A comparison of disease caused by Shigella and Campylobacter species: 24 months community based surveillance in 4 slums of Karachi, Pakistan

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Summary Despite the efforts of the international community diarrheal diseases still pose a major threat to children in children less than five years of age. Bacterial diarrhea has also emerged as a public health concern due to the proliferation of drug resistant species in many parts of the world. There is a paucity of population-based data about the incidence of shigellosis and Campylobacter infections in Pakistan. We report country specific results for Shigella diarrhea that were derived from a multicenter study conducted in six Asian countries. Disease surveillance was conducted over a 24 month period in urban slums of Karachi, Pakistan, a city with a population of 59,584. Cases were detected through passive detection in study treatment centers. Stool specimens or rectal swabs were collected from all consenting patients. Between January 2002 and December 2003 10,540 enteric infection cases were detected. The incidence rate of treated diarrhea in children under 5 was 488/1000/year. In children, 5 years and older, the diarrhea rate was 22/1000/year. 576 (7%) Campylobacter isolates were detected. The predominant Campylobacter species was C. jejuni with an increase of 29/1000 year in children under 5 years. Shigella species were isolated from 394 of 8032 children under 5 years of age. Shigella flexneri was the dominant species (10/1000/year in children under 5 years) followed by Shigella sonnei (3.9/1000/year), Shigella boydii (2.0/1000/year) and Shigella dysenteriae (1.3/1000/year). Shigellosis and Campylobacter infection rates peaked during the...
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Introduction

Despite efforts of the global community to control and prevent the diarrheal diseases, they still remain a major cause of morbidity and mortality in children especially in impoverished areas of South East Asia [1,2] moreover the incidence of dysentery (which is an aggravated diarrheal condition characterized by frequent passage of stool containing blood and mucus) has also increased. Much of the dysentery is considered to be of bacillary origin species of Shigella (S. flexneri, S. sonnei, S. dysenteriae, and S. boydii) and Shigellosis has become a public health issue [3].

On a global level, it is estimated that about 165 million cases of diarrhea due to Shigella occurs annually, 99% occur in developing countries, and in developing countries 69% of episodes occur in children under five years of age. About 1.1 million deaths are attributed to Shigella infections in developing countries, 60% of which occur in the under-five age group [3]. A multicenter study conducted in six Asian countries illustrates incidence rates of Shigellosis up to 13% [4]. A combination of disease severity and antibiotic resistance is posing a real dilemma especially in young children [5,6].

The recognition of extended range beta lactamases in Shigella strains may well jeopardize the effectiveness of antibiotics including third-generation cephalosporins [7–9]. The appearance of resistance against the majority of antimicrobials has added urgency to the development of vaccines which can protect against shigellosis while to date only a single vaccine to protect against shigellosis is accredited worldwide [10].

Campylobacter infection is also a common cause of acute gastroenteritis both in the developed and developing countries and like other bacterial infections incidence is much higher in the developing nations due to poor water and sanitary conditions and mishandling of food [11,12]. Based on the studies from Thailand and Mexico the incidence rates are estimated to be 40,000 per 100,000 for children younger than five years [11]. In developing countries, Campylobacter infections in children commonly occur under the age of two years and can sometimes leads to death and other complications [12]. In several community-based surveys Campylobacter jejuni was the most commonly isolated enteropathogen in diarrheal stools from children aged less than 5 years [13].

Like shigellosis Campylobacter infections are also wide spread and C. jejuni is considered to be a common cause of acute bacterial gastroenteritis globally. The organism becomes more serious due to its association with serious post-infection neurological complications. A study conducted by Clarence et al. reveals a much increased risk of Gullien Barre Syndrome (GBS) among Campylobacter enteritis patients compared with previously reported studies [14]. Campylobacter are widespread in both developed and developing countries but due to increasing incidence and complication much attention is required to address the problem in developing countries [15].

Drug resistance is also an important factor while addressing Campylobacter infections. Addressing these infections in many developed countries is a priority due to the emergence of increased levels of macrolide resistance [16]. Further the infections portray the same situation of drug resistance even in the developing countries which is evident from the studies conducted in Thailand by Serichanta-lergs and colleagues [17].

