Estimating the burden of shigellosis in Thailand: 36-month population-based surveillance study

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Objective To estimate incidence of shigellosis in the Kaengkhoi district, Saraburi Province, Thailand.
Methods Population-based surveillance of shigellosis based in treatment centres. The detected rates of treated shigellosis were corrected for the number of cases missed due to the low sensitivity of microbiological culture methods and participants' use of health-care providers not participating in the study.
Findings The overall uncorrected incidence of shigellosis was 0.6/1000 population per year (95% confidence interval (CI) = 0.5–0.8). The unadjusted incidence of treated shigellosis was highest among children less than 5 years old (4/1000 children per year; 95% CI = 3–6) and significantly lower among people aged ⩾ 5 years (0.3/1000 population per year; 95% CI = 0.2–0.5; $P < 0.001$). Adjusting for cases likely to be missed as a result of culture and surveillance methods increased estimates approximately five times. The majority of *Shigella* isolates (122/146; 84%) were *S. sonnei*; the rest were *S. flexneri*. Of the 22 *S. flexneri* isolates, the three most frequently encountered serotypes were 2a (36%), 1b (23%) and 3b (28%). A total of 90–95% of *S. sonnei* and *S. flexneri* isolates were resistant to tetracycline and co-trimoxazole. In contrast to *S. sonnei* isolates, more than 90% of the *S. flexneri* isolates were also resistant to ampicillin and chloramphenicol ($P < 0.0001$).
Conclusion Estimates of incidence of *Shigella* infection in the community are 10-fold to 100-fold greater than those found from routine government surveillance. The high prevalence of *Shigella* strains resistant to multiple antibiotics adds urgency to the development of a vaccine to protect against shigellosis in this region of Thailand.

Keywords Dysentery, Bacillary/epidemiology/microbiology; Diarrhea/epidemiology; Epidemiologic surveillance; Shigella/isolation and purification; Shigella flexneri; Shigella sonnei; Drug resistance, Microbial; Health facilities; Patient acceptance of health care; Epidemiologic studies; Thailand (*source: MeSH, NLM*).

Mots clés Dysenterie bacillaire/épidémiologie/microbiologie; Diarrhée/épidémiologie; Surveillance épidémiologique; Shigella/isolement et purification; Shigella flexneri; Shigella sonnei; Résistance microbienne aux médicaments; Equipement santé; Acceptation des soins; Etude analytique (Epidémiologie); Thaïlande (*source: MeSH, INSERM*).

Palabras clave Disentería bacilar/epidemiología/microbiología; Diarrea/epidemiología; Vigilancia epidemiológica; Shigella/aislamiento y purificación; Shigella flexneri; Shigella sonnei; Resistencia microbiana a las drogas; Instituciones de salud; Aceptación de la atención de salud; Estudios epidemiológicos; Tailandia (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: الزحار، الزحار العصوي، وبائيات الزحار، مكروبيولوجيا الزحار، الإسهال، وبائيات الإسهال، ترصُّد وبائي، الشيغيلا، استفراد وتنقية الشيغيلا، الشيغيلا الفلكسنرية، الشيغيلا السونية، المقاومة للأدوية، مقاومة المكروبات للأدوية، المرافق الصحية، قبول المرضى للرعاية الصحية، دراسة وبائية، تايلاند. (**المصدر: رؤوس الموضوعات الطبية، المكتب الإقليمي لشرق المتوسط**)

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Voir page 745 le résumé en français. En la página 745 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية في صفحة **745**.

Introduction

As Thailand makes the transition from a developing country to an industrialized one, the shift from rural to urban living, increased life expectancy and other demographic changes are transforming the health problems of its population. For example, the incidence of bacillary dysentery detected by the government's routine national surveillance system decreased more than 6-fold between 1991 and 1999, from 1.3/10 000 population per year to 0.2/10 000 population per year (1, 2). Over the past decade, the reported average annual incidence

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of bacillary dysentery among children less than 5 years old was 2.7/10 000 children per year. But in contrast to government data, the incidence of shigellosis detected by active surveillance among children in this age group in the 1980s in urban Bangkok was more than 100-fold higher at 640/10 000 children per year (3).

The observed discrepancy between government statistics obtained by passive surveillance and shigellosis rates detected by active surveillance highlights a fundamental problem in the surveillance methods used. In studies using passive surveillance, cases are detected when patients present to a health-care provider participating in surveillance. In active surveillance studies, health-care providers or other study staff visit each member of the study population at regular intervals and enquire about disease episodes occurring since the last visit. Passive surveillance should ideally detect all treated episodes. But there is always a risk that patients may seek treatment from health-care providers who are not participating in surveillance activities. Thus, rates estimated by passive surveillance may underestimate true incidence rates.

Active surveillance may detect more disease-episodes. However, these episodes will include mild episodes of enteric infection that do not require treatment and may, from the policy-maker's perspective, be irrelevant. In addition, active surveillance requires considerable logistical and financial resources. On balance, experts frequently prefer passive surveillance to estimate the relevant disease burden of diarrhoeal diseases, such as shigellosis, as well as for trials of other vaccines to protect against diarrhoeal diseases (4, 5). A second limitation that may lead to an underestimate of true disease rates is the lack of sensitivity of traditional microbiological culture methods. *Shigella* is a sensitive organism that will perish in a less than optimal environment. Delays in plating or being kept at an unsuitable ambient temperature will result in a substantial reduction in case-detection rates. Reliance on traditional culture methods therefore leads to an underestimate of the actual burden of shigellosis.

