Review and Meta-analysis

Prevalence of gastrointestinal pathogens in developed and developing countries: systematic review and meta-analysis

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Significance for public health

This research is significant in that it provides an evidence base for the advancement in understanding global disease burden and the development of public health and research priorities. Understanding that people in both developed and developing settings are affected by similar pathogens to different degrees and requires cross border sharing and learning for their control. The prevalence of rotavirus underscores the need for improved access to rotavirus vaccines in both settings. Rotavirus vaccines have efficaciously reduced gastroenteritis burden where they have been introduced and hence likely to do so in developing settings. The global public health community should support efforts to make rotavirus vaccines available at affordable costs to the poorest people of the world, where disease burden and mortality is highest. Developed countries should support developing regions to implementation effective programs for the prevention and control of gastrointestinal infections, since infectious pathogens know no boundaries.

Abstract

Diarrhoeal illness is a leading cause of child mortality and morbidity worldwide. There are no precise or current estimates of the types and prevalence of pathogens associated with diarrheal illnesses in developed and developing settings. This systematic review assessed data from 60 studies published in the English language from five developing regions and developed countries worldwide to provide regional estimates of enteric pathogens affecting children. The random-effect method was used to establish the weighted average prevalence of pathogens in adults and children for each region. Significantly more pathogens were reported by studies from developing regions compared with Organisation for Economic Co-operation and Development countries (P<0.016). The identification rates of pathogens from community based and hospital based studies were similar (58.5% and 58.1% respectively, P<0.619). The overall detection of enteric pathogens in developing countries was higher in adults (74.8%; 95% CI 63.1-83.8%) compared with children (56.7%; 95% CI 53.0-60.4%) (P<0.001). Rotavirus was the most frequently detected pathogen in all regions with the highest rate, 24.8% (95% CI 18.0-33.1%), detected in the developed countries. This systematic review is the first to provide an estimate of the prevalence of enteric pathogens associated with diarrhoeal illnesses in adults and children in developed and developing settings. While pathogen detection rate is greater in developing regions the consistently high prevalence of rotavirus in both developed and developing settings underscores the urgent need for access to rotavirus vaccines. Increased travel between developing and developed countries increases disease risk, and hence developed countries have a vested interest in supporting vaccine accessibility in developing settings.

Introduction

Gastrointestinal (GIT) illnesses contribute significantly to the burden of illness from infectious diseases worldwide. Diarrhoea is the second leading cause of preventable illness in children under age five.[1-3] Despite the strong association between gastrointestinal illnesses and factors such as poor sanitation, inadequate access to safe drinking water and other risk factors, both resource-rich and less developed countries alike are impacted by gastrointestinal illness.[3,4] The risk factors however appear to be distributed differently between developed and developing countries and as a result, the incidence of specific pathogens may differ between each setting.[5] Several studies have described the pathogens, associated risk factors and the costs and burden of illness on health care. However, there are few studies that estimate the prevalence of pathogens affecting populations in different regions worldwide. Developing countries world often experience similar sanitation and poverty related risk factors, which predisposes their population to diarrhoeal illnesses. However, the incidence of illness in developed countries tend to be less generic and more related to seasonality, travel and food borne transmission.[4]

Several enteric micro-organisms are responsible for GIT illnesses and are bacterial, viral or parasitic in nature.[6] A review of the literature world-wide indicates that a causative organism is identified in about 50% of symptomatic cases.[7-10] In resource-limited settings under-reporting is possible, with the data biased towards certain pathogens and relate mainly to specific age groups.[1,11,12]

There are few estimates of the prevalence and distribution of pathogens that cause GIT illnesses, which indicate there may be significant differences in the prevalence of certain pathogens in circulation in developing and developed settings.[13-15] Determining the prevalence of pathogens on a regional basis will assist in the development of appropriately targeted prevention and control strategies, identify gaps in surveillance and provide support for the strengthening of laboratory diagnostic capacity at the regional level. It can also assist in the management of the health needs of travelers to different regions.

This paper provides an overview of gastrointestinal illnesses and a systematic review of the literature to provide region-specific GIT pathogen detection rates associated with cases in developed countries and developing regions. Firstly, an overview of gastrointestinal illnesses including definitions, and disease transmission and risk factors are presented. Then an estimate of the detection of enteric pathogens is provided based on studies worldwide.

Definition of gastrointestinal illness

The term *gastrointestinal illness* refers to several conditions affecting the gastrointestinal system that exhibits watery or unformed stools and are usually caused by infections or intoxications with a biological

agent.[16] Because of the various causes, variable symptomology, and numerous different terms used to describe disease of the gastrointestinal tract, no standard definition of *gastrointestinal diseases* has been presented in the medical literature.[17] For the purposes of this study, gastrointestinal illness refers to any illness of the gastrointestinal tract caused by a microbe causing chronic or acute diarrhea, whether or not accompanied by nausea, or vomiting, combined with abdominal pain, or systemic symptoms such as fever. A suspected case is any case having met the criteria for a clinical diagnosis (see below). A confirmed case is any suspect case that has a laboratory confirmation of an enteric disease pathogen isolated from a clinical specimen.

Diarrhoeal illness is usually divided into three main categories based on its clinical presentation:[18]

- *Acute watery diarrhoea* associated with several pathogens such as *Vibrio cholera* and rotavirus, usually last for several days, and poses a high risk for dehydration which can be fatal especially in young children, the elderly and immuo-compromised persons.[18]
- *Acute bloody diarrhoea* or dysentery is usually evidence of infection with *Campylobacter, Salmonella, Shigella,* enterohaemorrhagic *E. coli* pathotypes*, Entamoeba histolytica* and other organisms, and can lead to dehydration. The major risks associated with this presentation include intestinal damage, sepsis and malnutrition.[18]
- *Persistent diarrhoea* lasts for 14 or more days and is usually associated with parasitic aetiology but can be due to non-infectious causes such as inflammatory bowel disease. Due to the prolonged duration of persistent diarrhoea there is a risk of nutrient deficiency, extra intestinal infection and dehydration especially in children, the elderly and immuno-compromised.[18]