The Campylobacter disease burden is also quite high in the south Asian region. Studies from Bangladesh, India and Pakistan reveals that it is one of the most frequent organisms causing gastroenteritis [18]. In Pakistan the presence of
Campylobacter organisms are quite high in food commodities which are usually used by the common man [19], which in turn results in an increased incidence of Campylobacter infections (12%) in all age groups [20]. Another study conducted at Rawalpindi reveals that C. jejuni is the most frequent cause of childhood diarrhea and dysentery in that setting [21].

Due to its epidemiological spread, Pakistan is a potential site for future vaccine trial and in grounding of future vaccine trial sites it is crucial to recognize the shigellosis incidence as shigellosis is much more notorious than the other enteric organisms. Our study is the foremost community based study to estimate the factual incidence of shigellosis on a population level. Earlier hospital based studies do not provide a denominator essential for incidence estimates [22–29]. Not only is it significant to appreciate the shigellosis incidence in a study area it is evenly imperative to understand the distribution of Shigella serogroups, types, and subtypes because the knowledge about cross protection between Shigella serotypes and subtypes is very limited at best [30]. We have consequently conducted shigellosis surveillance in 4 urban slums of Karachi over a 24 months period. The unexpectedly high detection rates of Campylobacter species have allowed us to evaluate and contrast the epidemiology as well as the clinical presentation of shigellosis and Campylobacter infections.

Methods

This study was done as a part of the Multicenter study for Shigella diarrhea in six Asian countries [4] to compare shigellosis with campylobacteriosis in four slum communities, in Karachi, Pakistan (Rehri Goth, Sherpao Colony, Sultanabad and Hijrat Colony). Pashto and Hazara migrants from the NWFP Province of Pakistan are the major population groups in the impoverished slum areas of Sherpao colony, Hijrat colony and Sultanabad. Rehri Goth is a much older fishing community mainly consisting of Sindhi speaking settlers. A census was conducted in each of the communities prior to the surveillance that demonstrated a population of 59,584 individuals including 8381 children less than 5 years. Karachi is a tropical area with hot summers lasting from April through October and more moderate temperatures for the rest of the year, rains are expected during the second half of each summer but can skip one or more years.

The health care system of these slums consisted of 79 private practitioners, among them 32 were the graduates from medical colleges [31]. The quackery medical practice was common and Quacks or "village doctors" who have no formal training or degree used to prescribe allopathic medications even antibiotics. Untrained pharmacy shopkeepers and registered pharmacists provide medication based on the description of the signs and symptoms of the patient over the counter. In addition, a variety of traditional healers (Hakims) and homoeopaths practiced in the study areas. Once these primary health care providers have been exhausted the residents of the study areas can seek treatment from hospitals. A study clinic was established in each of the 4 slums for more than a year before the surveillance started, these clinics were equipped with trained doctors, medicines and relevant laboratory equipment. The clinics provided free medical services for residents. The availability of free healthcare in the study clinics had been announced during community meetings when residents were asked to attend the study clinics in case of diarrhea. The presence of the study clinics was further publicized during the census.

We estimated the burden of enteric diseases through a population-based, surveillance system. A passive case detection system was used which captured patients when they visited the study clinics. Each household was visited weekly and the household head or a representative was asked about diarrhea cases in the preceding 7 days. If a diarrhea case was reported the patient was asked to come to the study clinic. The study followed a generic protocol, which was adapted to local needs by staff and collaborating centers [32]. Verbal consent was obtained from each participant (parent or guardian for children) following an explanation of the purpose of the study.