To estimate the burden of shigellosis in a semi-rural area of Thailand more accurately, we conducted a comprehensive passive surveillance study of treatment centres and corrected our findings to account for missed cases and the use of traditional microbiology methods that have limited sensitivity.

Methods

Study population

The study area is located in the Kaengkhoi district, Saraburi Province, Thailand, which is approximately 100 km north of Bangkok. The area includes a small city with some industry; it is surrounded by rural villages and residents depend on agriculture for their income. Data from the 2001 census maintained by government health-care officers show a total population of 80 141 in the catchment area, including 5686 (7%) children less than 60 months of age.

Health-care system

Health-care utilization in the Kaengkhoi district has been reviewed in detail (6). In brief, the health-care system has three tiers with the first point of contact being the community health centre; this is usually a free-standing structure staffed by one or more nurses who provide basic health services, stabilize emergency patients for transport elsewhere and perform uncomplicated deliveries. There are 20 community health centres in the catchment area. Patients who cannot be adequately cared for at the community centre are transferred to the district hospital in Kaengkhoi, which is staffed by internists, paediatricians and surgeons. Patients who require subspecialty services or therapies not available in the district hospital are transferred to the provincial hospital near Kaengkhoi. Some doctors working at government hospitals earn extra income by seeing patients at their private clinics in the evenings. A survey conducted in 2000 identified 16 private clinics in the study area. Not all patients seek care at public or private clinics; some patients treat themselves with over-the-counter pharmaceuticals or traditional products. Residents are assigned to government health centres, which may be the community health centre or the outpatient department of a hospital. Government policy encourages patients to see their assigned primary health-care provider by charging reduced fees for seeing the assigned provider. All community health centres in the study area, the district hospital and the provincial hospital participated in the surveillance study.

Study design

We estimated the burden of diarrhoea and shigellosis in the Kaengkhoi district occurring between 1 May 2000 and 1 May 2003 using population-based, surveillance of treatment centres. The study followed a generic protocol (5), which was adapted by staff and collaborators of the Diseases of the Most Impoverished Programme. Consenting patients of all ages with diarrhoea or dysentery who presented to participating health-care providers were included in the study. Diarrhoea was defined as three or more loose bowel movements occurring during a 24-hour period; dysentery was defined as one or more loose bowel movements with visible blood; persistent diarrhoea was defined as diarrhoea lasting for more than 14 days; and fever was defined as an axillary temperature of $\geqslant$ 37.5 °C. New episodes of diarrhoea were defined as those occurring after three or more days free of diarrhoea or dysentery. All consenting patients who had a history of diarrhoea lasting for three days or more were eligible to participate.

For every patient presenting with diarrhoea, a case-report form, describing demographic information, medical history and the care plan, was completed and two specimens, rectal swabs or bulk stool, were obtained. One swab was placed in buffered glycerol saline (BGS) for plating and the other in phosphate-buffered saline for polymerase chain reaction (PCR) at a later time. The specimens were refrigerated and transported daily in a cool box to the central laboratory.

Patients with laboratory-confirmed shigellosis who enrolled after 1 May 2002 were visited on days 3, 7, 14 and 90 after presentation. At these follow-up visits, a questionnaire was completed that recorded demographic information, past medical history, intercurrent events since presentation and planned management. No additional specimens were obtained during these visits. (Before 1 May 2002 there was no structured follow-up schedule so no data are available for patients presenting before this date.)

Treatment uptake

To estimate the proportion of cases of diarrhoea and dysentery missed by passive surveillance, we conducted a community-based cluster survey of treatment-seeking behaviour in 2002 (6). In brief, interviews were conducted with 224 of 19 786 households who were part of the study population to determine their first choice of treatment for diarrhoea and dysentery.

Respondents were asked where they sought care for diarrhoea and dysentery occurring in children (aged < 5 years) and adults (aged > 15 years). Health centres or hospitals were the first treatment choice for 78% of households where children had dysentery (95% confidence interval (CI) = 63–94%); and they were the first choice for 64% of households where children had diarrhoea (95% CI = 54–74%). Health centres and hospitals were also the first choice of 61% of households where adults had dysentery (95% CI = 40–82%) and 35% of households where adults had diarrhoea (95% CI = 17–54%). However, 6% of households said their first choice for treatment was a drug vendor, self-treatment or private practitioner for children with dysentery (95% CI = –2% to 13%); these options were the first choice for 7% of households where children had diarrhoea (95% CI = 0–14%). In 3% of households, these options were the first choice for adults with dysentery (95% CI = –1% to 8%), and in 6% of households they were the first choice for adults with diarrhoea (95% CI = –2% to 13%). Private practitioners were not included in the survey because only a relatively small proportion of patients with diarrhoea and dysentery chose them, and logistical considerations would have made it disproportionately difficult to include them in the network.

Microbiology

Nearly half of the specimens for which transport time was recorded (46%; 2515/5423) arrived at the laboratory on the day of collection; 34% (1859/5423) arrived on the day after collection; and 10% (547/5423) arrived two days after collection. The remaining 9% (502/5423) were transported within 3–4 days of collection.