Overview of gastrointestinal illness

Gastrointestinal illnesses can be either acute self-limiting infections or chronic idiopathies.[19] Both acute and chronic infections can be caused by pathogenic bacteria, viruses and parasites. Diarrhoea can also be caused by idiopathic diseases arising from internal dysfunctions of gastrointestinal tract include diseases such as Idiopathic bowel disease, Crohn's disease and ulcerative colitis.[19,20] The majority of gastrointestinal illnesses are self-limited,[19] however, certain risk factors such as malnutrition, immunosuppression, and young age predisposes the development of persistent diarrhea.[18] Patients with immune deficiencies (congenital, iatrogenic or acquired) are unusually more susceptible to infections and are at an increased risk for malignancy.[21]

Disease transmission and risk factors

Infectious gastrointestinal illnesses are transmitted through a variety of routes including contaminated food or water borne, the faecal oral route, and person-to-person.[16,22] A significant proportion, about 36%, of gastrointestinal illnesses is attributable to food borne transmission.[23,24] Among all illnesses attributable to food borne transmission, 30% are caused by bacteria, 3% by parasites, and 67% by viruses.[23] In the USA for example, nontyphoidal Salmonella spp. (35%), norovirus (26%), Campylobacter spp. (15%), and Toxoplasma gondii (8%) were the leading causes of hospitalization in 2000-2008.[23,25] *Salmonella*, *Listeria*, *Toxoplasma*, and norovirus are responsible for more than 75% of deaths related to known causes of food borne illness each year.[6,23,25] In Australia about 32% of all gastroenteritis are foodborne, and *Campylobacter,* non-typhoid *Salmonella,* pathogenic *E. coli* and norovirus are responsible for over 80% of foodborne illness from *known* pathogens.[26,27] In Australia the highest rates of gastroenteritis in the general population has been reported among young children and their adult carers.[28]

The majority of gastrointestinal illnesses can be transmitted through the faecal-oral route. Infections with pathogenic *E. coli* strains are usually considered an indication of poor hygiene. Up to 63% of children with persistent diarrhoea in low and middle income countries have tested positive for *E. coli* strains.[10] Travel-associated diarrhoea has been described and travel to a developing region is a risk factor among patients presenting with diarrhoea in developed settings.[29,30] Studies have reported that travellers to low and middle income countries are between 9 and 151 times more likely to develop diarrhoeal illness,[14,31] with the highest risk associated with travel to areas in South America, Africa and South Asia.[14,32,33]

Methodology for estimating pathogen detection rates

Search strategy

Studies reporting the aetiology of diarrhoeal illness were identified from a search of databases including Science Direct, PubMed, PubMed Central, and Google scholar for articles published from 1980 and 2010. The search was not restricted to publications in the English Language, only to studies that had abstracts in English. The key subject terms included one or combinations of the following: *infectious intestinal pathogen AND humans, diarrhea (or diarrhoea) and pathogen, aetiology (etiology) of acute gastroenteritis OR diarrhoea, enteric infectious pathogens.* Boolean operators (*not*, *and*, *or*) were also used in succession to narrow and widen the searches. Other articles were identified by using the PubMed option of *related articles* and checked the reference lists of the original and review articles.

Eligibility and study selection criteria

Eligibility of studies for inclusion includes the following criteria:

- Detailed results of microbiological analysis of stool samples and the number of samples tested;
- Subjects defined as clinically symptomatic or asymptomatic;
- Number of study subjects and positive results for both cases/controls;
- Definition of symptomatic subjects (case) as persons who had diarrhoea (defined as three or more loose/watery stools in a 24 hour period), or loose stools associated with gastrointestinal symptoms including: vomiting, abdominal pain or cramps, and blood or mucus in stool.[34]

Detection rates for adults and children were provided as age-specific.

Excluded studies

Studies were excluded where data were provided without adequate information for the detection and age-specific rates to be calculated, where the focus was on a single pathogen, or data were presented as the number of diarrhoeal episodes rather than samples tested.

Data abstraction and analysis

Selected studies were summarised in tabular format to include data on study design, study population, source of sample and sample size, methods to detect enteric pathogens, and detection rates. Where studies included combined age-groups that provided adequate data for children and adults separately, the data for children and adults were recorded separately. Countries were categorised into developing regions categories, based on the World Bank List of Economies published in July 2009,[35] including: East Asia Pacific (EAP), Latin America and Caribbean (LAC), Middle East and Northern Africa (MENA), Sub-Saharan Africa (SSA), and South Asia and the Pacific (SAP). Developed

countries were categorised based on the Organisation for Economic Co-operation and Development (OECD) category of countries.[35,36] Two non-OECD developed countries [Republic of (South) Korea and Turkey] were also included in this category (Supplementary Table S1).

Analysis and synthesis of results

Estimates of the prevalence of diarrhoeal pathogens were calculated by region. As studies were conducted in different regions using different methods and approaches the pooled prevalence of pathogens was estimated using the DerSimonian-Laird random-effect (RE) method.[37] The pooled or weighted RE estimate of pathogen prevalence was calculated using the Comprehensive Meta-analysis (CMA) programme.[38] The estimated mean prevalence was reported with 95% Confidence Intervals (95% CI).

Estimating the prevalence of gastrointestinal pathogens

Description of studies

The search produced 10,288 papers and the abstracts of 121 were included in our critical review. Data from 60 studies (from 47 developing and 13 developed countries) met the inclusion criteria for analysis.[7,8,39-97] The studies included are summarised in Table 1. Of the studies reviewed, one presented multi-country data (two in EAP, one in LAC, two in SAP) which was tabulated and analysed under individual country/region.[40] Three studies had sufficient data to allow the tabulation and analysis of findings for children and adults separately.[62,94,95] These brought the total number of studies reviewed to 67. Most studies (73%, 44/60) recruited subjects from hospital settings and the remainder (17%, 16/60) were recruited from community or mixed settings. Studies were classified into six groups: five developing regions and OECD (developed) countries.