Consenting patients of all age groups with diarrhea or dysentery presenting to the study clinics were eligible to participate in the study. Diarrhea was defined as three or more loose bowel movements during a 24-h period, dysentery as one or more loose bowel movements with visible blood, and fever as an axillary temperature of 37.5 °C or higher. Diarrhea following three days or more of normal bowel movements was considered a new diarrhea episode. For every patient presenting with diarrhea, a case report form (CRF), describing demographics and medical history & examination was completed and two rectal/stool swabs or a stool specimens were obtained. All the cases were provided with the standard treatments as outlined in the protocols. All consenting patients with a history of dysentery or diarrhea for three days or more were eligible to participate in the study. The study received approval from the Aga Khan University Ethics Review Committee and the Secretariat

To isolate the exact organism we set up a standard laboratory at every clinic. We obtained three rectal swabs one for buffered glycerol saline (BGS), one for alkaline peptone water APW and one for phosphate buffered saline PBS and along with that we ask the patient to bring a stool sample in a container for stool culture. All these medias were used for the enrichment and transport of the isolates to the Central Lab at Aga Khan University, Karachi, Pakistan. The collected stool samples were also plated immediately onto XLD-, SS-, MacConkey's-agar and incubated at 37°C for 18—24h before transport at the center. All swabs and stool samples were stored refrigerated and transported daily in a cool box to the Central Laboratory at Aga Khan University, Karachi following the standard protocols. The Central Laboratory at Aga Khan University is one of the state of the art laboratories in the South Asian region. To ensure the robust implementation of laboratory procedures, the doctors of the health centers received an extensive training for all laboratory procedures.

On arrival specimens in BGS were plated on MacConkey’s agar and Salmonella-Shigella agar. Biochemical reactions of lactose negative colonies were evaluated with Triple Sugar Iron agar and Lysine Indole Motility medium isolates producing reactions consistent with shigella were serologically confirmed by slide agglutination with appropriate group-specific polyvalent antisera, followed by type-specific monovalent antisera (Denka-Seiken, Tokyo, Japan). In cases where no agglutination occurred with live bacteria, the test was repeated with boiled suspensions of bacteria. Campylobacter was identified after 48h by colony morphology, oxidase test, Gram staining, and motility. The organisms were identified to species level by a positive catalase test, a negative urease test, failure to produce H2S, and non-fermentation in TSI, resistance to cephalotin, nitrate reaction and hippurate hydrolysis. Although in the main study of Shigella diarrhea the investigators look for Shigella using PCR but that was not done in Pakistan. All PCR studies were conducted at the USAFRIMS, Bangkok, Thailand [4].

All Case Record Forms were archived serially in the box files and then were double entered into a custom-made data entry programs (FoxPro, Microsoft, Redmond, WA, USA). The data management programs included error as well as consistency and range check programs. Chi-square tests were used for binary data analysis. For the analysis of non-normally distributed data, Wilcoxon rank sum test was applied. Data were analyzed with SAS software (SAS Institute Inc., Cary, NC, USA) and Stata/SE 8 (Stata Corp., Texas, USA). A $p$-value less than 0.05 (2-tailed) was considered significant. Incidence rates were calculated by using age-specific denominators of the population residing in the catchment area in 2001. We calculated 95% CI for the incidence rates by the Wilson score method [33]. As the observation period was 24 months, we assumed that each person residing in the study area contributed 24 months of person time to the denominator. The number of age-specific disease episodes was used as numerator. For the comparison of clinical presentations only patients were included from whom a single organism was isolated. Patients with multiple infections (co-infections) were excluded.

Throughout the surveillance period, the senior level staff did regular ongoing monitoring and evaluation of various process and outcome indicators. The data management unit produced an indicator report on weekly basis that reflected the flow of the project activities. To ensure the proper implementations of the project, regular refresher trainings were provided to the staff involved in the project.

**Results**

During the 24 month study period, which started 1st January 2002 and ended on 31st December
2003 10,540 enteric infection cases were detected (Fig. 1). The incidence rate of treated diarrhea in children under 5 years was 488/1000/year compared to 22/1000/year in the older population. This high incidence in young children is a clear evidence that the enteric infections still prevail in the younger populations.

Enteric infections (diarrhea, dysentery) and specifically Campylobacter infections and shigellosis increased during the warmer months of the year (Fig. 2a and b). There was no correlation between changes in enteric infections rate and rainfall in 2003.

