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REVIEW ARTICLE
Part II. Analysis of data gaps pertaining to *Shigella* infections in low and medium human development index countries, 1984–2005

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SUMMARY

The global incidence of *Shigella* infection has been estimated at 80–165 million episodes annually, with 99% of episodes occurring in the developing world. To identify contemporary gaps in the understanding of the global epidemiology of shigellosis, we conducted a review of the English-language scientific literature from 1984 to 2005, restricting the search to low and medium human development countries. Our review yielded 11 population-based studies of *Shigella* burden from seven countries. No population-based studies have been conducted in sub-Saharan Africa or in low human development countries. In studies done in all age groups, *Shigella* incidence varied from 0·6 to 107 episodes/1000 person-years. *S. flexneri* was the most commonly detected subgroup in the majority of studies. Case-fatality rates ranged from 0% to 2·6% in population-based studies and from 0% to 21% in facility-based studies. This review highlights the large gaps in data on the burden of *Shigella* infections for low human development index countries and, more specifically, for sub-Saharan Africa.

INTRODUCTION

The global incidence of *Shigella* infections has been estimated at 80–165 million episodes annually. An estimated 99% of episodes occur in the developing world and children aged <5 years bear the majority of the burden [1]. Common presenting features of shigellosis can include diarrhoea that is bloody or watery, with or without mucus, fever, abdominal cramps, and tenesmus. The infectious dose, which can be as low as 10 organisms, facilitates person-to-person spread [2].

Members of the family Enterobacteriaceae, the Shigellae are Gram-negative, non-motile, lactose-non-fermenting rods. The four subgroups of Shigellae are *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*. *S. dysenteriae* type 1 produces Shiga toxin, among the most potent toxins known, and can cause large outbreaks of dysentery, particularly in conditions of overcrowding and poor water and hygiene infrastructure [1]. In general, *S. sonnei* and *S. boydii* tend to cause milder illness than *S. flexneri* and *S. dysenteriae*. Antimicrobial resistance is increasingly found among Shigellae worldwide, with a high prevalence of resistance to first-line drugs such as ampicillin and trimethoprim–sulfamethoxazole [1]. The Integrated Mangement of Childhood Illness strategy recommends 'the selection of effective first-line and

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This is the second of three papers, appearing in successive issues of the Journal, reviewing the analysis of data gaps pertaining to infections in low and medium human development index (HDI) countries.

second line antibiotics' for treating dysentery based on local antimicrobial resistance patterns [3]. Current guidelines from the World Health Organization encourage providers to use ciprofloxacin as first-line therapy for bloody diarrhoea where recent local data on antimicrobial resistance patterns are not available [1].

To identify contemporary gaps in the understanding of the global epidemiology of shigellosis, we conducted a review of the recent scientific literature. We summarize below recent available data on morbidity and mortality burden, the age, geographic and temporal distribution of shigellosis, the isolation of *Shigella* in context with various other diarrhoeagenic pathogens, and the frequency of the four *Shigella* subgroups. Because of the relevance to vaccine development, we examine the relative frequency of the numerous serotypes of *S. flexneri*. In order to provide context to the global epidemiology of shigellosis, we also describe *Shigella* diagnostics and pathogen-specific preventive measures. Finally, data gaps and existing research needs are discussed.

METHODS

We systematically searched the English-language scientific literature published between 1984 and 2005 using the Medline database, restricting the search to low and medium human development countries according to the United Nations Development Programme's Human Development Index (HDI) (http://hdr.undp.org/2004; accessed 15 January 2007). A set of articles including the relevant epidemiological terms were cross-linked with a set of articles including the relevant pathogen-specific terms (Table 1). The resulting cross-linked set was reviewed for publications addressing *Shigella* morbidity, mortality, age distribution, geographic distribution, temporal distribution, pathogen-specific preventive measures, and diagnostics. Particularly for morbidity and mortality burden, population-based studies with culture confirmation of cases were considered primary data sources. When these were limited, hospital- and clinic-based studies were included. Publications were then evaluated for their contribution to an understanding of the global epidemiology of shigellosis, and gaps in the data were identified.

Crude incidence figures are given, without correction for sensitivity of stool culture, or for the proportion of diarrhoeal episodes for which stool specimens were not collected. Publications were sought with information on the incidence of the infection by region according to the 21 regions of the United Nations Department of Social and Economic Affairs, Population Division (http://esa.un.org/unpp/index.asp?panel=5; 2004 revision, accessed 15 January 2007). We examined the correlation between the incidence of *Shigella* infection and the national *per capita* gross domestic product (GDP) in year 2000 US dollars, adjusted for purchasing power parity (PPP), at the time that the studies were conducted (http://unstats.un.org/unsd/cdb/cdb_series_xrxx.asp?series_code=29922; accessed 15 January 2007). We searched for publications with information on the age-specific incidence, morbidity, and mortality. We also examined the frequency of *Shigella* relative to other diarrhoea-causing pathogens including *Salmonella*, *Vibrio cholerae* O1, enterotoxigenic *Escherichia coli* (ETEC), *Campylobacter*, and rotavirus. In studies that included healthy controls in addition to persons with diarrhoea, we report the frequency of *Shigella* isolation only among those with diarrhoea. Where stools were tested at two different times of the year, we report data from the period during which a greater number of stool specimens were collected.

Table 1. *Terms used in literature search to identify gaps in data on enteric disease burden*

Burden of disease
Epidemiology
Morbidity
Mortality
Disease outbreaks
Incidence
Prevalence
Seasons
Population surveillance
Age distribution
Longitudinal survey
Pathogen-specific terms for shigellosis
Dysentery
Bacillary dysentery
Shigella
Shigella, *dysenteriae*, *flexneri*, *boydii*, and *sonnei*.

RESULTS

Morbidity

Incidence

A 1999 review of published data from 1966 to 1997 estimated the annual global incidence of shigellosis

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to be approximately 164·7 million episodes, with 163·2 million of those occurring in the developing world [4]. These figures were derived by estimating the total number of diarrhoeal cases and multiplying that by the proportion attributable to shigellosis, as determined by the yield of *Shigella* in stool culture from persons with diarrhoea. While this review distinguished 'developing' countries from 'industrialized' countries, few studies were available from sub-Saharan Africa or from low-HDI countries, which contributes to uncertainty regarding the true global incidence of shigellosis.

Our review of the published literature from 1984 to 2005 yielded 11 population-based studies of *Shigella* burden from seven countries (Table 2) [5, 6, 7–16]. Incidence data were reported in six studies and calculated by one of the authors (P.K.R.) based on data provided for five studies. All 11 studies were conducted in medium-HDI countries; no population-based incidence data were available from low-HDI countries. The geographical distribution of shigellosis has been modelled based on available population-based data (Fig. 1). Studies were conducted in Asia (7), Africa (2), and Latin America (2), with both African studies conducted in Egypt. In this limited group of studies, *Shigella* incidence did not correlate with national GDP ($R = -0{\cdot}11$, $P = 0{\cdot}75$) (data not shown).

Among the five studies that included surveillance in all age groups, *Shigella* incidence varied from 0·6 episodes/1000 person-years in Thailand [6] to 107/1000 person-years in Egypt [7]. In six studies limited to infants and young children, annual incidence ranged from zero cases (Thai children aged <6 months) [14] to 949 cases/1000 person-years (Bangladeshi children aged <24 months with wasting) [10]. *Shigella* incidence was higher among Egyptian infants aged <6 months (30/1000 child-years) than among infants aged $\geqslant 6$ months (23 episodes/1000 child-years) [7]. In contrast, the incidence among Thai children aged 0–5 months was zero, compared to 86 episodes/1000 person years among children aged 6–11 months [14, 16].

Frequency of Shigella *relative to other diarrhoeagenic pathogens*

Sixty-seven publications reported on the frequency of *Shigella* and other enteric pathogens in sporadic diarrhoeal illness. Twenty-two studies reported the frequency of *Shigella* isolation among subjects of all ages (Table 3*a*), and 45 studies reported on restricted age groups (Table 3*b*). Data were available from Asia (39 studies), Africa (20), and Latin America (7); one study reported data from four Asian countries [17].

Studies varied widely with respect to specific pathogens tested, and diagnostic techniques used. Often, it was not clear whether a given pathogen was tested for and not detected or whether it was not tested for at all. Notably, the frequency of ETEC isolation was reported by 11 of the 20 studies conducted in Africa, 31 out of 40 Asian studies, and four out of seven studies from Latin America. Rotavirus isolation results were reported in 10 (50%) African, 32 (80%) Asian, and four (57%) Latin American studies. Few investigations reported parasitic aetiologies of diarrhoea.

Shigella was isolated from diarrhoeal or dysenteric stools with similar frequency in Asia and Africa (median isolation rate 6%), and with lower frequency in Latin America and the Caribbean (median 3%) (Fig. 2). *Shigella* was the first or second most frequently isolated pathogen in 10 studies conducted in Africa ($n = 20$), 15 studies in Asia ($n = 43$), and two studies in Latin America ($n = 7$). Rotavirus was tested for in two of the African studies in which *Shigella* ranked first or second, in six such studies from Asia, and in none of the studies from Latin America and the Caribbean.

The isolation rate of *Shigella* from diarrhoea stools was highest among children aged 1–5 years, with isolation among infants aged <6 months relatively similar to isolation among infants aged 6–12 months (Fig. 3) [18–31]. Measles may increase the risk of shigellosis among children, as noted in two papers describing outbreaks of shigellosis following outbreaks of measles [32, 33].

Subgroups

The relative frequency of the four *Shigella* subgroups in endemic shigellosis was reported by 56 studies (Table 4*a*). Studies reporting subgroups of fewer than five *Shigella* isolates were excluded. The median rate of isolation of *S. flexneri*, *S. dysenteriae*, *S. boydii*, and *S. sonnei* were 57%, 10%, 8%, and 17%, respectively (Fig. 4). *S. flexneri* was the most commonly detected subgroup in 48 studies and *S. dysenteriae* was most common in four studies.

The frequency of *S. dysenteriae* isolation was inversely correlated with *per capita* GDP (Fig. 5) ($R = -0{\cdot}54$, $P < 0{\cdot}0001$), and the frequency of *S. sonnei* isolation was directly correlated with *per capita* GDP at the time of the study (Fig. 6) ($R = 0{\cdot}55$, $P < 0{\cdot}0001$).