At the laboratory at Saraburi Regional Hospital, specimens in BGS were plated on MacConkey agar and *Salmonella–Shigella* agar. Biochemical reactions of colonies were evaluated in triple sugar iron agar and lysine–indole motility medium. Colonies 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. Antimicrobial susceptibility testing was done by disc diffusion following standardized National Committee for Clinical Laboratory Standards methods. Strains were stored at –70 °C for confirmation. The species, serotype and subtype of *Shigella* strains collected between May 2000 and April 2002 were confirmed at the WHO National *Salmonella* and *Shigella* Center, Ministry of Public Health, Nonthaburi, and from May 2002 until the end of the study in May 2003 at Thammasat University, Rangsit Center, Patumthani.

Polymerase chain reaction

To estimate the proportion of cases missed by the use of traditional microbiology, we used PCR to detect *Shigella* DNA in 320 faecal specimens. The methods used in this study have been described previously (7).

Data management and analysis

Data from all case-report forms were double entered into customized data-entry programmes (FoxPro, Microsoft, Redmond, WA, USA). Data management included programs to check errors as well as consistency. Binary data analysis was performed using χ^2 tests. Student's *t*-test was used to analyse normally distributed data; for non-normally distributed data, the Wilcoxon rank-sum and Kruskal–Wallis tests were applied. A logistic regression model was used to test the association between clinical presentation and shigellosis. The model was adjusted for the age of the individuals because this is likely to influence presentation. Data were analysed with SAS software (SAS Institute, Cary, NC, USA). A two-tailed *P*-value < 0.05 was considered significant.

Incidences were calculated using age-specific denominators for the population residing in the catchment area in 2001. We calculated 95% confidence intervals for the differences in incidences using the Wilson score method (8). Because the observation period lasted 36 months, we assumed that each person residing in the study area contributed 36 months of person–time to the denominator. The number of age-specific disease-episodes was used as the numerator.

Estimates of the crude incidence of shigellosis were corrected by calculating the number of cases missed due to the low sensitivity of microbiological culture methods and the number of patients who did not make use of health-care providers participating in the study; this is analogous to the approach suggested by Crump et al. (*9*). Rates were corrected for four subgroups: children < 60 months of age with diarrhoea, participants ⩾ 60 months of age with diarrhoea, children < 60 months of age with dysentery, and participants ⩾ 60 months of age with dysentery. Because the health-care utilization surveys did not enquire about treatment behaviour for children aged between 5 years and 15 years it was assumed that the treatment behaviour for this age group was similar to that of participants > 15 years of age.

The proportion of culture-negative *Shigella* cases that tested positive by PCR was multiplied by the number of culture-negative *Shigella* cases of diarrhoea and dysentery detected during the surveillance period. This product expresses the estimated number of cases missed by culture methods. The fraction of cases missed by passive detection was estimated on the basis of a health-care utilization survey (6). The total number of cases (missing + detected cases) was computed as follows: (detected cases)(1/fraction missed by culture)(1/fraction missed by incomplete health-care utilization). The calculation is shown in the Appendix (available on web version only at: http://www.who.int/bulletin). Incidence calculations were computed using Excel XP spreadsheets (Microsoft, Redmond, WA, USA).

Ethical approval and informed consent

Verbal consent was obtained from each participant (or the parent or guardian in the case of children) following an explanation of the purpose of the study. The study received approval from the local government of Kaengkhoi district, Saraburi Province, Thailand; the Ministry of Public Health at Nonthaburi; the ethics review committee of the London School of Hygiene and Tropical Medicine; and the WHO Secretariat Committee for Research Involving Human Subjects.

Results

During the 3 years of the study, 8612 individuals presented to health facilities with diarrhoea; 2076 were not included because they refused to give consent or did not meet the criteria for diarrhoea or dysentery described above (Fig. 1). Of the remaining 6536 patients enrolled, 1622 (25%) were children aged < 5 years. The estimated incidence of treated diarrhoea in the population of children younger than 5 years was 95 cases/1000 children per year (95% CI = 88–103); the

Fig. 1. **Flow of participants through the study**

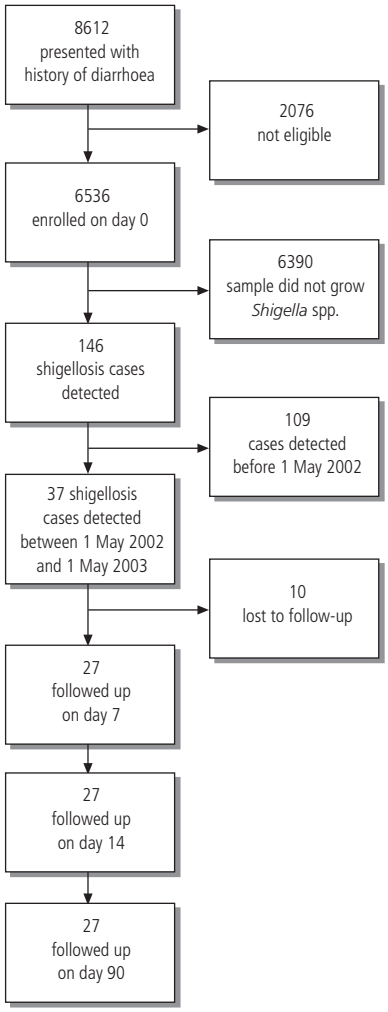
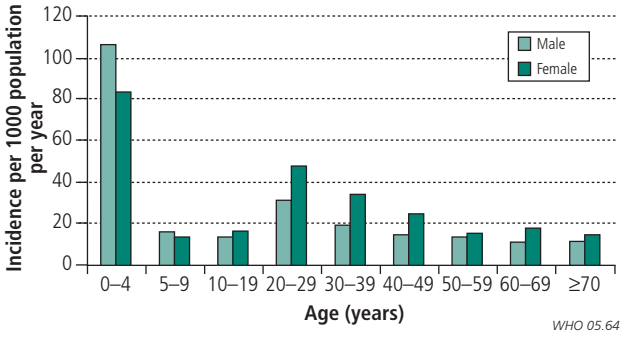