From 8032 stool specimens 394 (5%) Shigella species were isolated. S. flexneri was the dominant species (10/1000/year in children under 5 years) followed by S. sonnei (3.9/1000/year), S. boydii (2.0/1000/year) and S. dysenteriae (1.3/1000/year). The dominant S. flexneri serotypes were 2a (38 of 89 isolates; 16%) followed by S. flexneri 6 (37 isolates; 15%), S. flexneri 1b (25 isolates; 10%), and S. flexneri 2b (23 isolates; 10%).

Figure 2 (a and b) Seasonality of enteric infections in relation to weather changes in Karachi, Pakistan in 2003.

Figure 3 Incidence of children under 5 years presenting with dysentery in Karachi, Pakistan.
A comparison of disease caused by Shigella and Campylobacter species

During the study period 576 (7%) Campylobacter isolates were detected. The most frequently isolated Campylobacter species was C. jejuni (29/1000/year in children under 5 years) followed by Campylobacter coli (1.4/1000/year in children under 5 years) and Campylobacter laridis (0.3/1000/year in children under 5 years) (see Fig. 3).

There were significant differences between the presentation of Campylobacter infections and shigellosis. Shigellosis patients were significantly older (mean age 6.3 years) compared to Campylobacter patients (mean age 2.8 years, \( p < 0.001 \); Table 2). As illustrated in Fig. 4a both shigellosis and Campylobacter infections peaked in the 2nd year of life and dropped below 10/1000/year by the 5th year of life. In contrast to Campylobacter infection rates, shigellosis rates increased with increasing age after age 30 (Fig. 4b).

Of the 10,540 enteric infections 1123 (11%) presented with dysentery. Out of which 123 (11%) were Shigella species and 54 (5%) were Campylobacter species respectively. The dysentery incidence was highest in S. flexneri patients (3.5/1000/year in children under 5 years) followed by C. jejuni (2.5/1000/year; Fig. 5).

Of 394 shigellosis patients 123 (31.2%) presented with dysentery in contrast only 54 (9.3%) of 576 patients with Campylobacter infections (Table 1). The percentage of Campylobacter and shigellosis patients presenting with dysentery varied with the age of the patient and the infecting species (Fig. 5). Of 173 children with S. flexneri infections 58 (34%) presented with dysentery in contrast to 31 of 69 (45%) adults \( (p = 0.05; \) Fig. 5). The percentages of Campylobacter infected patients presenting with dysentery were identical to the percentages patients presenting with dysentery from whom no organism could be isolated.

Discussion

Surveillance in impoverished areas of Karachi found relatively high shigellosis and even higher rates of Campylobacter infection. Consistent with previous studies the dominant Campylobacter species was C. jejuni and the dominant Shigella species was S. flexneri [34]. The infection rates were highest in the extremes of age. Both infections peaked in the second year of life. Newborns may be protected against shigellosis and Campylobacter infection by
Figure 5  The percentage of patients with Shigella or Campylobacter infections presenting with dysentery (the 95% confidence intervals are shown as whiskers). *No organism isolated.

Table 1  Total population, number of cases over a 24 months observation period, incidence rates and 95% confidence intervals in Karachi, Pakistan.