Table 2. *Population-based studies of* Shigella *incidence published 1984–2005*

Area	Region	Country	HDI	Year(s)	Age groups under study	Persons under surveillance	No. person-years of observation	Crude incidence*	High incidence group (incidence)*	Low incidence group (incidence)*	CFR (%)	Incidence calculation†	Ref.
Africa	N Africa	Egypt	Medium	1981–83	All	2563	3458	14–107	1–2 yr (107)	>15 yr (14)	2·6	Author	[7]
	N Africa	Egypt	Medium	1995–98	<3 yr	397	695	200	12–23 mo. (310)	24–35 mo. (110)	0	Author	[11]
Asia	SC Asia	Bangladesh	Medium	1978–79	<2 yr	125	14–38	657–949	Weight for length ⩽79% (949)	Weight for length ⩾90% (657)	n.r.	PKR-calc	[10]
	E Asia	China	Medium	1986–87	All	20 488	19 410	12	n.r.	n.r.	n.r.	PKR-calc	[13]
	SC Asia	Bangladesh	Medium	1988–89	<5 yr	705	573	35	n.r.	n.r.	n.r.	PKR-calc	[8]
	SE Asia	Thailand	Medium	1988–89	<5 yr	452	449	0–86	6–11 mo. (864)	0–5 mo. (0)	0	Author	[14, 16]
	SE Asia	Vietnam	Medium	1998–99	<5 yr	1655	1655	80	0–11 mo. (180)	24–59 mo. (50)	0	Author	[15]
	SE Asia	Thailand	Medium	2000–03	All	80 141	240 423	0·6	<5 yr (4)	⩾5 yr (0·3)	1·4	Author	[6]
	E Asia	China	Medium	2002	All	75 630	75 630	3–32	3–4 yr (32)	10–30 yr (3)	0	Author	[5]
Latin America/ Caribbean	S America	Brazil	Medium	1978–79	All	189	304	52	n.r.	n.r.	n.r.	PKR-calc	[9]
	S America	Peru	Medium	1982–84	<1 yr	153	132	144	n.r.	n.r.	n.r.	PKR-calc	[12, 116]

HDI, Human development index; CFR, case-fatality rate; n.r., not reported.

* Crude incidence reported as no. cases/1000 persons per year.

† Author: incidence reported by author of paper; PKR-calc: incidence calculated by this investigator.

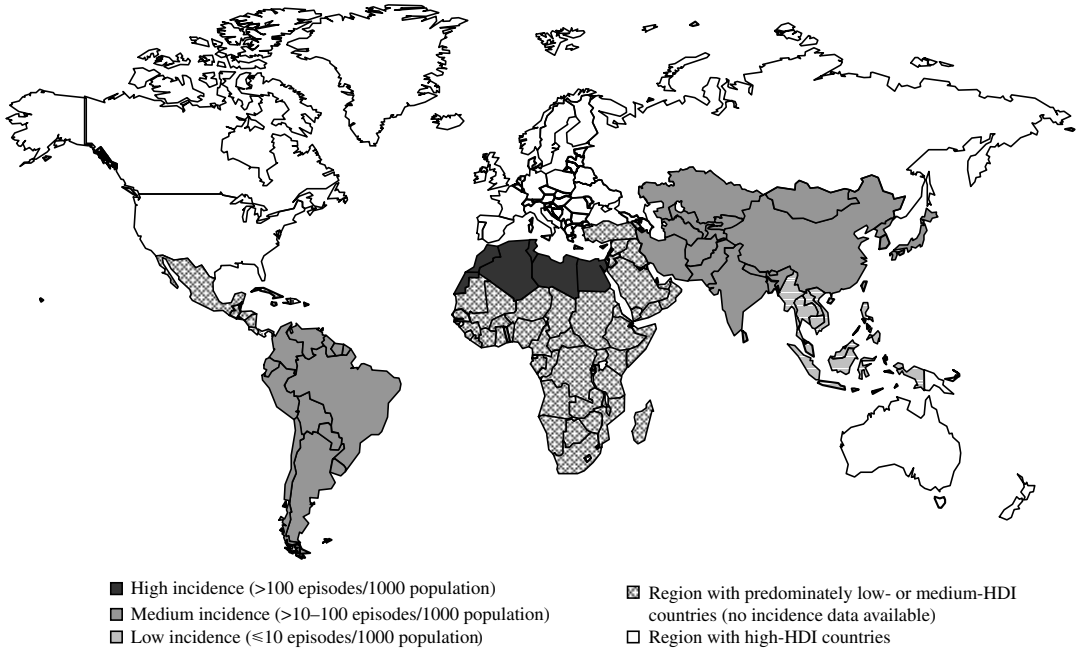

Fig. 1. Incidence of shigellosis, by geographic region, 1984–2005. Countries contributing incidence data: China [5], Thailand [6], Egypt [7], Bangladesh [8] and Brazil [9].

S. sonnei was the most frequently isolated subgroup in two studies from Thailand published in 2002 and 2005, one from Brazil published in 2005, and one from Turkey published in 2005 [6, 19, 21, 34].

None of the population-based studies provide age-specific incidence of *Shigella* subgroups or serotypes. Among studies reporting isolation rates, three provide data on age-specific isolation of *Shigella* subgroups [26, 28, 31]. In Bangladesh, *S. flexneri* was the most frequently isolated subgroup among all age groups except for the 5–9 years group, among whom *S. dysenteriae* type 1 was more common [31]. In every age group studied in the Philippines, *S. flexneri* accounted for at least 75% of *Shigella* infections including 75% among the 1–2 years age group and 88% among those aged 10–14 years [26]. Based on only 123 total isolates from Iran, *S. flexneri* was most common among children aged 1–5 years and persons aged ⩾12 years; *S. sonnei* was most common among children aged <1 year and was as frequent as *S. flexneri* among children aged 5–12 years [28].

Fourteen studies assessed the relative frequency of *Shigella* subgroups during epidemics; 11 focused on persons with dysentery (variably defined as blood with or without mucus in stools) (Table 4*b*). None of these studies were conducted in Latin America and the Caribbean. Twelve identified a predominance of *S. dysenteriae* infections, specifically serotype 1, and two identified a predominance of *S. flexneri* infections.

Serotypes

S. dysenteriae is comprised of 15 serotypes, of which type 1 has the capacity to cause large outbreaks [1]. Between 2002 and 2004, numerous publications documented circulating *S. dysenteriae* type 1 strains resistant to commonly used fluoroquinolones, including ciprofloxacin and ofloxacin [35–41]. The organism remained susceptible only to azithromycin, pivmecillinam, and third-generation cephalosporins.

The World Health Organization (WHO) Collaborating Centre for *Shigella* at the Centers for Disease Control and Prevention recognizes six serotypes of *S. flexneri*, which can be further classified into numerous subserotypes, as well as *S. flexneri* X and Y. Thirteen studies (eight published after 2000), report *S. flexneri* serotypes in endemic shigellosis (Table 5). Serotype 2a was the most commonly detected serotype in four studies, accounting for 35–67% of *S. flexneri* isolates; all four studies were conducted in Asia [6, 19, 42, 43]. Serotype 1a was the most frequently isolated in a population-based study in China [5]. Serotype 1b was the most frequently detected serotype in Malaysia and the Peruvian Amazon [44, 45]. Subserotype 3c was reported from Malaysia and Pakistan, with reports of serotypes 7, 8, and

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10 from Pakistan as well [45, 46]. Subserotype 1c has also been reported from Bangladesh and Egypt [47, 48].

Complications

Few complications were reported in population-based studies of *Shigella* infection. Dehydration was reported in 11% and 16% of patients [11, 12]. Wang *et al*. reported no cases of rectal prolapse or other gastrointestinal complications in China [5]. *Shigella* diarrhoea was associated with decreased linear growth rates in a study by Black and colleagues, with the per cent of days of *Shigella* diarrhoea negatively correlated with linear growth [49]. Two studies reported a prolonged duration of diarrhoea with *S. flexneri* infection compared to infection with other *Shigella* subgroups [5, 6].

Facility-based studies of shigellosis, albeit probably skewed towards very ill patients and those who can access health-care services, provide additional insight. The rate of hospitalization has ranged from 11% to 47% [44, 50–53]. Dehydration was documented in 2–70% of patients [52, 54–56]. Gastrointestinal complications of *Shigella* infection include persistent diarrhoea (7–38%) [56–59], intestinal obstruction (3–5%) [56, 60], rectal prolapse (3–38%) [56, 58], and protein-losing enteropathy (3%) [61]. The risk of persistent diarrhoea following *Shigella* infection appears to be increased among young children, in dysenteric episodes of confirmed shigellosis, following infections caused by multiply-resistant Shigellae, or when nalidixic acid (NAL) is administered for infections caused by NAL-resistant organisms [59]. Intestinal perforation was reported anecdotally in one study [62].

Haemolytic–uraemic syndrome (HUS), was diagnosed in 1–24% of persons hospitalized with *S. dysenteriae* type 1 [58, 61, 63]. In Bangladesh, HUS was diagnosed in 27% of *Shigella*-confirmed patients with intestinal obstruction, and none without obstruction [60]. Three studies reported treatment with antimicrobial agents to which the pathogen is resistant as a risk factor for HUS [63–65]. Acute renal failure was documented in 1% [58] and 25% [56] of hospitalized patients; neither study specified the proportion of renal failure cases occurring in the context of HUS. Electrolyte imbalances were documented in 42% of patients; both hyponatraemia and hyperkalaemia have been reported [50, 56].

Central nervous system (CNS) manifestations of *Shigella* infection were noted in 45% of patients in one series [50]. This, and other studies describe complications including seizures (5–27%) [50, 54, 66] and loss of consciousness (10%) [50, 56]. Factors significantly associated with CNS manifestations include age <15 years, electrolyte imbalance, severe dehydration, fever, shorter duration of illness, higher median weight-for-age, and increased immature leukocytes [50].

