *Campylobacter jejuni/coli* and non-*jejuni/coli* infections have been frequently underdetected or misidentified.
- The burden of gastroenteritis as well as long-term consequences associated with *Campylobacter* infection in developing countries remains to be clearly defined.
- Significant progress has been made towards a *Campylobacter* vaccine, and epidemiologic studies of the importance of specific capsular serotypes are needed to help guide development.