Fig. 2. **Incidence of treated diarrhoea in Kaengkhoi district, Saraburi Province, Thailand, by age and sex, 2000–03**



incidence among those ⩾ 5 years of age was 22/1000 population per year (95% CI = 21–23). The incidence was greatest among children aged < 10 years and among adults aged 20–30 years (Fig. 2). Among 6536 patients with diarrhoea, 539 (8%) reported a history of dysentery. The estimated incidence of treated dysentery was 15/1000 children aged < 5 years per year (95% CI = 12–19) and 1/1000 population aged ⩾ 5 years per year (95% CI = 1.0–1.5).

Of 6536 stool specimens from patients with diarrhoea or dysentery, 146 (2%) grew *Shigella* organisms by standard culture methods (Fig. 1). In all, *Shigella* species were isolated in 39 (7%) of the 539 patients with a history of dysentery. A real-time PCR targeting *ipaH*, a gene characteristic of all four *Shigella* species as well as enteroinvasive *Escherichia coli*, was positive in 19 (95%) of 20 culture-positive specimens (95% CI = 77–100%). In 12 (24%) of 50 *Shigella* culture-negative specimens (95% CI = 13–38%) from children aged < 60 months who presented with dysentery, *ipaH* was detected. Similarly, PCR was positive for 12 (24%) of 50 *Shigella* culture-negative specimens (95% CI = 12–38%) from adults presenting with dysentery, 10 (10%) of 100 specimens (95% CI = 5–17%) from children with culture-negative diarrhoea, and 14 (14%) of 100 specimens (95% CI = 8–23%) from adults with diarrhoea.

The overall uncorrected incidence of shigellosis was 0.6/1000 population per year (95% CI = 0.5–0.8). The unadjusted incidence of treated shigellosis was highest among children aged < 5 years (4/1000 children per year; 95% CI = 3–6) and significantly lower among individuals aged ⩾ 5 years (0.3/1000 population per year; 95% CI = 0.2–0.5) ($P < 0.001$) (Fig. 3). When we considered the number of cases likely to have been missed due to the lack of sensitivity of traditional culture methods plus the number of people who did not use health-care providers participating in surveillance, the overall incidence of shigellosis was 10/1000 population per year (95% CI = 10–11). The incidence of shigellosis among children aged < 5 years was 22/1000 children per year (95% CI = 19–27); among participants aged ⩾ 5 years the incidence was 9.5/1000 population per year (95% CI = 9–10). (See the Appendix (available on web version only at: http://www.who.int/bulletin) for additional information.)

Children aged < 5 years were more likely to be febrile (41%; 659/1618) than patients aged ⩾ 5 years (15%; 758/4918; $\chi^2 = 460$; $P < 0.0001$). Of the patients from whom *Shigella* organisms were isolated, 59% (86/146) had fever at the time of presentation in contrast to 26% (1331/5059) of non-*Shigella* patients ($\chi^2 = 121$; $P < 0.0001$). After adjusting for age, isolation of *Shigella* species remained associated with the presence of fever ($P < 0.0001$). Fever was detected in a similar percentage of patients infected with *S. flexneri* and *S. sonnei*.

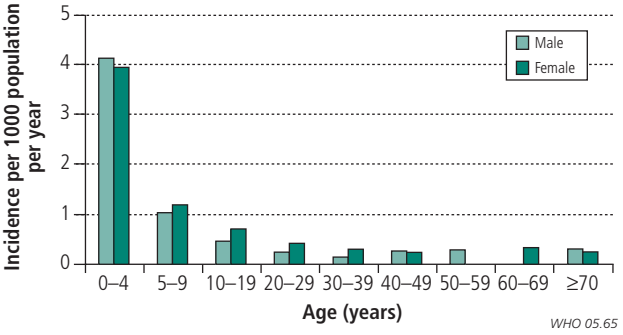
Of 37 patients with culture-confirmed shigellosis who were enrolled between 1 May 2002 and 1 May 2003, 27 (73%) were followed up until day 90 (Fig. 1). Patients with *S. flexneri* infections had diarrhoea for a longer period (median duration = 3 days; 95% CI = 2–6 days) than those with *S. sonnei* infection (median = 2 days; 95% CI = 2–6 days), but this difference was not statistically significant ($P = 0.149$) (data not shown). Two of 146 shigellosis patients (aged 25 years and 4 years) were hospitalized but had uneventful recoveries. Two patients died: a 33-year-old patient who had been treated for AIDS and persistent diarrhoea and a 72-year-old patient who died 2 days after being admitted with dysentery.