Although a recognized complication, this literature search yielded only three reports of reactive arthritis as sequelae to *S. flexneri* infections [64, 65, 67]. Bacteraemia is a relatively rare complication and young age is an important risk factor [68]. Among the handful of adult patients reported to have *Shigella* bacteraemia, immunocompromising conditions, such as HIV/AIDS are common. One case report from the United States documented recurrent infection with *S. boydii* in an HIV-infected patient despite 10 days of ceftriaxone therapy, suggesting the need for prolonged therapy in persons with HIV/AIDS and *Shigella* bacteraemia [69].

Poor nutritional status appears to increase the risk of shigellosis associated with fever, severe dehydration, severe neurological manifestations such as seizures or coma, or requiring hospitalization [53, 57, 70].

Mortality

Only six population-based studies of *Shigella* incidence included case-fatality rates (CFR) (Table 2). These ranged from 0% [5, 11, 14] to 2·6% (Egypt) [6, 7]. In facility-based studies that reported deaths of hospitalized patients with culture-confirmed endemic *Shigella* infection, CFRs ranged from 0% to 21% (Table 6).

In one study from Bangladesh, patients with shigellosis who were discharged from the hospital (CFR 5%) had a significantly higher risk of post-hospitalization death than persons with watery diarrhoea (CFR 3%) [71]. Reported risk factors for death include young age [31, 50, 56, 72], poor nutritional status [56, 72, 73], and CNS manifestations such as altered consciousness or seizures [50, 72]. In a series from North India, 75% of patients who died had renal failure and 25% had *Shigella* bacteraemia [56]. Notably, none of these hospital-based studies specifically reported HUS as a risk factor for death. Among severely malnourished children with *S. dysenteriae* type 1 and *S. flexneri*, risk factors for death included hypothermia, altered consciousness, low serum blood glucose, and pneumonia [74].

Table 3*a*. *Relative frequency of endemic* Shigella *isolation, community- and facility-based studies conducted among all age groups, 1984–2005*

Area	Region	Country	HDI	Years	Setting	Age	Symptoms	No. samples tested	% pos. for any pathogen	Sa	ETEC	VC O1/ O139	Ca	RV	Sh	Sh rank	Ref.
Africa	N Africa	Egypt	Medium	1981–83	Community	All	Diarrhoea	3243	n.r.	1%	not clear	n.r.	1%	3%	2%	6	[7]
	N Africa	Egypt	Medium	1986–93	Facility	All	'Acute enteric infections'	6278	14%	7%	n.r.	n.r.	2%	n.r.	4%	2	[117]
	E Africa	Djibouti	Low	1989	Facility	All	Diarrhoea	209	n.r.	3%	11%	0	3%	n.t.	8%	3*	[118]
	E Africa	Ethiopia	Low	1992–93	Facility	All	Diarrhoea	630	27%	3%	n.r.	n.r.	14%	n.r.	12%	2	[119]
	E Africa	Ethiopia	Low	1994–96	Facility	All	Not clear	1709	n.r.	3%	n.r.	n.r.	n.r.	n.r.	8%	1	[120]
	W Africa	Nigeria	Low	1995–96	Facility	All	Diarrhoea	852	21%	4%	2%	n.r.	n.r.	n.r.	5%	2*	[121]
	E Africa	Kenya	Low	1997–98	Facility	All	Diarrhoea	729	33%	5%	n.t.	6%	10%	n.r.	15%	1	[122]
Asia	SC Asia	Bangladesh	Medium	1980–81	Facility	All	Diarrhoea	3251	n.r.	3%	n.r.	68%	n.r.	n.r.	13%	2	[73]
	SC Asia	India	Medium	1982–83	Facility	All	Diarrhoea	240	n.r.	<1%	12%	33%	7%	9%	5%	5	[123]
	SE Asia	Thailand	Medium	1982–83	Community	All	Diarrhoea	177	n.r.	n.r.	10%	n.r.	n.r.	n.r.	7%	3*	[124]
	SE Asia	Thailand	Medium	1982–83	Facility	All	Diarrhoea	299	41%	n.r.	17%	n.r.	n.r.	n.r.	9%	2	[125]
	SC Asia	Bangladesh	Medium	1983–84	Facility	All	Diarrhoea	2635	69%	1%	14%	39%	11%	n.r.	11%	3	[18]
	SE Asia	Philippines	Medium	1983–84	Facility	All	Diarrhoea	2908	n.r.	9%	4%	3%	3%	31%	12%	2	[126]
	E Asia	China	Medium	1986–87	Community	All	Diarrhoea	2265	39%	<1%	14%	<1%	3%	n.r.	11%	2	[13]
	SE Asia	Thailand	Medium	1991	Facility	All	Diarrhoea	363	n.r.	8%	7%	<1%	5%	19%	16%	2	[127]
	SC Asia	Bangladesh	Medium	1995	Facility	All	Diarrhoea	113	n.r.	1%	36%	24%	5%	10%	8%	5*	[128]
	SE Asia	Lao PDR	Medium	1996–97	Facility	All	Diarrhoea	880	43%	<1%	20%	0	4%	6%	17%	n.c.†	[30]
	SE Asia	Indonesia	Medium	1999–00	Facility	All	Diarrhoea	6760	9%	2	n.r.	<1%	<1%	n.r.	4	1	[129]
	SE Asia	Indonesia	Medium	2000–01	Facility	All	Diarrhoea	489	n.r.	3%	15%	<1%	<1%	n.r.	3%	2	[130]
	SC Asia	India	Medium	2002	Community	All	Diarrhoea	348	n.r.	1%	n.r.	n.r.	14%	n.r.	3%	2	[131]
Latin America/ Caribbean	S America	Brazil	Medium	1984–86	Facility	All	Diarrhoea	50	52%	n.r.	14%	n.r.	n.r.	22%	2%	5*	[132]
	S America	Peru	Medium	1992–93	Facility	All	Diarrhoea	143	52%	4%	22%	31%	3%	n.r.	3%	4	[133]

HDI, Human development index; Sa, *Salmonella* (includes typhoidal and non-typhoidal serotypes); ETEC, enterotoxigenic *E. coli*; VC, *Vibrio cholerae*; Ca, Campylobacter; RV, Rotavirus; Sh, *Shigella*; n.t., not tested; n.r., not reported.

* Ranking reported by study author based on identification of other pathogens.

† n.c., Ranking not calculable because testing performed on varying number of samples.

Table 3*b*. *Relative frequency of endemic* Shigella *isolation, community- and facility-based studies conducted among restricted age groups, 1984–2005*

Area	Region	Country	HDI	Years	Setting	Age	Symptoms	Number samples tested	% pos. for any pathogen	Sa	ETEC	VC	Ca	RV	Sh	Sh rank	Ref.
Africa	E Africa	Somalia	Not listed	1992–93	Facility	Adults	Diarrhoea	113	52%	1%	16%	n.r.	0	1%	33%	1	[134]
Africa	E Africa	Somalia	Not listed	1983–84	Facility	Children	Diarrhoea	1667	n.r.	4%	11%	0	8%	25%	9%	3	[20]
Asia	E Asia	China	Medium	1989	Facility	Children	Diarrhoea	221	57%	12%	20%	n.r.	2%	7%	3%	9*	[135]
Asia	SC Asia	Iran	Medium	1986–87	Facility	Infants and young children	Diarrhoea	1158	n.r.	7%	17%	0	n.r.	n.r.	5%	4*	[136]
Latin America/ Caribbean	S America	Peru	Medium	1995	Facility	⩾13 yr	Diarrhoea	336	62%	3%	n.r.	53%	n.r.	n.r.	4%	2	[137]
Africa	Middle Africa	Central African Republic	Low	1981–82	Facility	<15 yr	Diarrhoea	1197	64%	5%	3%	0	11%	18%	3%	3	[138]
Latin America/ Caribbean	S America	Brazil	Medium	2002–03	Facility	<15 yr	Diarrhoea	1991	13%	5%	n.r.	n.r.	n.r.	n.r.	7%	1	[21]
Asia	W Asia	Saudi Arabia	Medium	1990–91	Facility	<12 yr	Diarrhoea	210	31%	11%	n.r.	n.r.	0	n.r.	17%	1	[139]
Asia	SE Asia	Thailand	Medium	1998–00	Facility	<12 yr	Dysentery	623	55%	18	6	<1	28	n.r.	9	3	[19]
Asia	SC Asia	Bangladesh	Medium	1982–83	Facility	<8 yr	Diarrhoea	104	59%	n.r.	9%	2%	20%	17%	5%	8*	[140]
Asia	SC Asia	India	Medium	1985–86	Facility	<6 yr	Diarrhoea	222	54%	3%	14%	0	6%	2%	2%	8*	[141]
Asia	SC Asia	Pakistan	Low	1990	Facility	<6 yr	Dysentery	152	32%	5%	n.r.	n.r.	8%	n.r.	19%	1	[24]
Latin America/ Caribbean	S America	Bolivia	Medium	1991–92	Facility	<6 yr	Diarrhoea	192	n.r.	<1%	3%	n.r.	n.r.	n.r.	3%	11*	[142]
Asia	SE Asia	Thailand	Medium	1982	Facility	<5 yr	Diarrhoea	221	n.r.	1%	14%	2%	n.r.	n.r.	9%	2	[143]
Asia	SE Asia	Myanmar	Medium	1982–83	Comm.	<5 yr	Diarrhoea	501	39%	<1%	18%	n.t.	2%	5%	2%	4	[144]
Africa	W Africa	Nigeria	Low	1984–85	Facility	<5 yr	Diarrhoea	914	n.r.	2%	n.r.	0%	4%	n.r.	13%	1	[29]
Asia	SC Asia	Pakistan	Low	1985–91	Comm.	<5 yr	Diarrhoea	Varied	73%	3%	23%	n.r.	12%	20%	5%	4	[25]
Africa	N Africa	Egypt	Medium	1986	Facility	⩽5 yr	Diarrhoea	151	n.r.	7%	17%	n.r.	7%	18%	5%	7*	[145]
Asia	SC Asia	Bangladesh	Medium	1988–89	Comm.	<5 yr	Acute and persistent diarrhoea	185	n.r.	0	12%	n.r.	16%	4%	5%	5*	[8]
Asia	SE Asia	Indonesia	Medium	1988–89	Facility	⩽5 yr	Diarrhoea	194	28%	19%	8%	3%	6%	n.r.	2%	5	[146]
Asia	SE Asia	Thailand	Medium	1988–89	Comm.	<5 yr	Diarrhoea	345	56%	9%	7%	<1%	9%	9%	5%	5	[14]
Asia	SE Asia	Thailand	Medium	1988–89	Comm.	<5 yr	Diarrhoea	345	54%	13%	7%	<1%	14%	12%	6%	5	[43]
Asia	SE Asia	Thailand	Medium	1989	Facility	<5 yr	Diarrhoea	1230	63%	12%	9%	0	13%	20%	13%	3	[147]