The summary of the laboratory procedures employed in each study is presented in Table S1. For the detection of bacteria, standard culture methods often coupled with serological tests, DNA hybridization, enzyme immunoassays (EIA) and polymerase chain reaction (PCR) were employed for the detection of different pathotypes of pathogenic *E. coli.* In some cases antibiotic susceptibility testing was performed by the disk diffusion or plate dilution methods. The majority of viral studies focused on rotavirus, employing mainly enzyme linked immunosorbent assay (ELISA), EIA, and less frequently, latex slide agglutination test and PCRs. Microscopic examination of permanently stained films have been generally used for the detection of ova cyst and parasites along with a modified Ziehl-Neelsen stain for coccidian parasites.

Overall detection of pathogens

Source of cases

There was no significant difference in the detection of total number of pathogens in community or hospital settings (P>0.05). In 13 community based studies from four regions, enteric pathogens were detected in an average of 57.8% (95% CI, 49.2-65.9%) of cases, ranging from 52.4% in the EAP region to 62.6% in the SSA region. There was a significant difference in detection rates from 44 hospital based studies across the six regions, (P=0.001). The average detection of enteric pathogens was 58.1% (95% CI, 54.0-62.0%) of hospitalised cases, with a range of 36.9% (95% CI, 31.7-56.2%) in the MENA region to 66.7% (95% CI, 58.9-72.4%) in the SAP region (Table 2).

Age groups

In children, a pathogen was detected on average 56.7% (95% CI, 53.0-60.4%) with the lowest detection rate of 43.6% (95% CI, 31.7-56.2%) in the MENA region and the highest detection rate of 64.4% (95% CI, 57.6-70.7%) in the SAP region. Conversely, the detection rate of pathogens in adults on average was 74.8% (95% CI, 63.1-83.8%). The highest rate was among adults from the MENA region (90.4%; 95% CI, 81.2-95.4%) and the lowest rates of detection was among adults from OECD countries (32.5%; 95% CI, 14.7-57.3%) (Table 2).

Regional distribution of enteric pathogens

Children

The weighted average detection rate for enteric organisms in children for each region identified rotavirus as the most frequently detected pathogen in children (Table 3). The rates ranged from a low of 4.8% (95% CI, 2.6-8.7%) in SSA region to as high as 24.8% (95% CI, 18.0-33.1%) in OECD countries. The detection of rotavirus from diarrhoeal cases was up to five times more in OECD countries than in developing regions. Adenovirus 4.5% (95% CI 3.3-6.1%) and norovirus 3.3% (95% CI, 1.9-5.7%) were also most frequently detected in OECD countries when compared with developing regions. On average, *E. coli* pathotypes [Enterotoxigenic *E. coli* (ETEC), Enteropathogenic *E. coli* (EPEC)] and other pathogenic *E. coli* spp. were prevalent across all developing regions. The highest rates of EPEC were detected in the SAP region (8.5%; 95% CI, 5.4-13.1%) followed by the LAC region (5.6%; 95% CI, 2.3-12.6%); while ETEC was most prevalent in the SAP region and other *E. coli* pathotypes were also common in the MENA region (10.6%; 95% CI, 4.2-24.3%). *Campylobacter* spp., was also frequently detected in developing regions with the highest rate of detection in the SAP (6.6%; 95% CI, 3.9-10.9) and LAC (5.5%; 95% CI, 2.8-10.4) regions. *Salmonella* spp and *Shigella* spp were frequently detected among children in developing regions with *Salmonella* (4.1%; 95% CI, 2.8-5.9%) and *Campylobacter* spp (3.4%; 95% CI, 2.3-4.9%) the most frequently detected bacterial pathogens in children in developed countries.

Parasites were less frequently detected; yet *Giardia intestinalis* was the most frequently detected protozoa in developing regions, with the highest prevalence found in SAP (3.0%; 95% CI, 1.5-5.9%) and SSA (2.7%; 95% CI, 1.8-4.3%) regions. *Entamoeba* spp were frequently detected in MENA (1.5%; 95% CI, 0.6-4.2%) and SSA (1.5%; 95% CI, 0.9-2.5%) regions while *Cryptosporidium* was more prevalent in in the MENA (1.0%; 95% CI, 0.2-4.9%) and SAP (1.7; 95% CI, 0.8-3.1%) regions. Another protozoa, *Dientamoeba fragilis,* was found in <1% of cases in each region.

Adult patients were assessed for only three regions: MENA, SSA and the OECD countries (Table 4). Amongst adult patients *Cryptosporidium* sp. (9.4%; 95% CI, 1.0-50.2%), *Salmonella* spp (4.0%; 95% CI, 0.2-43.5%), other pathogenic *E. coli* (3.6%; 95% CI 0.3-36.2%), and *Shigella* sp. (2.2%; 95% CI, 1.1-4.5%) were quite common in the SSA region. Frequent viral pathogens detected in stools of adults from OECD countries were norovirus (10.5%; 95% CI, 7.5-14.7%), rotavirus (3.6%; 95% CI, 1.4-9.2%) and *Campylobacter* (3.3%; 95% CI, 0.9-12.0%).

Discussion

The paucity of information concerning the prevalence of diarrhoeal pathogens in different world regions has resulted in the conduct of this systematic review. This is the first study that has attempted to provide an estimate of the prevalence of enteric pathogens in both developed and developing settings. Several fundamental conclusions can be drawn from these findings. This review found i) developing regions have significantly more pathogens isolated than the OECD countries,

Table 1. Summary of 60 studies included in the systematic review of gastrointestinal pathogens worldwide.