<table>
<thead>
<tr>
<th></th>
<th>&lt;60 months</th>
<th>≥60 months</th>
<th>Total n = 59,584a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 8381a</td>
<td>n = 51,203a</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8174</td>
<td>2276</td>
<td>10,450</td>
</tr>
<tr>
<td></td>
<td>488 (477—498)</td>
<td>22 (21—24)</td>
<td>88 (86—90)</td>
</tr>
<tr>
<td>Dysentery</td>
<td>761</td>
<td>362</td>
<td>1123</td>
</tr>
<tr>
<td></td>
<td>45 (41—50)</td>
<td>4 (3—4)</td>
<td>9 (9—10)</td>
</tr>
<tr>
<td>Campylobacter infections</td>
<td>515</td>
<td>61</td>
<td>576</td>
</tr>
<tr>
<td></td>
<td>31 (27—35)</td>
<td>0.6 (0.4—0.9)</td>
<td>5 (4—5)</td>
</tr>
<tr>
<td>Shigellosis</td>
<td>292</td>
<td>102</td>
<td>394</td>
</tr>
<tr>
<td></td>
<td>17 (15—21)</td>
<td>1 (0.7—1.3)</td>
<td>3 (2.9—3.90)</td>
</tr>
<tr>
<td>Shigellosis dysentery</td>
<td>82</td>
<td>41</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>5 (4—7)</td>
<td>0.4 (0.2—0.6)</td>
<td>1.0 (0.8—1.3)</td>
</tr>
<tr>
<td>Campylobacter dysentery</td>
<td>45</td>
<td>9</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>3 (2—4)</td>
<td>0.1 (0.0—0.2)</td>
<td>0.5 (0.3—0.7)</td>
</tr>
</tbody>
</table>

a  Denominator.

Table 2  Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Shigellosis patients</th>
<th>% Age</th>
<th>Campylobacter patients</th>
<th>% Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>372a</td>
<td>551b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>207</td>
<td>56%</td>
<td>320</td>
<td>58%</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>6.3</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (median)</td>
<td>2</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysentery</td>
<td>119</td>
<td>50</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Ever watery stools</td>
<td>236</td>
<td>413</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Mucous stools</td>
<td>95</td>
<td>125</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>46</td>
<td>43</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>1</td>
<td>2</td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>135</td>
<td>224</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>46</td>
<td>70</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>17</td>
<td>27</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Number of stools in the last 24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 or less</td>
<td>139</td>
<td>201</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>6—10</td>
<td>118</td>
<td>141</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>11—30</td>
<td>10</td>
<td>9</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Too many to count</td>
<td>105</td>
<td>200</td>
<td>36%</td>
<td></td>
</tr>
</tbody>
</table>

a  22 patients with co-infections have been excluded.

b  25 patients with co-infections have.
trans placental antibodies, breast milk, and perhaps lower exposure rates [35–39]. Following a peak in the first years of life the rates for both infections dropped by more than an order of magnitude. After age 30 a trend for increasing shigellosis rates was observed but not for Campylobacter. This finding may be explained by waning immunity against shigellosis with increasing age. There is no apparent waning of immunity against Campylobacter infections.

Alternatively transmission of shigellosis may increase with increasing age. Shigellosis is thought to be mostly transmitted from person to person. Flies may in some places play a role in the transmission of this disease [40]. The transmission of Campylobacter is less well understood. It is thought that most poultry and many household pets are Campylobacter carriers in Pakistan [41]. The age distribution of C. jejuni infections is very different in the USA where after a peak in the first years of life a second peak of infections is observed during the third decade of life [42]. Not surprisingly the age distribution of C. jejuni cases in Bangladesh described by Glass and coworkers more than 20 years ago was strikingly similar to our findings in Pakistan [43].

Shigellosis and Campylobacter infections were also significantly different in their presentation. A significantly larger proportion of shigellosis patients presented with dysentery compared to patients with Campylobacter infections. Indeed the percentage of Campylobacter infected patients presenting with dysentery was similar to the percentage in patients from whom no organism could be identified. It cannot be excluded that co-infection with agents responsible for the background rates of dysentery also cause dysentery in Campylobacter infection patients. Older patients presented more frequently with dysentery compared to children less than 5 years. This finding may be best explained by differences in health care utilization. Adult patients may only seek care for severe disease including dysentery. Children may be brought to health care providers for more trivial disease episodes.

Two thirds of the shigellosis patients had at some stage of their diarrhea episode watery diarrhea. The proportion of patients who had at some stage watery diarrhea was even higher in patients with Campylobacter infections. An observation that challenges the notion which associates shigellosis exclusively with dysentery. Abdominal pain was more frequently associated with shigellosis than with Campylobacter infections. While shigellosis appears to cause more pain and dysentery. C. jejuni infections caused more frequent bowel movements. These findings are in agreement with findings from Bangladesh as well as other countries [42,43].