Africa	W Africa	Nigeria	Low	1989–90	Facility	<5 yr	Diarrhoea	215	75%	3%	14%	0	n.r.	22%	5%	5*	[148]
Asia	SC Asia	Bangladesh	Medium	1991–92	Facility	<5 yr	Diarrhoea	451	n.r.	1%	12%	n.r.	n.r.	17%	10%	5*	[149]
Africa	E Africa	Zambia	Low	1992–93	Facility	<5 yr	Diarrhoea	639	30%	1%	n.t.	n.r.	n.r.	n.r.	10%	2*	[150]
Asia	SC Asia	Bangladesh	Medium	1990–94	Facility	<5 yr	Diarrhoea	9993	n.r.	n.r.	n.r.	8%	n.r.	22%	10%	2*	[57]
Asia	SC Asia	Bangladesh	Medium	1993–94	Facility	⩽5 yr	Diarrhoea	814	75%	2%	17%	10%	17%	20%	9%	6*	[151]
Asia	W Asia	Jordan	Medium	1993–94	Facility	<5 yr	Diarrhoea	265	51%	5%	6%	0	2%	33%	5%	5*	[152]
Asia	SE Asia	Indonesia	Medium	1994	Comm.	<5 yr	Diarrhoea	148	n.r.	2%	14%	3%	2%	n.r.	<1%	7*	[153]
Asia	SE Asia	Vietnam	Medium	1998–99	Comm.	<5 yr	Diarrhoea	2160	22%	<1%	7%	n.r.	7%	n.r.	6%	3	[15]
Asia	SC Asia	India	Medium	1995–00	Facility	<5 yr	Dysentery	2855	60%	3	n.r.	n.r.	2	7	6	2	[42]
Africa	E Africa	Tanzania	Low	1997	Facility	<5 yr	Diarrhoea	103	63%	0	16%	n.r.	0	4%	13%	2	[154]
Africa	W Africa	Nigeria	Low	n.r.	Facility	<5 yr	Diarrhoea	187	n.r.	<1%	2%	n.r.	n.r.	n.r.	1%	6*	[155]
Asia	E Asia	China	Medium	1982–85	Facility	<3 yr	Diarrhoea	594		5%	6%	0	17%	13%	18%	1	[17]†
Asia	SC Asia	India	Medium	1982–85	Facility	<3 yr	Diarrhoea	916		4%	14%	2%	15%	18%	20%	1	[17]†
Asia	SC Asia	Pakistan	Low	1982–85	Facility	<3 yr	Diarrhoea	813		1%	26%	<1%	2%	22%	3%	3	[17]†
Asia	SE Asia	Myanmar	Medium	1982–85	Facility	<3 yr	Diarrhoea	758		3%	17%	2%	10%	14%	6%	4	[17]†
Asia	SC Asia	Pakistan	Low	1983–84	Facility	<3 yr	Diarrhoea	250	76%	3%	14%	n.r.	n.r.	10%	4%	3*	[156]
Asia	SC Asia	India	Medium	1985–86	Comm.	<3 yr	Diarrhoea	179	44%	3%	15%	0	6%	2%	2%	8*	[157]
Asia	SC Asia	Bangladesh	Medium	1988–89	Facility	<3 yr	Diarrhoea	969	64%	<1%	16%	5%	27%	29%	3%	6	[158]
Africa	S Africa	South Africa	Medium	n.r.	Facility	<3 yr	Diarrhoea	78	77%	1%	39%	0	14%	13%	4%	8*	[159]
Africa	S Africa	South Africa	Medium	1981–83	Facility	<2 yr	Diarrhoea	478	46%	6%	4%	1%	11%	12%	4%	5*	[160]
Africa	N Africa	Egypt	Medium	1995–98	Comm.	<2 yr	Diarrhoea	3477	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	2%	1*	[11]
Africa	S Africa	South Africa	Medium	1981–82	Facility	<1 yr	Dehydrating diarrhoea	545	49%	11%	n.r.	n.r.	18%	16%	6%	4	[94]
Latin America/ Caribbean	S America	Peru	Medium	1982–84	Comm.	<1 yr	Diarrhoea	952	n.r.	<1%	7%	<1%	10%	3%	2%	5	[12]
Latin America/ Caribbean	S America	Brazil	Medium	1985–86	Facility	<1 yr	Diarrhoea	500	55%	8%	7%	n.r.	3%	14%	5%	5*	[161]
Asia	E Asia	China	Medium	1989	Facility	<1 yr	Diarrhoea	174	34%	0	4%	0	10%	13%	<1%	4*	[162]

HDI, Human development index; Sa, *Salmonella* (includes typhoidal and non-typhoidal serotypes); ETEC, enterotoxigenic *E. coli*; VC, *Vibrio cholerae*; Ca, Campylobacter; RV, Rotavirus; Sh, *Shigella*; Comm., community; n.t., not tested; n.r., not reported.

* Ranking reported by study author based on identification of other pathogens.

† Data from four countries reported in a single publication.

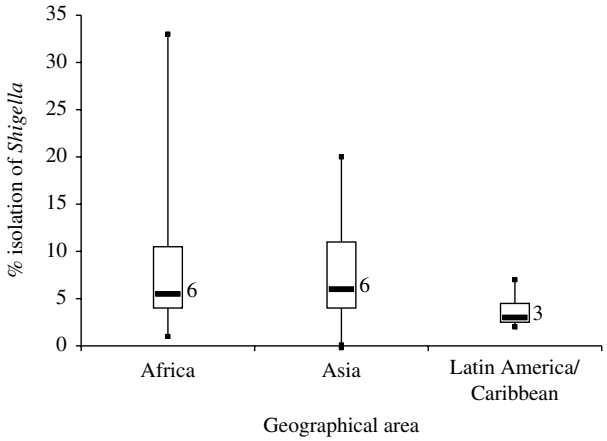

Fig. 2. Frequency of *Shigella* isolation in diarrhoeal or dysenteric stools for all age groups, by geographical area, in studies from medium and low human development index (HDI) countries ($n = 70$ studies).

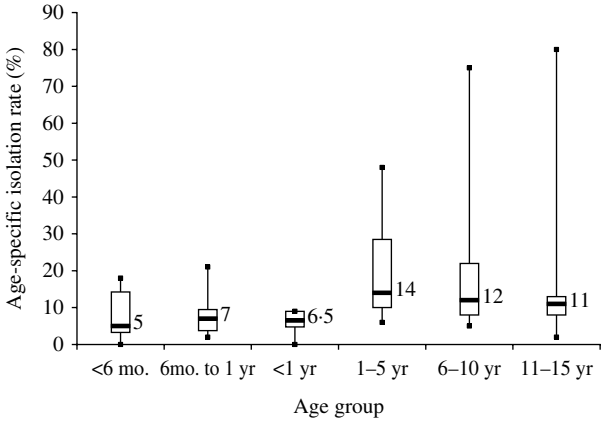

Fig. 3. Frequency of *Shigella* isolation in diarrhoeal or dysenteric stools by age group, among children aged <15 years, in studies from medium and low human development index (HDI) countries, 1984–2005 ($n = 70$ studies).

A total of 21 studies, all from Africa or Asia, report CFRs of 0% [36, 75] to 40% [76] (median 4%) for epidemic *S. dysenteriae* type 1 (Table 7). In large epidemics, *S. dysenteriae* type 1 can account for 0·25–40% of all-cause mortality [51, 77, 78]. Young children are at increased risk of death from epidemic *S. dysenteriae* type 1 [33, 51, 61, 78–83]. Additional risk factors include CNS complications [38], malnutrition [61], the constellation of symptoms and signs associated with HUS [58, 84], intestinal perforation [84], and treatment with antimicrobial agents to which the pathogen is resistant [76].

Temporal distribution

Among 32 studies reporting on seasonal distribution of *Shigella* infection, 10 were conducted over a period of $\leqslant 1$ year and four studies were conducted over a period of $\geqslant 1$ year and < 2 years. A total of 17 studies were conducted over $\geqslant 2$ years, among which seasonality was reported using a variety of terms, including the specific months of the year, the quarters of the year, or more vague terms such as 'rainy season' and 'dry season'. No clear patterns emerged, even when studies were segregated according to northern or southern hemisphere (data not shown).

Pathogen-specific preventive measures

A 2004 review summarizes the current status of *Shigella* vaccines [85]. Immunity to *Shigella* infection, which is directed against the O antigen, is type-specific. Four candidate vaccines using oral formulations (SC 602, CVD 1203, CVD 1204, CVD 1208) and one candidate using the parenteral route (*S. flexneri* 2a LPS conjugated to recombinant *Pseudomonas* exoprotein A) target *S. flexneri* 2a. One oral (WRSS1) and one parenteral vaccine (*S. sonnei* LPS conjugated to *Pseudomonas* exoprotein A) target *S. sonnei*.

Poor toilet and hand hygiene practices play an important role in facilitating *Shigella* transmission in industrialized and developing countries. Shigellae are also effectively transmitted through contaminated water and survival in water appears to vary by subgroup: *S. dysenteriae* (2–3 days), *S. flexneri* (6–47 days), and *S. sonnei* (35–39 days) [83, 86–89]. Foods, particularly contaminated produce, are well-recognized as vehicles for *Shigella* transmission [52, 83, 90]. Flies have been implicated and may be especially important in settings where latrines are in close proximity to food preparation or consumption areas [91–94]. Promotion of handwashing with soap has been linked to reduced *Shigella* transmission in endemic and epidemic settings [95, 96]. Specific latrine behaviour may be important. Anal cleansing rags used communally were implicated in one outbreak of *S. dysenteriae* type 1 [51]. To the extent that the use of toilet paper reduces hand contamination with stool, this simple intervention may also be useful for reducing *Shigella* transmission [97]. Notably, one study has demonstrated dramatic reductions in *Shigella* incidence with aggressive measures to control houseflies, which may breed in latrines [92].