Region (studies)	Country	First author/ year (ref)	Study details					Laboratory analysis (tests done)	
			Study period	Study design	Source of specimen	Sampling method	Age groups (yrs)	Sample size	Bacterial culture
EAP (13)	Burma	Tin 1989 (39)	1982-1983	Case control	Community	Consecutive	0-5	501 cases, 374 controls	Bacteriology, virology
	China	Huilan Sima 1991 (40)	1982-1985	Case control	Hospital	Consecutive	0-3	594 cases, 562 controls	Bacteriology, virology, parasitology
	China	Kain Kevin 1991 (41)	1989-1989	Case control	Hospital	Consecutive	0-5	221 cases, 108 controls	Bacteriology, virology, parasitology
	Indonesia	Soenarto 1983 (43)	1978-1979	Case control	Hospital	Consecutive	0-12	338 cases, 69 controls	Bacteriology, virology, parasitology
	Myanmar	Huilan 1991 (40)	1982-1985	Case control	Hospital	Consecutive	0-3	813 cases, 813 controls	Bacteriology, virology; parasitology
	Vietnam	Hien. 2007 (50)	2002-2004	Case control	Community	Consecutive	0-6	111 cases, 111 controls	Bacteriology, virology; parasitology
	Vietnam	Isenbarger 2001 (47)	1998-1999	Case control	Hospital/PHC	Consecutive	0-5	2160 cases, 203 controls	Bacteriology,
	Vietnam	Nguyen 2006 (49)	2000-2002	Case control	Hospital/ community	Consecutive	0-5	587 cases, 249 controls	Bacteriology, virology
	China	Yu 2008 (42)	2006-2007	Cross-sectional	Hospital	Consecutive	0-5	1216 cases	Virology
	Laos PDR	Yamashiro 1998 (44)	1996-1997	Cross-sectional	Hospital/PHC	Consecutive	0-15	880 cases	Bacteriology, virology
	Taiwan	Liu 2005 (45)	2000-2001	Cross-sectional	Hospital	Consecutive	0-3	657 cases	Bacteriology, virology
	Taiwan	Lu 2006 (46)	2001-2002	Cross-sectional	Hospital	Systematic random	0-5	768 cases	Bacteriology, virology
	Thailand	Bodhidatta 2002 (48)	1998-2000	Cross-sectional	Hospital	Consecutive	0-12	623 cases	Bacteriology
LAC (80)	Brazil	Seigel 1996 (51)	1994-1994	Case control	Hospital	Consecutive	0-5	112 cases, 106 controls	Bacteriology, virology
	Mexico	Huilan 1991 (40)	1982-1985	Case control	Hospital	Consecutive	0-3	559 cases, 559 controls	Bacteriology, virology; parasitology
	Mexico	Paniagua 2007 (55)	2004-2006	Case control	Hospital	Consecutive	>2 -<12	300 cases, 80 controls	Bacteriology, parasitology
	Peru	Pazzaglia 1991 (56)	1988-1989	Case control	Hospital	Consecutive	0-2	391 cases, 138 controls	Bacteriology, virology;
	Peru	Ochoa 2009 (54)	2006-2007	Case control	Community	Consecutive	0-1	936 cases, 424 controls	Bacteriology, virology;
	Brazil	Barreto 2006 (52)	2000-2002	Cross-sectional	Community	Random	0-3	1233 cases	Bacteriology, virology; parasitology
	Mexico	Flores-Abuxapqui 1994 (53)	1991-1991	Cross-sectional	Community	Consecutive	0-2	148 cases	Bacteriology, virology; parasitology
	Uruguay	Torres 2001 (57)	1990-1994	Cross-sectional	Hospital	Consecutive	0-4	224 cases	Bacteriology, virology; parasitology
MENA (8)	Tunisia	Al-Gallas 2007(62)	2001-2004	Case control (divided into 2 age gps)	Hospital/PHC	Consecutive	0-15 18-80	115 cases, 73 controls; 54 cases, 29 controls	Bacteriology, virology; parasitology
	Egypt	El-Mohamady 2006 (58)	2003-2003	Cross-sectional	Hospital	Consecutive	0-5	356 cases	Bacteriology, virology; parasitology
	Gaza	Elamreen 2007 (59)	2005-2005	Cross-sectional	Hospital	Consecutive	0-5	150 cases	Bacteriology
	Jordan	Youssef 2000 (61)	1993-1994	Cross-sectional	Hospital	Consecutive	0-5	265 cases	Bacteriology, virology; parasitology
	Saudi Arabia	El-Sheikh 2001 (60)	1995-1996	Cross-sectional	Hospital/PHC	Consecutive	0-5	576 cases	Bacteriology, virology; parasitology
nOECD (2)	Rep. of Korea (South)	Kyung-Hee 1989 (73)	1984-1985	Case control	Hospital	Consecutive	0-15	231 cases, 104 controls	Bacteriology, virology; (no in controls)
	Turkey	Uysal 1997 (75)	1993-1994	Cross-sectional	Hospital	Consecutive	0-14	400	Bacteriology, virology; Parasitology
OECD (11)	Denmark	Olesen 2005 (65)	2000-2001	Case control	Hospital	Consecutive	0-5	424 cases, 866 controls	Bacteriology, virology; parasitology
	Australia	Barnes 1998 (63)	1980-1993	Cross-sectional	Hospital	Consecutive	0-14	3785 cases,	Bacteriology, virology; parasitology
	Australia	McIver 2001 (64)	1997-1998	Cross-sectional	Hospital	Random	0-5	412 cases,	Bacteriology, virology; parasitology
	England	O'Neill 2002 (95)	2000-2001	Cross-sectional	Hospital	Consecutive	10-90 0-5	735 cases 1051 cases	Virology; parasitology

To be continued on the next page.

Table 1. Continued from previous page.