Of the 146 *Shigella* strains isolated during the surveillance period, 22 (15%) were *S. flexneri* and the others were *S. sonnei*. No *S. dysenteriae* or *S. boydii* strains were detected. Of the 22 *S. flexneri* isolates, the three most frequently encountered serotypes were 2a (36%), 1b (23%) and 3b (28%). Of 124 *S. sonnei* isolates tested, 111 (90%) were resistant to tetracycline, 94% to co-trimoxazole (trimethoprim–sulfamethoxazole), 6% to ampicillin, and 2% to chloramphenicol. Of the *S. flexneri*

isolates tested, 21 of 22 (96%) were resistant to tetracycline, and 18 of 20 (90%) were resistant to co-trimoxazole. Altogether, 18 of 20 (90%) *S. flexneri* isolates were also resistant to ampicillin in contrast to only 7 of 117 (6%) *S. sonnei* isolates ($P < 0.0001$). Similarly 14 of 14 *S. flexneri* isolates were resistant to chloramphenicol but only 2 of 95 *S. sonnei* isolates were resistant (Table 1).

There was a seasonal pattern of dysentery and episodes of infection with *S. sonnei* and *S. flexneri* (Fig. 4). The yearly peak of dysentery and *S. sonnei* incidence followed the hottest months of the year, April–May, and coincided with the onset of the rainy season. During the summer months of 2001, higher numbers of cases of dysentery and *S. sonnei* were detected compared with the preceding and following years. The lowest shigellosis rates were observed during the cooler winter months, November–March.

Fig. 3. **Incidence of culture-proven shigellosis in Kaengkhoi district, Saraburi Province, Thailand, by age and sex, 2000–03**



Discussion

Our surveillance study, conducted over 3 years in a semi-rural part of Thailand, made several new observations about the burden, severity and seasonality of shigellosis. The *Shigella* isolates detected during the surveillance study provide new information about the serogroups and types in circulation as well as their antimicrobial resistance.

We found an overall culture-confirmed shigellosis incidence of 0.6/1000 population per year and an incidence of 4.1/1000 children aged < 5 per year. Government statistics — which like our surveillance study make use of surveillance in treatment centres but, unlike our study, do not systematically collect faecal specimens to culture *Shigella* — estimated the national incidence of shigellosis among children < 60 months of age at 2.7/1000 children per year during the 1990s (*1*). By following the approach used by Crump et al. (*8*) to estimate the true burden of typhoid fever in Bilbeis, Egypt, we adjusted our directly measured incidence for two parameters that may lead to underestimation: the escape of cases from the surveillance system and the lack of sensitivity of traditional microbiological culture methods. We estimated the number of cases we had missed for four separate subgroups chosen based on perceptions of vulnerability (children versus adults) and disease severity (dysentery versus diarrhoea). When we adjusted for the cases likely to have been missed, the overall incidence of shigellosis increased by more than 1 order of magnitude: from 0.6 to 10.4/1000 population per year. The shigellosis incidence in children < 60 months old increased roughly 5-fold: from 4.1 to 22.4/1000 children per year.

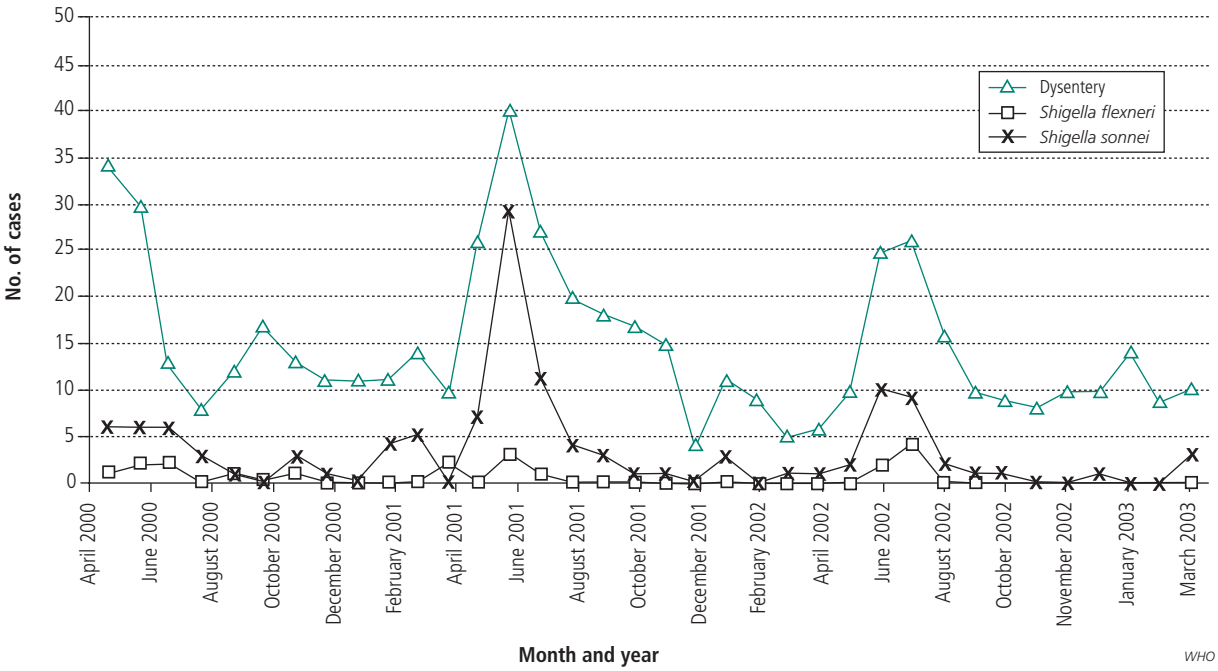
Our approach has two limitations. First, we assume that all diarrhoea patients with stool specimens containing *ipaH* are infected with *Shigella* species. It seems unlikely that *ipaH* at this site is derived from organisms other than *Shigella* species, but the presence of *Shigella* could indicate colonization and not infection. Studies using the same laboratory methods failed to detect *ipaH* in healthy volunteers from Bangkok (O. Sethabutr et al., unpublished data, 2003) which makes colonization without