Diagnostics

Culture of whole stools or stool collected by rectal swab is the most widely used technique for diagnosis of *Shigella* infection. However, Shigellae are relatively fragile organisms compared with other enteric pathogens. Yield from stool culture is increased when the specimen is placed in transport medium and held at refrigeration temperatures (4 °C) if not cultured immediately [98]. Buffered glycerol saline is the preferred medium but Cary–Blair medium is also acceptable. Polymerase chain reaction (PCR) techniques have been used to identify *Shigella* genes coding for the invasion plasmid antigen H (*ipaH*), which is present in all Shigellae and in enteroinvasive *E. coli*, and Shiga toxin (*stx*), which is present in *S. dysenteriae* type 1 and in enterohaemorrhagic *E. coli*. When compared with PCR testing for *Shigella* primers, the sensitivity of culture has been estimated at 72% [99].

Recent data suggest that an innovative transport technique (DNA/RNA Protect™, Sierra Diagnostics Inc., Sonora, CA, USA) permits detection of *ipaH* from stool specimens held for prolonged periods at room temperature [100]. An enzyme-linked immunosorbent assay (ELISA) is available for detection of Shiga toxin 1. The ELISA was evaluated in a single study in Bangladesh, and demonstrated 95% sensitivity and 85% specificity for detection of *S. dysenteriae* type 1 [101].

DISCUSSION

This review highlights the large gaps in data on the burden of *Shigella* infections for low-HDI countries and, more specifically, for sub-Saharan Africa (Table 8). It also identifies additional research needed with respect to the burden of disease among infants and population-based rates of *Shigella*-associated complications and mortality. Comprehensive microbiological, clinical, and epidemiological studies using newer and more sensitive diagnostic methods to determine the relative importance of *Shigella* and other diarrhoeal pathogens could help address these data gaps and further inform prevention efforts.

The absence of population-based incidence data from sub-Saharan Africa and from low-HDI countries is our most striking finding. Because of their low development status, and limited access to improved water supplies and sanitation facilities, these countries may be expected to have a higher burden of *Shigella* infections than the medium-HDI countries where population-based studies have been conducted. Moreover, given the additional lack of substantial data on shigellosis in the context of HIV disease, active population-based surveillance studies conducted in this important geographic region to elucidate overall disease burden, frequency of subgroups, serotypes, and subserotypes, are critical for understanding the true global burden of *Shigella* infections.

This review detected wide variation in the incidence of *Shigella* infections from the few available population-based studies, ranging from 0 episodes/1000 person-years [14] to 949 episodes/1000 person-years [10]. However, comparisons between these studies is challenging because of variations in the age groups under study, methodologies for surveillance, and techniques for specimen collection, transport, and culture.

Several population-based studies included only young children; others, which included all age groups, reported incidence data only by age group and not for the population as a whole. Where possible, future population-based studies should describe age group-specific and total incidence, and include isolation rates for all *Shigella* and for the specific subgroups and serotypes.

The risk of shigellosis among young infants is poorly characterized. This review identified very few studies that separated out infants aged <6 months who are likely to be breastfeeding and, thus, exposed to maternal IgA [102]. Population-based data on the incidence of *Shigella* infections among infants aged <6 months and 6–11 months could help inform this discussion, which is critical to the development and deployment of *Shigella* vaccines.

Our attempts to estimate the frequency of *Shigella* relative to other diarrhoeal pathogens revealed important variations in the spectrum of pathogens sought. Rotavirus, the most common cause of severe diarrhoeal illness worldwide [103], was not tested for in a majority of the ten African studies that found *Shigella* to be the first or second leading cause of diarrhoea. This review underscores the need for comprehensive stool analyses, including identification of Rotavirus, the different groups of diarrhoeagenic *E. coli*, and parasitic infections, in aetiological studies of diarrhoeal disease. Moreover, such studies are particularly needed in sub-Saharan Africa.

A vast amount of data has been published between 1984 and 2005 regarding the relative frequency of the four *Shigella* subgroups. The predominance of *S. flexneri* above other subgroups, particularly in

Table 4*a*. *Frequency of* Shigella *subgroups in endemic disease, 1984–2005*

Area	Region	Country	HDI	Year(s)	Setting	Facility type*	Age	Symptoms	No. *Shigella* isolates	% dys†	% Sd1 among dys‡	% flex†	% boydii†	% sonnei†	Ref.
Africa	S Africa	South Africa	Medium	1968–85	Facility	Hospital	All	Confirmed *Shigella* infection	1562	3%	0	72%	5%	20%	[111]
	N Africa	Libya	Medium	1975–80	Facility	n.r.	All	Diarrhoea	917	7%	5%	66%	8%	18%	[23]
	W Africa	Nigeria	Low	1980–84	Facility	Clinic	All	Diarrhoea	368	14%	6%	60%	21%	5%	[163]
	W Africa	Nigeria	Low	1984–85	Facility	Clinic	<5 yr	Diarrhoea	116	37%	n.r.	60%	3%	0%	[29]
	W Africa	Nigeria	Low	1986–88	Facility	Hospital	All	Diarrhoea	108	24%	50%	55%	16%	6%	[22]
	N Africa	Egypt	Medium	1986–93	Facility	Hospital	All	'Acute enteric infections'	258	18%	n.r.	48%	15%	19%	[117]
	E Africa	Djibouti	Low	1989	Facility	Clinic	All	Diarrhoea	16	13%	n.r.	75%	13%	0%	[118]
	W Africa	Nigeria	Low	1989–90	Facility	Hospital	<5 yr	Diarrhoea	11	18%	n.r.	45%	27%	9%	[148]
	E Africa	Zambia	Low	1992–93	Facility	Hospital	<5 yr	Diarrhoea	65	68%	n.r.	15%	17%	0%	[149]
	E Africa	Ethiopia	Low	1994–96	Facility	Hospital	All	n.r.	142	37%	33%	59%	5%	0%	[120]
	N Africa	Egypt	Medium	1995–98	Comm.	n.r.	<2 yr	Diarrhoea	134	19%	n.r.	55%	2%	22%	[11]
	E Africa	Tanzania	Low	1997	Facility	Clinic	<5 yr	Diarrhoea	13	0%	0%	92%	0%	8%	[154]
	W Africa	Nigeria	Low	1997–98	Facility	n.r.	0–65 yr	Diarrhoea	25	8%	0	48%	24%	20%	[164]
	E Africa	Kenya	Low	1997–98	Facility	Both	All	Diarrhoea	107	44%	47%	48%	2%	7%	[122]
	W Africa	Nigeria	Low	1999–00	Facility	Both	All	Diarrhoea	62	18%	n.r.	52%	18%	12%	[165]
	E Africa	Ethiopia	Low	2000	Facility	Clinic	⩽14 yr	Diarrhoea	77	30%	n.r.	40%	20%	10%	[31, 166]
Asia	SC Asia	Bangladesh	Medium	1978–87	Facility	Hospital	All	Diarrhoea	3440	30%	91%	53%	11%	6%	[31]
	S Africa	South Africa	Medium	1981–82	Facility	Hospital	<1 yr	Dehydrating diarrhoea	31	3%	n.r.	48%	7%	42%	[94]
	SC Asia	Bangladesh	Medium	1981–83	Facility	Hospital	<35 mo.	Confirmed *Shigella* infection	540	11%	61%	75%	6%	8%	[53]
	SC Asia	Bangladesh	Medium	1982–83	Facility	Hospital	<8 yr	Diarrhoea	5	0%	0%	60%	40%	0%	[140]
	SE Asia	Philippines	Medium	1982–88	Facility	Hospital	All	Diarrhoea	343	8%	n.r.	70%	8%	14%	[26]
	SC Asia	Bangladesh	Medium	1983	Facility	Hospital	All	Confirmed *Shigella* infection	9780	n.r.	30%#	56%	n.r.	n.r.	[72]
	SC Asia	India	Medium	1984–87	Facility	Hospital	<5 yr	Diarrhoea	75	27%	100%	55%	8%	1%	[167]
	SE Asia	Thailand	Medium	1985–86	Facility	Clinic	<5 yr	Diarrhoea	155	0%	0%	53%	3%	44%	[147]
	SE Asia	Thailand	Medium	1985–93	Facility	Hospital	All	n.r.	309	<1%	0%	74%	2%	23%	[50, 66]
	SC Asia	Bangladesh	Medium	1987–88	Facility	Hospital	All	Confirmed *Shigella* infection	792	n.r.	20% of all Shigella	64%	n.r.	n.r.	[54]
	SC Asia	Bangladesh	Medium	1987–89	Comm.	n.r.	<5 yr	Diarrhoea	219	22%	68%	60%	12%	6%	[168]