Region (studies)	Country	First author/ year (ref)	Study details Study period	Study design	Source of specimen	Sampling method	Age groups (yrs)	Laboratory analysis (tests done) Sample size	Bacterial culture
	Russia	Podkolzin 2009 (94)	2005-2007	Prospective	Hospital	Consecutive	14-60 0-5	1354 cases 2848 cases	Virology
	Finland	Rautelin 1989 (66)	1985-1986	Cross-sectional	Hospital	Consecutive	15-60	253 cases,	Bacteriology, virology; parasitology
	Germany	Jansen 2008 (96)	2005-2007	Cross-sectional	Hospital	Consecutive	18-60	132 cases,	Bacteriology, virology; parasitology
	Greece	Levidiotou 2009 (67)	2000-2006	Cross-sectional	Hospital	Consecutive	0-5	4604 cases,	Virology
	Italy	Colomba 2006 (68)	1999-2000	Cross-sectional	Hospital	Consecutive	0-12	215 cases,	Bacteriology, virology; parasitology
	New Zealand	Montgomery 2006 (74)	2005-2005	Cross-sectional	Hospital	Consecutive	0-15	128	Bacteriology, virology; parasitology
	USA	Klein 2006 (72)	1998-2001	Cross-sectional	Hospital	Consecutive	0-5	372 cases,	Bacteriology, virology; parasitology
SAP (7)	Bangladesh	Albert 1999 (69)	1993-1994	Case control	Hospital	Systematic random	0-5	814 cases, 814 controls	Bacteriology, virology; parasitology
	India	Huilan 1991 (40)	1982-1985	Case control	Hospital	Consecutive	0-3	916 cases, 587 controls	Bacteriology, virology; parasitology
	India	Ghosh 1991 (70)	1986-1988	Case control	Hospital	Consecutive	0-1	218 cases, 102 controls	Bacteriology, virology; parasitology
	Nepal	Hoge 1995 (78)	1994-1994	Case control	PHC	Consecutive	0-5	124 cases, 103 controls	Bacteriology, virology; parasitology
	Pakistan	Huilan 1991 (40)	1982-1985	Case control	Hospital	Consecutive	0-3	758 cases, 758 controls	Bacteriology, virology; parasitology
	Bangladesh	Haque 2003 (71)	1999-2002	Cross-sectional	Community	Consecutive	0-5	289 cases,	Bacteriology, virology; parasitology
	India	Dutta 1991 (8)	1990	Cross-sectional	Hospital	Consecutive	0-5	383 cases,	Bacteriology, virology; parasitology
SSA (18)	Central African Rep	Georges 1984 (7)	1981-1982	Case control	Hospital	Consecutive	0-15	1197 cases, 748 controls	Bacteriology, virology; parasitology
	Central African Rep	Germani 1998 (77)	1995-1996	Case control	Hospital	Consecutive	18-80	290 cases, 140 controls	Bacteriology, virology; parasitology
	Ghana	Reither 2007 (79)	2005-2006	Case control	PHC	Consecutive	0-12	243 cases, 124 controls	Bacteriology, virology; parasitology
	Nigeria	Ogunsanya 1994 (83)	1989-1990	Case control	Hospital	Consecutive	0-5	215 cases, 100 controls	Bacteriology, virology; parasitology
	Zaire De Mol 1983 (90)		1979-1979	Case control	Hospital	Consecutive	0-5	355 cases, 320 controls	Bacteriology, virology; parasitology
	Zaire	Henry 1995 (91)	1990-1990	Case control	Hospital/PHC	Cluster random	0-5	173 cases, 155 controls	Bacteriology, virology; parasitology
	Burkina Faso	Djeneba 2007 (76)	2006	Cross-sectional	GP	Consecutive	0-5	66 cases,	Virology; parasitology
	Cameroon	Yongsi 2008 (80)	2000-2005	Cross-sectional	Community	Stratified random	0-5	437 cases,	Bacteriology, virology; parasitology
	Nigeria	Olowe 2003 (84)	2001-2002	Cross-sectional	Hospital	Consecutive	0-5	135 cases,	Bacteriology,
	Nigeria	Cajetan 2010 (87)	2008-2008	Cross-sectional	Hospital	Random	0-5	404 cases,	Bacteriology,
	Tanzania	Vargas 2004 (89)	1996-1997	Cross-sectional	Hospital	Consecutive	0-5	451 cases,	Bacteriology, virology; parasitology
	Uganda	Musiime 2009 (88)	2008-2008	Cross-sectional	Hospital	Consecutive	0-5	190 cases,	Bacteriology,
	Zambia	Kelly 1996 (92)	1994	Cross-sectional	Hospital/ community	Consecutive	18-80	77 cases,	Parasitology
	Nigeria	Ogbu O 2008 (82)	2005-2006	Case control	PHC	Consecutive	0-3	150 cases, 50 controls	Bacteriology, virology; parasitology
	Uganda	Brink 2002 (86)	1995-1997	Case control	PHC	Consecutive	0-15	357 cases, 127 controls	Bacteriology, parasitology
	Zambia	Nakano 1998 (93)	1992-1993	Cross-sectional	PHC	Consecutive	0-5	639 cases,	Bacteriology
	Nigeria	Anynwu 1997 (81)	1997-1997	Case control	Hospital	Consecutive	0-5	1015 cases, 401 controls	Bacteriology
	Kenya	van Eijk 2009 (85)	1997-2001	Prosp. cohort	Hospital	Consecutive	0-2	630 cases	Bacteriology, virology; parasitology

Specimens were obtained from persons seen at hospitals, Primary Health Care Centre (PHC), General Practitioner (GP), or from the community. Sampling methods include taking consecutive (or convenience or census) specimen, systematic random, random, stratified random sampling and some studies collected samples from routine surveillance programmes. Cas cont. = case control study; cross-sect. = cross sectional; Cohort = prospective follow-up studies. MENA = Middle East and North Africa; EAP= East Asia & the Pacific; SAP= South Asia; LAC= Latin America and the Caribbean; SSA= Sub-Saharan Africa; OECD= Developed Countries including non-OECD. Source: World Bank Country Classification July 2009. Available at http://go.worldbank.org/D7SN0B8YU0. Accessed December 29, 2009.

ii) the identification of pathogens from community based studies was similar to those in hospital based studies, iii) the overall detection of enteric pathogens is higher amongst adults than in children in developing settings, iv) enteric viruses (rotavirus, adenovirus and norovirus) were more frequently detected in paediatric cases in developed countries than in developing countries, and v) bacterial pathogens are frequently detected amongst children and adults in developing regions.

This review found that developing regions had significantly more pathogens isolated than the OECD countries. A WHO report indicated that in 2008 the SSA and SAP regions accounted for more than three quarters of the deaths in children from diarrhoeal disease.[11] Several travel based studies suggest that travel to South America, Africa, and South Asia poses the greatest risk for travelers' diarrhoea.[14,32,33] South Asia continues to be affected by a disproportionately higher incidence of diarrhoeal illness in countries such as India and Bangladesh. Support to developing regions for the development of targeted interventions such as food safety programs that can successfully reduce the rates of travelers' diarrhoea amongst tourists,[98-100] and provide evi-

Table 2. Age specific and source related regional estimate of overall pathogen detection.