Shigellosis and Campylobacter infections appear to have a similar seasonality. Consistent with previous reports from Karachi, shigellosis and Campylobacteriosis rates increased in the hot summer months and dropped during the colder months of the year [44]. The notion that ‘the seasonal variation of C. jejuni infection appears to be influenced by rainfall’ was not supported by our findings [45]. The increase in all enteric infections including C. jejuni started well before the onset of rains in 2003 in Karachi.

Several hospital-based studies of enteric infections have been conducted in Pakistan including Karachi. The studies found that from between 3% and 19% of stool specimens were Shigella positive [22–24,26,44]. In hospital based campylobacteriosis was isolated from 17% to 25% of stool specimens [41,42,46–48]. In our study Shigella species were isolated from less than 5% of stool specimens that is at the lower end of the expected range. Campylobacter species were isolated from 7% of specimens which is below the expected range.

Our study differs from previous reports in that it was community-based and included patients of all ages hence patients with a potentially different disease severity and prevalence. Furthermore our study was set up to detect shigellosis cases and methods were optimized to detect Shigella species. Campylobacter unlike Shigella species are highly fastidious and may have escaped detection. A cohort study conducted in Mexico found that children under 5 years had 2.1 episodes of Campylobacter infections per year [48]. In a hospital based study in the US Campylobacter spp. were isolated from 5% of stool specimens [42]. A study in Bangladesh C. jejuni in 14% of outpatients presenting with diarrhea to a research hospital [43]. However C. jejuni was isolated less frequently from village children with diarrhea (5%).

The findings of our study were consistent with another done in Peru [49]. The Peruvian study reveals that C. jejuni was the leading cause of diarrhea and is more frequent in malnourished children with low socioeconomic background. The participants in our study also belonged to a low socioeconomic stratum of society. The Peruvian study also found an excess risk of GBS among Campylobacter enteritis patients [14]. We followed our cases and did not find such trends.

Our study made use of passive surveillance. Patients were captured when they presented to study clinics. This method has the advantage that trivial diarrhea cases that usually would not seek
treatment are not included. Passive surveillance however has the disadvantage that patients who seek care outside the study clinics will escape the surveillance. Furthermore 23% of diarrhea patients who were captured by the surveillance did not provide a stool specimen. For these reasons it seems likely that our study underestimated the true Shigellosis and Campylobacter infection rates.

Shigellosis and Campylobacter infection incidence rates were highest in the second year of life. Decreasing rates after the second year of life could be due to acquired immunity. The trend for increasing shigellosis rates in old age which was observed for shigellosis but not for Campylobacter infections could be due waning of immunity or differences in exposure. Shigellosis presented significantly more often frequently with abdominal pain and dysentery than Campylobacter infections indicating that shigellosis may be a more severe illness and have worse clinical consequences than Campylobacter infections.

Conclusion

It is established that Campylobacteriosis and Shigellosis are the most common organisms causing diarrhea. The shigellosis is comparatively a severe form of enteric infection that needs instant attention. There has also been a perceptible increase in ciprofloxacin resistance in our centre as also in other parts of country, which could be attributed to unrestricted administration of antibiotics for diarrhea irrespective of aetiology. Many cases the diarrhea are empirically treated with fluoroquinolones particularly ciprofloxacin in general practice clinics.

Due to increased disease burden, increased symptom severity and proliferating drug resistance both campylobacteriosis and shigellosis have become significant health problems; moreover they are the diseases of poor and impoverished people who do not have access to clean water and sanitary conditions, health care services and optimal treatment. In the face of these facts it is empirically important to develop a low cost vaccine that will protect the affected populations for a longer duration. However the barrier to develop a vaccine against campylobacteriosis and shigellosis for use in developing countries is the poor response therefore further research studies of promising campylobacteriosis and shigellosis vaccine candidates are immediately desirable after confirmation of protection, immunogenicity, and safety in volunteer settings.

Conflict of interest statement

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A comparison of disease caused by Shigella and Campylobacter species


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