	SC Asia	Bangladesh	Medium	1988–89	Facility	Hospital	<3 yr	Diarrhoea	33	n.r.	n.r.	52%	33%	6%	[158]
	SE Asia	Thailand	Medium	1988–89	Comm.	n.r.	<5 yr	Diarrhoea	21	0%	0%	57%	0%	43%	[43]
	E Asia	China	Medium	1989	Facility	Clinic	Children	Diarrhoea	6	0%	0%	67%	0%	33%	[135]
	SC Asia	Pakistan	Low	1990	Facility	Hospital	<6 yr	Dysentery	29	35%	n.r.	42%	17%	7%	[24]
	W Asia	Saudi Arabia	Medium	1990–91	Facility	Hospital	<12 yr	Diarrhoea	36	0%	0%	61%	0%	39%	[139]
	SE Asia	Thailand	Medium	1991	Facility	Both	All	Diarrhoea	72	n.r.	n.r.	74%	n.r.	19%	[127]
	W Asia	Jordan	Medium	1991–92	Facility	Hospital	<15 yr	Confirmed *Shigella* infection	66	7%	n.r.	65%	11%	17%	[54]
	SC Asia	Bangladesh	Medium	1995	Facility	Hospital	All	Diarrhoea	63	59%	100%	39%	0	2%	[169]
	SC Asia	India	Medium	1995–00	Facility	Hospital	<5 yr	Dysentery	166	5%	n.r.	57%	8%	28%	[42]
	W Asia	Turkey	Medium	1995–02	Facility	Hospital	Children	Diarrhoea	274	1%	n.r.	23%	2%	72%	[34]
	SE Asia	Lao PDR	Medium	1996–97	Facility	Both	All	Diarrhoea	148	1%	0%	55%	3%	41%	[30]
	SE Asia	Malaysia	Medium	1997–00	n.r.	n.r.	n.r.	n.r.	100	11%	0%	88%	1%	0%	[45]
	SC Asia	Pakistan	Low	1997–99	n.r.	n.r.	All	Diarrhoea	77	61%	16%	16%	n.r.	n.r.	[170]
	SE Asia	Vietnam	Medium	1998–99	Comm.	n.r.	<5 yr	Diarrhoea	143	7%	n.r.	65%	17%	11%	[15]
	SE Asia	Thailand	Medium	1998–00	Facility	Hospital	<12 yr	Dysentery	56	0%	0%	29%	0%	71%	[19]
	SE Asia	Indonesia	Medium	1999–00	Facility	Hospital	All	Diarrhoea	286	5%	n.r.	81%	0%	14%	[129]
	SC Asia	Bangladesh	Medium	2000–01	Facility	Hospital	All	Blood and/or mucus	227	20%	18%	54%	16%	10%	[171]
	SE Asia	Indonesia	Medium	2000–01	Facility	Hospital	All	Diarrhoea	16	0%	0%	75%	0%	25%	[130]
	SE Asia	Thailand	Medium	2000–03	Comm.	n.r.	All	Diarrhoea	146	0%	0%	15%	0%	85%	[5]
	SC Asia	India	Medium	2001–02	Facility	Hospital	Children	Diarrhoea	80	6%	60%	56%	13%	29%	[41]
	SC Asia	Iran	Medium	2001–02	Facility	Both	All	Diarrhoea	123	15%	n.r.	45%	9%	31%	[28]
	E Asia	China	Medium	2002	Comm.	n.r.	All	Diarrhoea	331	0%	0%	93%	0	7%	[3]
	SC Asia	Pakistan	Low	2002–03	Facility	n.r.	Children	Diarrhoea	193	11%	5%	58%	15%	16%	[46]
	SC Asia	India	Medium	n.r.	Facility	n.r.	<12 yr	Diarrhoea	53	57%	n.r.	36%	4%	4%	[56]
Latin America/ Caribbean	S America	Brazil	Medium	1978–79	Comm.	n.r.	All	Diarrhoea	16	0%	0%	69%	0%	31%	[9]
	S America	Peru	Medium	1987–90	Comm.	n.r.	2–27 mo.	Diarrhoea	82	9%	n.r.	59%	13%	19%	[172]
	S America	Bolivia	Medium	1991–92	Facility	Hospital	<6 yr	Diarrhoea	6	17%	n.r.	83%	0%	0%	[142]
	S America	Peru	Medium	2002	Facility	Clinic	18–26 yr	Diarrhoea	90	0%	0%	92%	8%	0%	[44]
	S America	Brazil	Medium	2002–03	Facility	Hospital	0–15 yr	Diarrhoea	141	0	0	0%	20%	80%	[21]

HDI, Human development index; n.r., not reported; Comm., community.

* Facility type: 'both' refers to patient recruitment in both hospital and clinic.

† % dys (*S. dysenteriae*), % flex (*S. flexneri*), % boydii, and % sonnei reflect the proportion of the total number of *Shigella* isolates.

‡ % Sd1 among dys: Sd1 data is presented as % of total Sd1, except where indicated by #, in which case % Sd1 reflects % of all *Shigella*.

Table 4*b*. *Frequency of* Shigella *subgroups in epidemic context, 1984–2005*

Area	Region	Country	HDI	Years	Setting	Facility type*	Symptoms	No. *Shigella* isolates	% dys†	% Sd1 among dys‡	% flex†	% boydii†	% sonnei†	Ref.
Africa	Middle Africa	Zaire/DRC	Low	1981	Facility	Hospital	Dysentery	13	92%	92%	8%	0%	0%	[75]
	E Africa	Tanzania	Low	1982	Facility	Hospital	Dysentery	11	18%	100%	81%	n.r.	n.r.	[173]
	E Africa	Burundi	Low	1990	Facility	Clinic	Dysentery	115	72%	99%	20%	0%	7%	[174]
	E Africa	Zambia	Low	1990–91	Facility	Hospital	Dysentery	56	75%	100%	25%	0%	0%	[83]
	E Africa	Zimbabwe	Low	1993–94	Facility	Hospital	Dysentery	47	94%	100%	9%	0%	0%	[58]
	Middle Africa	Zaire/DRC	Low	1994	n.r.	n.r.	Diarrhoea	9	89%	100%	11%	0%	0%	[175]
Asia	SE Asia	Myanmar	Medium	1984–85	Facility	Hospital	Dysentery	12	100%	100%	0%	0%	0%	[176]
	SC Asia	India	Medium	1985	Comm.	n.r.	Dysentery	n.r.	100%	n.r.	n.r.	n.r.	n.r.	[33]
	SC Asia	India	Medium	1986	Comm.	n.r.	Dysentery	10	80%	100%	20%	0%	0%	[32]
	SC Asia	India	Medium	1986	Facility	Hospital	Dysentery	47	n.r.	91%#	n.r.	n.r.	n.r.	[177]
	SC Asia	India	Medium	1988	Facility	Both	Dysentery	26	69%	100%	31%	0%	0%	[178]
	SC Asia	India	Medium	1988	Facility	Hospital	Dysentery	54	69%	100%	31%	0%	0%	[82]
	SE Asia	Thailand	Medium	1991	Facility	Hospital	Diarrhoea	48	n.r.	n.r.	30%	n.r.	n.r.	[179]
	SE Asia	Thailand	Medium	1991–92	Facility	Clinic	Diarrhoea	90	4%	0%	67	1%	28%	[52]

HDI, Human development index; n.r., not reported.

* Facility type: 'both' refers to patient recruitment in both hospital and clinic.

† % dys (*S. dysenteriae*), % flex (*S. flexneri*), % boydii, and % sonnei reflect the proportion of the total number of *Shigella* isolates.

‡ %Sd1 among dys: Sd1 data is presented as % of total Sd1, except where indicated by #, in which case % Sd1 reflects % of all *Shigella*.

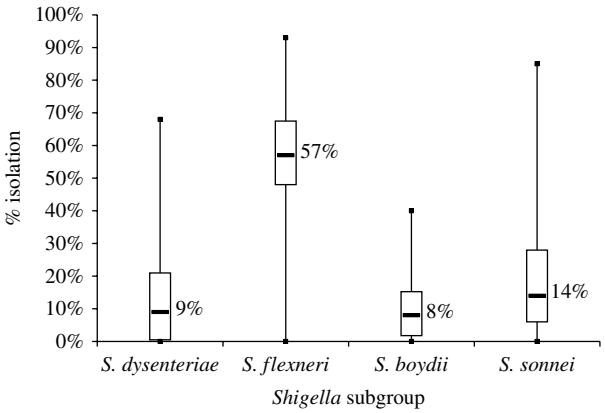

Fig. 4. Frequency of *Shigella* subgroups detected among *Shigella* isolates from medium and low human development index (HDI) countries, 1984–2005 ($n = 56$ studies).

endemic shigellosis, is clear. *S. sonnei* remains the most frequently isolated subgroup in industrialized countries [4]. Even among medium- and low-HDI countries, there is a significant correlation between the GDP of the country at the time of the study and the frequency of *S. sonnei* isolation. The predominance of *S. sonnei* over *S. flexneri* in recent studies from Thailand, Brazil, and Turkey probably reflects the expanding economies in these three countries.

Given their respective importance to epidemics and frequency of isolation, we focused this review on *S. dysenteriae* serotype 1 and on the serotypes of *S. flexneri*. Large epidemics of *S. dysenteriae* type 1 were documented in Central America in the 1960s and 1970s, across Africa during the 1980s and 1990s and in South Asia during the early part of each decade between 1970 and the present [104–106]. Studies reporting on the frequency of *Shigella* subgroups in the epidemic context indicate that during an epidemic period, a single subgroup, particularly *S. dysenteriae* serotype 1, can explain the majority of *Shigella* infections [77]. With each reemergence, *S. dysenteriae* type 1 has exhibited an expanding resistance profile. Most recently, strains of *S. dysenteriae* type 1 circulating in South Asia have demonstrated resistance to multiple fluoroquinolones, with susceptibility only to azithromycin, pivmecillinam and third-generation cephalosporins [35–42, 105]. Studies of the efficacy of these agents against *S. dysenteriae* type 1 are rare and have only been conducted in adults [107, 108]. It is vital to better characterize effective antimicrobial agents and regimens for the treatment of multiply-resistant *S. dysenteriae* type 1 infection in children and adults ahead of the next epidemic. Indeed, multi-drug resistance (MDR) is a common feature of the other *Shigella* subgroups as well. Identifying the best therapeutic strategies for MDR *Shigella* remains a central research priority in the study of shigellosis.

Information on the subserotypes of *S. flexneri* is relevant because of the implications for vaccine development; most recent studies identified in this review provided that information. Currently, subserotypes 1c and 3c, and serotypes 7, 8, and 10, are not recognized by the WHO Collaborating Centre for Shigella at the Centers for Disease Control and Prevention (CDC). The International Committee on Systematic Bacteriology Subcommittee on the Taxonomy of Enterobacteriaceae recognized only two subserotypes within *S. flexneri* serotype 1 (1a and 1b) and serotype 3 (3a and 3b) in 1984 [109]. It is important to confirm the identification of serotypes 7, 8, and 10 reported from Pakistan and to assess their contribution to *S. flexneri* disease elsewhere.

A large number (18%) of untypable *S. flexneri* isolates was reported from Pakistan, a finding also noted in studies from Vietnam and Bangladesh, in which 40% and 12% of *S. flexneri*, respectively, could not be definitively serotyped [15, 46, 110]. Several studies reported the serotype of <100% of *S. flexneri* infections [6, 23, 44, 111], suggesting that some isolates could not be definitively serotyped. The prevalence of untypable *S. flexneri* isolates in geographical regions other than South and South East Asia, and the implications of these findings for vaccine development demand further study.