Overall detection rate	Children		Adults		All cases		Hospital	Community
Regions	Number of studies	Detection rate (95% CI)	Number of studies	Detection rate % (95% CI)	Number of studies	Detection rate % (95% CI)	Detection rate % (95% CI)	Detection rate % (95% CI)
SAP	7	64.4 (57.6-70.7)	0	N/R	13	54.1 (43.9-63.9)	66.7 (58.3-74.1)	58.7 (55.6-61.7)
LAC	8	61.0 (51.2-70.1)	0	N/R	8	61.0 (51.2-70.1)	65.0 (56.3-72.8)	52.6 (35.6-69.1)
SSA	16	59.4 (48.5-69.3)	2	69.7 (39.6-89.0)	6	54.5 (40.2-68.1)	52.8 (39.9-65.4)	62.6 (43.3-78.6)
EAP	13	54.1 (43.9-63.9)	0	N/R	7	64.4 (57.6-70.7)	59.4 (49.7-68.5)	52.5 (27.7-76.1)
MENA	5	43.6 (31.7-56.2)	1	90.4 (81.2-95.4)	18	60.5 (50.6-69.7)	36.9 (22.0-54.9)	N/R
OECD	11	50.1 (42.5-57.7)	4	32.5 (14.7-57.3)	15	45.2 (37.2-53.5)	50.4 (42.5-58.3)	N/R
Total	60	56.7 (53.0-60.4)	7	74.8 (63.1-83.8)	67	57.2 (53.4-60.9)	58.1 (54.0-62.0)	58.5 (55.6-61.4)

Random-Effect estimate [Q (df) P-value] for difference between hospital and community based studies = 0.25 (1) 0.619; Adults = (20.7 (2) 0.001 and children = 13.2 (5) 0.022; regions = 13.9 (5) 0.016. The weighted mean detection rate is calculated by dividing number of positive stool tests for individual pathogens by the total number of specimen tested. DerSimonian-Laird random-effect (RE) method was calculated on the basis of the Cochran's Q-test with alpha set at the 5% level. Regions: EAP=East Asia & the Pacific; MENA = Middle East and North Africa; SAP= South Asia; LAC= Latin America and the Caribbean; SSA= Sub-Saharan Africa; OECD= Developed Countries including non-OECD developed countries. N/R= not reported.

Table 3. Weighted average prevalence of enteric pathogens from children 0-12 years in developing regions and OECD countries.

N. of studies (60)	EAP 13	LAC 8	MENA 5	OECD 11	SAP 7	SSA 16
Pathogens	Detection rate % (95% CI)	Detection rate % (95% CI)	Detection rate % (95% CI)	Detection rate % (95% CI)	Detection rate % (95% CI)	Detection rate % (95% CI)
Bacteria						
Aeromonas	0.1 (0.0-0.6)	0.3 (0.00-6.9)	0.7 (0.3-1.9)	0.1 (0.04-0.2)	2.9 (1.4-6.1)	0.3 (0.2-0.6)
Campylobacter jejuni	2.1 (1.0-4.2)	5.5 (2.8-10.4)	2.4 (1.1-5.5)	3.4 (2.3-4.9)	6.6 (3.9-10.9)	2.7 (1.5-4.8)
EPEC	2.9 (1.7-4.8)	5.6 (2.3-12.6)	1.4 (0.3-6.6)	0.2 (0.1-0.9)	8.5 (5.4-13.1)	3.2 (2.0-5.2)
ETEC	4.1 (2.2-7.5)	5.9 (3.1-11.2)	5.4 (1.7-15.6)	0.1 (0.01-1.6)	12.7 (8.6-18.3)	1.0 (0.5-2.1)
Other diarrh E. coli pathotypes	1.7 (0.8-3.4)	1.9 (0.5-6.8)	10.6 (4.2-24.3)	0.4 (0.1-1.2)	1.8 (0.5-5.6)	4.3 (2.1-8.6)
Salmonella spp.	2.8 (1.5-5.4)	1.7 (0.3-9.2)	3.2 (1.6-6.5)	4.1 (2.8-5.9)	2.5 (1.6-3.8)	3.6 (2.5-5.0)
Shigella spp.	4.4 (2.8-7.0)	2.9 (1.4-6.1)	3.5 (2.4-5.3)	0.5 (0.1-2.1)	5.6 (3.0-10.1)	4.3 (2.6-7.0)
Vibrio cholerae	0.2 (0.1-0.4)	0.2 (0.1-0.5)	0.2 (0.1-0.7)	0.1 (0.04-0.3)	2.1 (1.0-4.8)	0.4 (0.1-0.9)
Viruses						
Astrovirus	0.1 (0.0-0.6)	0.4 (0.2-0.8)	0.2 (0.1-0.7)	1.3 (0.7-2.7)	0.1 (0.04-0.3)	0.2 (0.1-0.7)
Adenovirus type 40/41	0.4 (0.2-0.9)	0.5 (0.2-1.6)	0.2 (0.1-0.7)	4.5 (3.3-6.1)	1.5 (0.6-3.4)	0.5 (0.2-1.5)
Norovirus	0.2 (0.1-0.7)	0.3 (0.1-1.6)	0.2 (0.1-0.7)	3.3 (1.9-5.7)	0.7 (0.3-1.8)	0.2 (0.1-0.9)
Rotavirus	12.1 (7.4-19.3)	12.0 (7.4-19.0)	14.4 (7.8-25.0)	24.8 (18.0-33.1)	7.9 (4.7-12.8)	4.8 (2.6-8.7)
Parasites						
Ascaris	0.2 (0.0-0.7)	0.3 (0.1-1.0)	0.5 (0.2-1.1)	0.1 (0.04-0.2)	0.1 (0.04-0.3)	0.3 (0.1-1.1)
Blastocystis spp.	0.1 (0.0-0.2)	0.1 (0.1-0.4)	0.2 (0.1-0.7)	0.1 (0.04-0.5)	0.1 (0.04-0.3)	0.2 (0.1-0.3)
Cryptosporidium sp	0.1 (0.1-0.2)	0.2 (0.1-2.0)	1.0 (0.2-4.9)	0.3 (0.1-0.5)	1.7 (0.8-3.1)	0.3 (0.1-0.9)
Dientamoeba fragilis	0.1 (0.1-0.2)	0.1 (0.1-0.4)	0.2 (0.1-0.7)	0.1 (0.03-0.2)	0.1 (0.1-0.3)	0.2 (0.1-0.3)
Entamoeba spp.	0.1 (0.1-0.9)	0.6 (0.1-6.5)	1.5 (0.6-4.2)	0.1 (0.03-0.4)	0.6 (0.1-2.5)	1.5 (0.9-2.5)
Giardia intestinalis	0.1 (0.1-0.3)	1.9 (0.6-6.5)	1.2 (0.5-3.2)	0.3 (0.1-0.8)	3.0 (1.5-5.9)	2.7 (1.8-4.3)