Table 1. **Antimicrobial susceptibility pattern of *Shigella* isolates collected in Kaengkhoi district, Saraburi Province, Thailand**

		Organism			
		Shigella flexneri		*Shigella sonnei*	
Drug	Zone[a]	No. samples tested	No. resistant[b]	No. samples tested	No. resistant
Amikacin	≤14	14	0 (0)	95	1 (1)
Ampicillin	≤13	20	18 (90)	117	7 (6)
Amoxicillin and clavulanic acid	≤13	8	4 (50)	29	2 (7)
Cefazolin	≤14	14	0	95	2 (2)
Cefotaxime	≤14	14	0	95	0
Cephalothin	≤14	20	5 (25)	124	12 (10)
Chloramphenicol	≤12	14	14 (100)	95	2 (2)
Ciprofloxacin	≤15	6	0	29	0
Co-trimoxazole	≤10	20	18 (90)	124	116 (94)
Doxycycline	≤12	14	13 (93)	95	92 (97)
Gentamicin	≤12	20	1 (5)	124	0
Kanamycin	≤13	20	0	124	0
Nalidixic acid	≤13	6	0	29	0
Norfloxacin	≤12	20	0	117	0
Streptomycin	≤11	14	14 (100)	95	94 (99)
Tetracycline	≤14	22	21 (95)	124	111 (90)

[a] Zone size is indicated in millimetres.
[b] Figures in parentheses are percentages.

Fig. 4. **Seasonal distribution of dysentery and shigellosis in Kaengkhoi district, Saraburi Province, Thailand, April 2000–March 2003**



infection a less likely explanation for the relatively high rate of *ipaH* detection in patients with culture-negative diarrhoea. However this finding cannot exclude *Shigella* colonization and, thus, there may be an alternative etiology for reported diarrhoea or dysentery episodes in some cases. Second, our health-care utilization survey indicated that a number of individuals first saw health-care providers who were not taking part in the surveillance study. These individuals may have attended hospitals and clinics participating in the study at a later stage in their disease. It is not clear what proportion of patients were thus detected at a later stage. Taking these limitations into consideration, our adjusted estimates have to be viewed as the highest potential disease rates.

In Thailand, the most commonly isolated Shigella species over the past two decades have been *S. flexneri* (79%) and *S. sonnei* (15%) (10–12). Only 4% of isolates were *S. dysenteriae*, and 2% were *S. boydii*. In our survey, *S. sonnei* was the dominant *Shigella* species. Previous studies have indicated that *S. sonnei* is dominant in more developed countries (13) so our findings may be confirming the successful economic transition in the study area, which is within commuting distance to Bangkok, Thailand's highly industrialized capital. In contrast to our community-based study, *S. flexneri* infections have been more frequently detected in hospital-based surveillance studies (10–12, 14). One explanation for this could be that *S. flexneri* infections result more frequently in hospitalizations than *S. sonnei* infections. The notion that *S. sonnei* is less virulent than *S. flexneri* is supported by the possibly shorter duration of diarrhoea occurring among patients infected with *S. sonnei* than among those with *S. flexneri* in our study.

A study at a rural hospital in Nakhon Nayok Province, Thailand, between 1985 and 1992 found resistance to ampicillin in 72–90% of *Shigella* strains and an increase in resistance to co-trimoxazole from 29% to 89% over the study period (15). No resistance was found against nalidixic acid or cefotaxime. A study in Bangkok in 1988 found resistance by the four *Shigella* species to commonly used antibiotics (11). Overall, 87% of *Shigella* isolates were resistant to ampicillin, 84% to co-trimoxazole, and 0.1% to nalidixic acid. We found that by 2003, at least 90% of *S. flexneri* isolates were resistant to ampicillin, co-trimoxazole and tetracycline, probably reflecting a survival advantage for resistant strains in the presence of frequent consumption of antimicrobials in the study site.