Reliable typing antisera for *S. flexneri* are not easily produced because of the need to absorb cross-reacting antibodies. In the past, quality assurance and quality control problems have been noted in commercially available typing antisera [112]. Improved quality assurance and quality control of commercially distributed typing antisera is necessary to better define the epidemiology of *S. flexneri*.

The literature search strategy yielded many reports about the complications of *Shigella* infection; however, most of these were from hospital-based studies that are biased towards the most severely ill patients with shigellosis. An important gap in the literature is the absence of population-based rates of *Shigella* complications. Such surveillance may require longer-term follow-up of larger populations than most demographic surveillance systems currently conduct.

Our review yielded *Shigella* mortality data from six population-based studies. None of the five population-based studies conducted before 1990 provided

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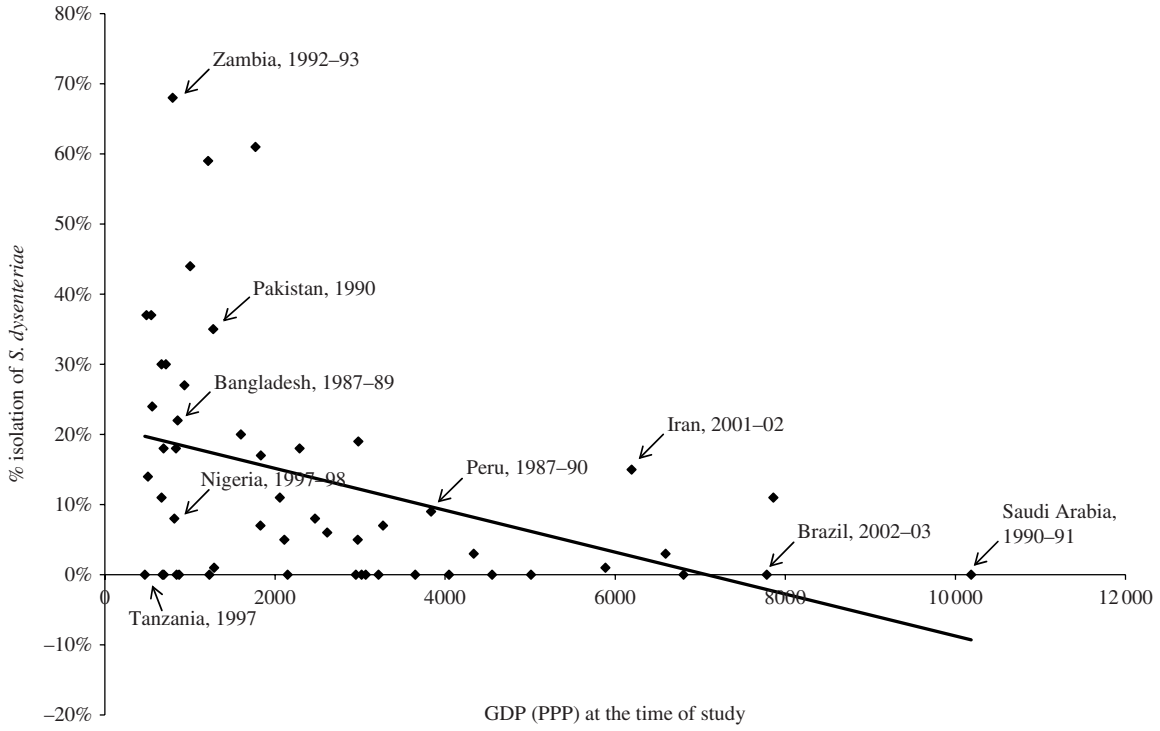

Fig. 5. Frequency of *S. dysenteriae* among *Shigella* isolates, by *per capita* gross domestic product (GDP) (adjusted for purchasing power parity, PPP) of medium and low human development index (HDI) countries, 1984–2005 ($n = 56$ studies) ($R = -0{\cdot}54$, $P < 0{\cdot}0001$). The names of study countries and the years of study are indicated for selected studies.

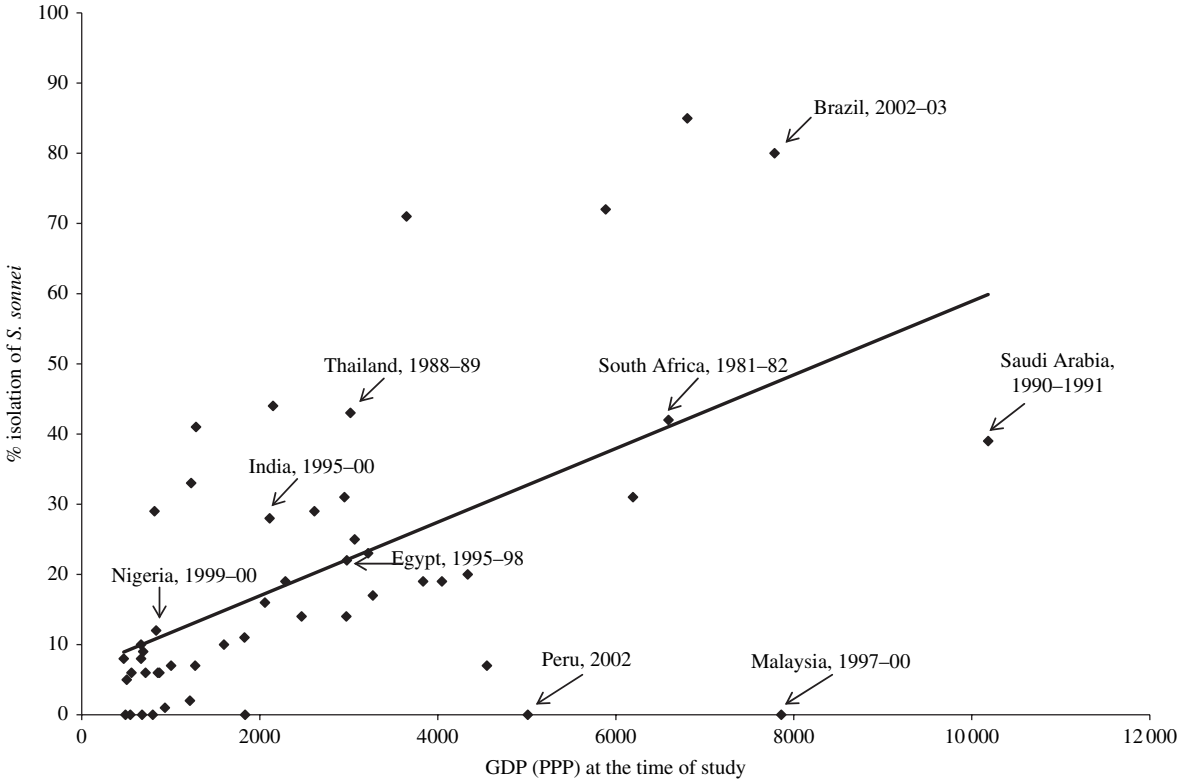

Fig. 6. Frequency of *S. sonnei* among *Shigella* isolates, by *per capita* gross domestic product (GDP) (adjusted for purchasing power parity, PPP) of medium and low human development index (HDI) countries, 1984–2005 ($n = 56$ studies) ($R = 0{\cdot}55$, $P < 0{\cdot}0001$). The names of study countries and the years of study are indicated for selected studies.

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Table 5. *Frequency of* S. flexneri *serotypes in endemic setting, 1984–2005*

Area	Region	Country	Years	No. *flexneri* isolates	1	1a	1b	2	2a	2b	3	3a	3b	4	4a	4b	4c	5	5a	5b	6	X	Y	Non-typable	Ref.
Africa	S Africa	South Africa	1968–85	1124				33%			33%			15%											[111]
	N Africa	Libya	1975–80	609	29%			32%			7%			14%							13%				[23]
	W Africa	Nigeria	1980–84	221	21%			67%			6%			4%				1%			1%				[163]
	W Africa	Nigeria	1986–88	59	7%			15%			9%							5%			64%				[22]
Asia	SE Asia	Thailand	1988–89	12					67%												33%				[43]
	SC Asia	India	1995–00	96					35%	11%		31%		9%							14%				[42]
	SE Asia	Malaysia	1997–00	*		3%	45%		31%			23%	1%		11%						1%		2%		[45]
	SE Asia	Vietnam	1998–99	93	13%			6%			4%			10%							17%		9%	40%	[15]
	SE Asia	Thailand	1998–00	16			6%		56%			19%		6%							13%				[19]
	SE Asia	Thailand	2000–03	22			23%		36%				28%												[5]
	E Asia	China	2002	306		34%			28%	<1%		<1%		2%				2%		<1%		33%	2%	<1%	[3]
	SC Asia	Pakistan	2002–03	112	13%	2%	4%	8%	6%	5%	4%	5%	1%	8%	3%	1%					13%			18%	[46]
Latin America/ Caribbean	S America	Peru	2002	83		25%	69%																		[44]

* Number of *S. flexneri* isolates for which serotype data is provided exceeds number of *S. flexneri* reportedly isolated in study.

Table 6. *Case-fatality rates in hospital-based studies of endemic shigellosis, 1984–2005*

Area	Region	Country	HDI	Year(s)	Age group	No. patients with *Shigella*	CFR	Comments	Ref.
Africa	W Africa	Nigeria	Low	1986–88	All	108	0%		[22]
Asia	SC Asia	Bangladesh	Medium	1974–88	All	9780	9%	Risk factors for death included decreased age, low serum protein, altered consciousness, and decreased platelets	[72]
	SC Asia	Bangladesh	Medium	1978–1987	All	3440	0·96%	CFR among children 5–9 years old was 2%	[31]
	SC Asia	Bangladesh	Medium	1980–81	All	436	17%	CFR was highest among persons aged >15 years but total number of cases in this age group relatively small; 77% of those who died had poor nutritional status	[73]
	SC Asia	Bangladesh	Medium	1980–82	<35 mo.	540	1%		[53]
	SC Asia	India	Medium	1984–87	<5 yr	32	21%		[167]
	SC Asia	Bangladesh	Medium	1987–88	All	792	11%	All deaths occurred among persons aged <15 years	[50]
	SE Asia	Thailand	Medium	1988–89	<5 yr	17	0%		[14]
	SC Asia	Bangladesh	Medium	1988	All	970	11%		[71]
	W Asia	Jordan	Medium	1991–92	<15 yr	66	3%	Two deaths were documented, one in a child with leukaemia and the second in a child with protracted diarrhoea and protein-losing enteropathy	[54]
	SC Asia	India	Medium	n.r. (published in 1995)	<12 yr	53	15%	All deaths occurred among patients aged <2 years and/or severely malnourished patients; 75% had renal failure; 25% had *Shigella* bacteremia	[56]
	SC Asia	Bangladesh	Medium	n.r. (published in 1991)	All	30 with GI obstruction and 30 without GI obstruction	10–33%	10% of patients without obstruction and 33% of patients with obstruction died	[60]

HDI, Human development index; CFR, Case-fatality rate; n.r., not reported; GI, gastrointestinal.