EAP=East Asia & the Pacific; MENA = Middle East and North Africa; SAP= South Asia; LAC= Latin America and the Caribbean; SSA= Sub-Saharan Africa; OECD= Developed Countries including non-OECD developed countries. EPEC- Enteropathogenic E. coli; ETEC- Enterotoxigenic *E. coli.*

dence for vaccine development should be a priority for developed countries.[101] While the source of difference in pathogen prevalence between both settings cannot be determined from the information provided in the studies, we suggest that it is likely to be related, in part, to factors such as socioeconomic status, access to potable water and sanitation solutions. These factors were not explicitly described in many studies but are known important predictors of diarrhoea incidence in developing settings.[102]

The identification of pathogens from community based studies was similar to those in hospital based studies; however regional differences may exist between the settings. Even though there were no significant differences in the overall detection of pathogens between community and hospital based studies, differences were observed within hospital based studies between regions. One explanation for this may be hospital setting cases have severe clinical symptoms and were more likely to be tested compared with cases from the community setting.

The overall detection of enteric pathogens was higher amongst adults than in children in developing settings. The contrary is true for developed settings. Whilst this may be due to underlying sample sizes and testing methodologies employed, there is some evidence to suggest that several new and emerging pathogens are not routinely detected in clinical laboratories. Considering the majority of the studies involving children were from developing regions, limited laboratory capacity may have precluded the identification of organisms that require very sensitive diagnostic techniques, such as viral pathogens and some enteric protozoa.[103-106] There is a need for the development of inexpensive sensitive and specific diagnostic methods to improve pathogen detection in clinical laboratories.[15,107-110] Some exposures increase the risk for infections in older children and adults, that could influence the types of pathogens that infect them including poor hygiene practices, foodborne infections and different environmental risk factors.[111]

Enteric viruses were more frequently detected in paediatric cases in developed countries than in developing countries. This finding is not unusual since rotavirus is considered to be the most common cause of childhood diarrhoea in both developed and developing countries.[112] Infections with enteric viruses have a strong relationship with seasons and may be the reason for the higher incidence in OECD countries. This relationship is particularly evident in OECD countries with a temperate climate where rotavirus and norovirus infections often peak in the cooler months.[113,114] There is a less obvious seasonal distribution in tropical countries.[115] The burden of rotaviral diarrhoea worldwide has resulted in the World Health Organization (WHO) placing priority on the development and distribution of rotavirus vaccines globally.[3] More recently, a gradually decrease in the number of hospitalizations from severe dehydrating diarrhoea in children has been observed since the introduction of the rotavirus vaccine in the USA, in 2006,[116] and in Australia in 2007.[117-119] Efficacy trials conducted in Africa,[120] and a post-marketing study conducted in Mexico, support the use of rotavirus vaccines in the developing countries.[121]

Norovirus infection in developed settings was prevalent in adults and nearly three times more common compared with children. Norovirus is recognized as a leading cause of epidemic gastroenteritis affecting all age groups, with sporadic cases occurring all year round with increased incidence observed in colder months.[113] In contrast to

Table 4. Weighted average prevalence of enteric pathogens from adults >12 years in developing regions and OECD countries.

Regions	MENA	OECD	SSA
No. of Studies (7)	1	4	2
Pathogens	Detection rate % (95%CI)	Detection rate % (95%CI)	Detection rate % (95%CI)
Bacteria			
Aeromonas sp.	0.7 (0.01-9.9)	0.2 (0.01-0.6)	0.3 (0.01-2.3)
Campylobacter jejuni	1.4 (0.2-9.1)	3.3 (0.9-12.0)	0.3 (0.01-2.3)
EPEC	N/R	0.1 (0.01-0.5)	0.3 (0.01-2.3)
ETEC	N/R	0.1 (0.01-0.5)	1.0 (0.3-2.7)
Other diarrh *E. coli* pathotypes	37 (26.7-48.6)	0.1 (0.01-0.5)	3.6 (0.3-36.2)
Salmonella spp.	0.7 (0.01-9.9)	1.9 (0.4-7.7)	4.0 (0.2-43.5)
Shigella spp.	4.1 (1.3-12.0)	0.2 (0.01-1.0)	2.2 (1.1-4.5)
Vibrio cholerae	0.7 (0.01-9.9)	0.1 (0.01-0.5)	N/R
Viruses			
Astrovirus	0.7 (0.01-9.9)	0.4 (0.01-2.9)	0.3 (0.01-2.3)
Adenovirus type 40/41	6.8 (2.9-15.4)	1.0 (0.4-2.4)	0.3 (0.01-2.3)
Norovirus	0.7 (0.01-9.9)	10.5 (7.5-14.7)	0.3 (0.01-2.3)
Rotavirus	1.4 (0.2-9.1)	3.6 (1.4-9.2)	0.3 (0.01-2.3)
Parasites			
Ascaris	0.7 (0.01-9.9)	0.1 (0.01-0.5)	0.3 (0.01-2.3)
Blastocystis spp.	0.7 (0.01-9.9)	0.2 (0.01-1.5)	4.0 (0.5-24.7)
Cryptosporidium sp	0.7 (0.01-9.9)	0.3 (0.01-3.1)	9.4 (1.0-50.2)
Dientamoeba fragilis	0.7 (0.01-9.9)	0.1 (0.01-0.5)	0.3 (0.01-2.3)
Entamoeba spp.	1.4 (0.2-9.1)	0.2 (0.01-0.6)	2.5 (1.2-5.1)
Giardia intestinalis	0.7 (0.01-9.9)	0.3 (0.01-2.3)	1.4 (0.6-3.2)