Our findings are likely to be important in vaccine development and introduction. Shigellosis still causes a considerable burden in Kaengkhoi. The observed fluctuations in incidence during the three-year surveillance period, including a cluster of cases in summer 2001, indicate the potential for outbreaks as have been previously described in Thailand (14, 16). Any vaccine designed to protect against shigellosis in this region of Thailand should protect against *S. flexneri*, which has caused more hospitalizations in the past, as well as *S. sonnei*, which caused the majority of shigellosis cases in this study. The dominant *S. flexneri* serogroups are 1b, 2a and 3b. It is uncertain whether cross-protection exists between *Shigella* serogroups, thus there may be a need for a polyvalent vaccine to protect against *S. flexneri* 1b, 2a, and 3b as well as *S. sonnei*. ■

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Résumé

Estimation de la charge de shigellose en Thaïlande : étude de surveillance en population sur 36 mois

Objectif Évaluer les taux d'incidence de la shigellose dans le district de Kaengkhoi, situé dans la province du Saraburi, en Thaïlande.

Méthodes Surveillance en population de la shigellose à partir des centres de traitement. Les taux d'incidence de la shigellose traitée obtenus ont été corrigés pour tenir compte du nombre de cas passés inaperçus en raison de la faible sensibilité des méthodes de culture microbiologique et du recours des sujets à des prestataires de soins de santé ne participant pas à l'étude.

Résultats L'incidence globale annuelle non corrigée de la shigellose était de 0,6/1000 habitants [intervalle de confiance à 95 % (IC) : 0,5-0,8]. L'incidence non ajustée de la shigellose traitée était plus élevée chez les enfants de moins de 5 ans (4 cas pour 1000 enfants et par an, intervalle de confiance à 95 % : 3-6) et notablement plus faible chez les individus de 5 ans et plus (0,3 cas pour 1000 habitants et par an, IC à 95 % : 0,2-0,5, $p < 0,001$). L'ajustement pour tenir compte des cas susceptibles de passer inaperçus en raison des méthodes de culture et de surveillance utilisées a conduit à multiplier par 5 environ les estimations. La majorité des isolats de *Shigella* (122/146, 84 %) étaient des isolats de *S. sonnei*, les autres étant constitués de *S. flexneri*. Parmi les 22 isolats de *S. flexneri*, on rencontrait le plus souvent les trois sérotypes suivants : 2a, (36 %), 1b (28 %) et 3b (28 %). Il a été constaté que 90 à 95 % des isolats de *S. sonnei* et de *S. flexneri* étaient résistants à la tétracycline et au co-trimoxazole. A la différence des isolats de *S. sonnei*, plus de 90 % des isolats de *S. flexneri* étaient également résistants à l'ampicilline et au chloramphénicol ($p < 0,0001$).

Conclusion L'étude aboutit à des estimations de l'incidence des infections à *Shigella* dans la communauté 10 fois à 100 fois supérieures à celles fournies par le programme de surveillance systématique mené par le gouvernement. La forte prévalence des souches de *Shigella* résistantes à plusieurs antibiotiques rend plus urgente encore la mise au point d'un vaccin apportant une protection contre la shigellose dans cette région de la Thaïlande.

Resumen

Estimación de la carga de shigelosis en Tailandia: estudio de vigilancia poblacional de 36 meses

Objetivo Estimar las tasas de incidencia de shigelosis en el distrito de Kaengkhoi de la provincia de Saraburi, en Tailandia.

Métodos Se adoptaron medidas de vigilancia poblacional de la shigelosis en los centros de tratamiento. Las tasas de shigelosis tratada detectadas se corrigieron en función del número de casos perdidos debido a la baja sensibilidad de los métodos de cultivo microbiológico y al hecho de que muchos participantes utilizaron los servicios de dispensadores de atención que no tomaron parte en el estudio.

Resultados La incidencia global no corregida de shigelosis fue de 0,6/1000 habitantes al año (intervalo de confianza (IC) del 95% = 0,5-0,8). La incidencia no ajustada de shigelosis tratada fue máxima entre los menores de 5 años (4/1000 niños al año; IC95% = 3-6) y significativamente inferior entre las personas ⩾ 5 años (0,3/1000 habitantes al año, IC95% = 0,2-0,5; $P < 0,001$). El ajuste en función de los casos probablemente perdidos como resultado de los métodos de cultivo y de vigilancia hizo que las estimaciones se multiplicaran aproximadamente por cinco. La mayoría de los aislados de *Shigella* (122/146; 84%) fueron de *S. sonnei*; el resto reveló la presencia de *S. flexneri*. De los 22 aislados de *S. flexneri*, los tres serotipos hallados con mayor frecuencia fueron 2a (36%), 1b (23%) y 3b (28%). El 90%-95% de los aislados de *S. sonnei* y *S. flexneri* eran resistentes a la tetraciclina y al cotrimoxazol. A diferencia de los aislados de *S. sonnei*, más del 90% de los aislados de *S. flexneri* eran también resistentes a la ampicilina y el cloranfenicol ($P < 0,0001$).

Conclusión Las estimaciones aquí obtenidas de la incidencia de infección por *Shigella* en la comunidad son entre 10 y 100 veces mayores que las reveladas por la vigilancia pública sistemática. La alta prevalencia de cepas de *Shigella* resistentes a varios antibióticos hace aún más apremiante el desarrollo de una vacuna que proteja contra la shigelosis en esta región de Tailandia.

ملخص

تقدير عبء داء الشيغيلات في تايلاند: دراسة ترصُّد مُرْتَكِزة على السكان دامت 36 شهراً

الهدف: تقدير معدلات حدوث داء الشيغيلات في مقاطعة كينخوري في إمارة سارابوري في تايلاند.