Table 7. *Case-fatality rates in epidemic* S. dysenteriae *type 1, 1984–2005*

Area	Region	Country	HDI	Year(s)	Age group	Symptoms	No. patients with *Shigella*	CFR (%)	Comments	Ref.
Africa	W Africa	Sierra Leone	Not listed	1999–00	All	Dysentery	4218	3%	CFR among persons aged <5 yr was 6% compared to CFR among persons ⩾5 yr at 2%.	[80]
	S Africa	South Africa	Medium	1994–96	⩽10 yr	HUS	81	17%		[64]
	E Africa	Burundi	Low	1992	All	Dysentery	n.r.	n.r.	Dysentery accounted for 12% of all-cause mortality during epidemic	[51]
	S Africa	South Africa	Medium	1995	<12 yr	Dysentery	159	13%	Severely malnourished and persons aged <2 yr were at increased risk of death	[61]
	S Africa	South Africa	Medium	1994	Adults	Dysentery	10	40%	All who died were treated with agents to which pathogen was resistant.	[76]
	E Africa	Zimbabwe	Low	1993–94	All	Dysentery	106	4%	Deaths occurred among patients with renal failure, HUS, anemia, rectal prolapse.	[58]
	E Africa	Mozambique	Low	1993	All	Dysentery	n.r.	13%	CFR of 13% was documented in a rural hospital population; CFR was 17% in paediatric wards of rural hospital. *S. dysenteriae* type 1 accounted for 0·25% of all-cause mortality nationwide.	[78]
	S Africa	South Africa	Medium	1994–95	Paediatric patients	Dysentery	72	11%	Deaths occurred in context of shock, 'sudden collapse', intestinal perforation, and hemolytic-uremic syndrome.	[84]
	Middle Africa	Zaire/DRC	Low	1994	All	Dysentery	n.r.	n.r.	About 40% of all deaths during the first month of the emergency were associated with dysentery, several cases of which were con firmed to be *S. dysenteriae* Type 1	[77]
	E Africa	Zambia	Low	1990–91	All	Dysentery	Varied	4–15%	Children were at increased risk of death with CFR of 15%, whereas adults had CFR of 4%	[83]
	Middle Africa	Zaire/DRC	Low	1981	All	Dysentery	46	0%		[75]
Asia	SC Asia	Bangladesh	Medium	2003	All	Dysentery	50	8%		[37]
	SC Asia	India	Medium	2003	All	Dysentery	169	0%		[36]
	SC Asia	India	Medium	2002	All	Dysentery	n.r.	n.r.	Deaths occurred among patients with anuria, hematuria, dyspnea, seizures, or encephalopathy	[38]
	SC Asia	India	Medium	2002	All	Dysentery	1728	0·9%		[39]
	SC Asia	India	Medium	1986	All	Dysentery	200	5%		[32]
	SC Asia	India	Medium	1986	All	Dysentery	47	2%		[177]
	SC Asia	Bangladesh	Medium	1985	All	Dysentery	626	11%	Community-based intervention led to decreased CFR (0·06%); pre-intervention CFR was highest among ages 3–4 yr (36%)	[81]
	SC Asia	India	Medium	1988	All	Dysentery	555	4%	About 75% of deaths occurred among pts aged <2 yr	[82]
	SE Asia	Myanmar	Medium	1984–85	All	Dysentery	328	0·6%		[176]
	SC Asia	India	Medium	1985	All	Dysentery	950	2%	About 91% of deaths occurred among children	[33]
	SC Asia	India	Medium	1984	All	n.r.	273	7%	All deaths occurred among children (age unspecified)	[79]

HDI, Human development index; CFR, Case-fatality rate; HUS, haemolytic–uraemic syndrome; n.r., not reported.

Table 8. *Data gaps and research needs for* Shigella *infections in medium and low human development index (HDI) countries*

Morbidity

Incidence

- Population-based incidence data from sub-Saharan Africa
- Population-based incidence data from low-HDI countries

Age-related morbidity

- Population-based data reporting on surveillance of all age groups, including young infants (<6 months of age)

Complications

- Population-based data on complications of *Shigella* infection

Burden of *Shigella* relative to other diarrheagenic pathogens

- Comprehensive stool analyses in population-based and facility-based studies of diarrhea etiology, with efforts to isolate *Rotavirus*, ETEC, EPEC, and parasitic infections

Subgroup-specific issues

- Confirmation of *S. flexneri* serotypes 7, 8, and 10 reported from Pakistan
- Prevalence of untypable *S. flexneri* isolates in geographic regions other than South and South East Asia

Shigellosis in the context of HIV co-infection

- Impact on incidence
- Occurrence of complications, in addition to bacteraemia

Mortality

- Population-based data on *Shigella*-associated mortality
- Identification of modifiable risk factors for *Shigella* mortality

Seasonality

- Reporting of seasonality data using standard terminology and study durations >2 years

Diagnosis

- Validation of improved methods for transporting stool and rectal swabs in resource-poor settings
- Development of gene-based diagnostic techniques for detection of *Shigella* to serotype level
- Evaluation of gene-based methods to distinguish detection of clinically relevant infections from asymptomatic carriage
- Improved quality assurance and quality control of commercially distributed typing antisera

Treatment

- Enhancement of treatment strategies for multi-drug resistant *Shigella* infection
- Efficacy of pivmecillinam and third-generation cephalosporins against *S. dysenteriae* type 1 among adults and children

Prevention

- Identification of an antigen that can elicit cross-reacting antibodies to the various *S. flexneri* serotypes
- Development of widely applicable, acceptable, and affordable vaccines for the most common *S. flexneri* serotypes
- Effectiveness of aggressive community-wide promotion of handwashing with soap
- Effectiveness of aggressive fly control measures
- Assessment of potential for modifying culturally based anal cleansing practices to prevent hand contamination

mortality information. Calculation of mortality rates in population-based studies are critical for estimating the true public health impact of shigellosis; however, such studies are rightfully conducted under strict human subjects research guidelines, mandating prompt and appropriate treatment for bloody

diarrhoea. Thus, it is difficult to study the natural history of *Shigella* complications or mortality in such a research setting. Although unbiased estimates of *Shigella* mortality may be difficult to obtain, the consistent use of verbal autopsy data and molecular diagnostic techniques in population-based surveillance may help. Risk factors for death in endemic shigellosis were available only from papers from South Central Asia and from one study in Jordan. Identification of modifiable risk factors for death from all regions and strategies for prevention of these risk factors are important needs in the study of *Shigella*.

Despite a number of studies reporting on the temporal distribution of *Shigella* infections, no clear patterns emerged with respect to seasonality. The use of non-standard terminology and data collection for <2 consecutive years make comparisons of seasonal trends across studies difficult. We recommend the collection and analysis of temporal distribution data for shigellosis over multi-year periods, using consistent descriptors and contextual environmental information such as rainfall and flooding.

Since Shigellae, like many other enteric pathogens, are transmitted through consumption of contaminated food and drinking water, improvements in sanitation, drinking water quality, and food preparation and storage practices in homes and in communities are expected to have dramatic impacts on the burden of shigellosis. Because the pathogen has a low infectious dose, the promotion of handwashing with soap after defecation would be expected to reduce the risk of *Shigella* transmission [1]. However, specific data regarding the beneficial effects and feasibility of scaling up of household-level control measures, such as promotion of handwashing with soap, improved latrine design to include handwashing stations, aggressive fly control, and modification of culturally ingrained anal cleansing habits are largely lacking.

A number of candidate *Shigella* vaccines are under development. Oral formulations would probably be most useful for the developing world. In September 2006, the International Vaccine Institute, with partners in various Asian countries, estimated the burden of *Shigella* infections and identified the frequency of subgroups and serotypes. Their work demonstrates that 90% of *S. flexneri* infections are caused by eight different serotypes and subserotypes [113, 114]. This diversity suggests that the identification of an antigen common to most or all of the *S. flexneri* serotypes would facilitate vaccine development significantly. While extensive attention has been paid to the development of *Shigella* vaccines, and data has been gathered regarding *Shigella* burden in Asia, relatively little information is available regarding the epidemiology of shigellosis and, importantly, the feasibility of introducing these vaccines in sub-Saharan Africa.

Finally, any estimation of the burden of *Shigella* infections must take into account the limitations of currently utilized specimen transport and diagnostic methods [98]. Thus, even the culture-based estimates of *Shigella* incidence reported above may underestimate the true burden of disease. Improved transport methods, such as the DNA/RNA Protect™ specimen collection system, must be validated for the detection of *Shigella* in clinical settings, especially in remote areas. Population-based surveillance for *Shigella* incidence using potentially more sensitive methods, such as PCR techniques, in addition to culture, may improve *Shigella* incidence estimates [115]. Moreover, development and evaluation of rapid gene-based diagnostic techniques for faecal specimen testing, available to the serotype level, may enhance measurement of the burden of *Shigella* and its various serotypes. However, given their potential for high sensitivity, these methods should be evaluated to understand the extent to which they detect clinically relevant infections *vs*. asymptomatic carriage.

In summary, this paper describes the acute need for population-based studies of *Shigella* morbidity and mortality from sub-Saharan Africa, and from low-HDI countries in general. Such information would be invaluable for the prioritization of precious public health resources for pathogen-specific interventions, such as vaccination programmes targeting *Shigella*. Additional data regarding complications, modifiable risk factors for mortality, the burden of disease among infants, effectiveness of non-vaccine prevention measures, and improved diagnostics would add greatly to our knowledge of *Shigella* infections.

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DECLARATION OF INTEREST

None.

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