EAP=East Asia & the Pacific; MENA = Middle East and North Africa; SAP= South Asia; LAC= Latin America and the Caribbean; SSA= Sub-Saharan Africa; OECD= Developed Countries including non-OECD developed countries. EPEC- Enteropathogenic E. coli; ETEC- Enterotoxigenic *E. coli*.

rotavirus, norovirus is the principal cause of healthcare associated viral diarrhoea.[122] Enteric adenoviruses types 40 and 41 and astrovirus are less frequently implicated but are also important causes of acute diarrhoeal illnesses in sporadic and outbreak settings.[114,122]

Campylobacter spp, *E. coli* pathotypes and *Shigella* spp are frequently detected in children from developing regions while adults are predominantly affected by *Cryptosporidium* spp, *Salmonella* and pathogenic *E. coli*. Bacterial diarrhoea can be spread through various routes including contaminated food, water and the faecal-oral route; providing multiple sources of infections among the exposed.[6,28] The relatively high prevalence of different strains of pathogenic *E. coli* found in both adults and children in developing settings has been previously described.[10] One recent estimate of multiple diarrhoea pathogens in older children and adults in outpatient and inpatient settings, found ETEC and *Vibrio cholera* as the leading causes of hospitalization and *Salmonella* sp, *Shigella sp*, and *E. hystolitica* as the leading causes in out-patients.[123] The prevalence of pathogenic *E. coli* in developed countries is usually sporadic and more closely associated with travel to a developing regions.[29,30,112] *Campylobacter* spp and *Salmonell*a spp were the most common bacteria isolated in patients from OECD countries. Evidence from the USA, New Zealand and Australia suggest that *Salmonella* infections are a major cause of hospitalizations and deaths annually, and are frequently associated with foodborne illnesses in industrialized countries.[124-126]

Enteric protozoa, mainly *Giardia intestinalis* and *Entamoeba* spp were common in children from developing regions compared with children from developed settings. A recent meta-analysis found that *Giardia intestinalis* was not associated with acute paediatric diarrhoea but was associated with persistent diarrhoea in developing countries. Adults, predominantly those in the SSA region, were mainly affected by *Cryptosporidium* spp and *Blastocystis* spp., which has been previously described in the SSA region.[22] The prevalence of parasitic infections is consistent with findings from other developing settings, where sanitation and access to clean water is compromised.[127-129] There are conflicting interpretations about the role of *Blastocystis* spp as a pathogen, and as a result some laboratories may not place priority on looking for or reporting the presence of this parasite.[130-132] However, several reports have established its association with abdominal pain, persistent diarrhoea and irritable bowel syndrome,[133-135] and other reports hypothesize that pathogenicity may be sub-type dependent.[136]

Limitations

In systematically reviewing the literature, it became apparent that only some studies utilised high level study design and analytical techniques that could identify a broad range of enteric pathogens. Accordingly, we limited our analysis to include only those studies that utilised a rigorous methodology and clearly defined the patient group (diarrhea cases) and the enteric pathogens detected. This study found a higher prevalence of enteric viruses in developed countries compared with developing countries. This difference however, might be due to the different methods used to identify viral pathogens in the different geographical areas, since some diagnostic methods are more sensitive than others. Similar findings however have been found by the recently completed GEMS study that employed a standardised protocol for several countries in sub-Saharan Africa and Asia.[103,137,138] Additionally, OECD countries are likely to have better testing regimes than many developing countries, and as such they are more likely to identify pathogens from infected persons. As such, care should be taken in making comparisons across developed and developing regions. Another limitation of this study was the lack of data to analyse the correlation between the prevalence of enteric pathogens and seasons in different countries. However, previous studies have shown correlations between the prevalence of some pathogens and specific seasons. For example, studies have described distinct seasonal patterns of increased prevalence of viral enteric infections in cooler months.[50,139-141] Despite regional variations, consistent summer peak in the incidence of bacterial diseases has been observed across transnational boundaries, for campylobacteriosis, salmonellosis and verotoxin producing *E. coli* (VTEC).[142] This consistent summer peak in bacterial diseases has been widely described for both developing and developed suggesting possible direct effects of large-scale environmental influences on a shared exposure routes.[143-147] For example increased incidence of infection with common foodborne bacteria (*e.g*. *Campylobacter*, *Salmonella* spp) has been reported in warmer months.[148,149] Understanding disease specific seasonal patterns is important for improving existing disease surveillance methods and developing appropriate prevention strategies.

Conclusions

This systematic review of the literature has attempted to provide an estimation of the types and prevalence of gastrointestinal pathogens associated with diarrhoeal illness in both developing and developed settings. To our knowledge this systematic review is the first to provide an estimate of the region specific prevalence of enteric pathogens associated with diarrhoeal illnesses in both developed and developing countries. Similar studies to provide a comparison were not found as this was the first study to employ a broad definition of diarrhoeal illness, for adults and children. The current study addresses the gap in the literature by providing region specific estimates of pathogen prevalence for adults and children worldwide. It concludes that pathogens are consistently detected in persons seeking medical attention for diarrhoeal illnesses in secondary or primary care settings. This review highlights the need for the development of inexpensive sensitive and specific diagnostic methods to improve pathogen detection in clinical laboratories. Global support is necessary for equitable access to rotavirus vaccines in developing settings and for continued research and development of cost effective interventions to prevent and control diarrhoeal illnesses worldwide.

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