الطريقة: أجريت دراسة ترصُّد مُرْتَكِزَة على السكان في مراكز معالجة داء الشيغيلات. وقد تم تصحيح معدلات كشف داء الشيغيلات المعالَج وذلك باحتساب عدد الحالات التي لم يتم احتسابها بسبب انخفاض الحساسية لطُرُق الزرع المكروبيولوجية أو باحتساب مدى انتفاع المشاركين بالدراسة من مقدمي الرعاية الصحية ممن لم يشاركوا في الدراسة.

الموجودات: بلغ معدل الحدوث الإجمالي غير المصحَّح لداء الشيغيلات 0.6 لكل ألف من السكان في العام، وذلك بفاصلة ثقة مقدارها 95% ، وتراوح معدل الحدوث بين 0.5 و 0.8. كما بلغ معدل الحدوث الإجمالي غير المصحَّح أعلى مستوى له بين الأطفال غير المعالَجين دون خمس سنوات من العمر 4 لكل ألف طفل في العام، بفاصلة ثقة مقدارها 95% وتراوح معدل الحدوث بين 3 و 6، فيما كان منخفضاً بشكل ملحوظ بين من تزيد أعمارهم عن 5 سنوات فبلغ 0.3 لكل ألف من السكان في العام، بفاصلة ثقة 95% وقيمة احتمال تقل عن 0.001. إن تصحيح معدل الحالات التي كانت ستفقد نتيجة لاستخدام المزارع وطُرُق الترصُّد يؤدي لزيادة التقديرات بمقدار قد يصل إلى خمسة أضعاف. وكان معظم المستفردات من الشيغيلات السونية، فيما كان البقية الباقية منها من الشيغيلات الفلكسنرية .ومن بين 22 من المستفردات الفلكسنرية، كانت الأنماط المصلية الأكثر مصادفة هي 2a في 36% من المستفردات، و 1b في 23% من المستفردات و 3b في 28% من المستفردات. وقد كان 90-95% من المستفردات من الشيغيلات السونية والفلكسنرية مقاومة للتتراسيكين وللكوتريموكسازول. وبالمقابل فإن أكثر من 90% من مستفردات الشيغيلات الفلكسنرية مقاومة للأمبيسلين وللكلورامفنكول بقيمة احتمال تقل عن 0.0001 وذلك على عكس الحال في مستفردات الشيغيلات السونية.

الاستنتاج: تبلغ تقديرات معدل حدوث العدوى بالشيغيلات في المجتمع 10-100 ضعف ما توضحه دراسات الترصُّد الروتينية الحكومية . ويضيف المعدل المرتفع لانتشار ذراري الشيغيلات المقاومة للمضادات الحيوية المزيد من الإلحاح على تطوير لقاح يقي من داء الشيغيلات في هذه المناطق من تايلاند.

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Appendix 1. **Incidence correction for missed cases**

Diagnosis by age group	Category											
	Population[a]	Cases[b]	Incidence[c]	All presentations[d]	Culture-negative presentations[e]	Polymerase chain reaction positive[f]	False negatives[g]	False negatives + culture proven cases[h]	Adjusted incidence[i]	Missed cases[j]	Adjusted cases[k]	Adjusted incidence[l]
Dysentery												
< 60 months	5 686	18	1.06	260	242	24%	58	76	4.5	22%	97	5.7
⩾ 60 months	74 455	21	0.09	280	259	24%	62	83	0.4	39%	136	0.6
Total (y)[m]	80 141	39	0.16	540	501	–	120	159	0.7	–	233	1.0
Diarrhoea												
< 60 months	5 686	51	2.99	1358	1307	10%	131	182	10.7	36%	284	16.7
⩾ 60 months	74 455	56	0.25	4638	4582	14%	642	698	3.1	65%	1994	8.9
Total (z)[n]	80 141	107	0.45	5996	5889	–	773	880	3.7	–	2278	9.5
All[o]												
< 60 months	5 686	69	4.05	1618	1549	–	189	258	15.1	–	382	22.4
⩾ 60 months	74 455	77	0.34	4918	4841	–	704	781	3.5	–	2130	9.5
Total	80 141	146	0.61	6536	6390	–	893	1039	4.3	–	2512	10.4

[a] Population in the study area in 2001.
[b] Culture-proven shigellosis cases collected over 36 months (April 2000–May 2003).
[c] Shigellosis incidence = b/a * 1000/3 = rate/1000 population per year.
[d] All presentations fulfilling enrolment criteria during the 36-month study period.
[e] Culture-negative presentations = d – b.
[f] % of culture-negative samples that were found to be positive by polymerase chain reaction.
[g] Estimated number of false negatives = e*f.
[h] Sum of estimated cases plus culture-proven cases = g + b.
[i] Shigellosis incidence adjusted for the estimated number of false negatives (column g) = h/a * 1000/3 = rate/1000 population per year.
[j] % of individuals who stated during interviews they would not make use of health-care providers participating in the study.
[k] Cases adjusted for false negatives and cases missed by passive surveillance = h*100/(100-j).
[l] Shigellosis incidence adjusted for number of false negatives (column g) and cases missed by passive surveillance = k/a*1000/3 = rate/1000 population per year.
[m] Total number of dysentery patients presenting with dysentery = number of patients aged < 60 months + number of patients aged ⩾ 60 months.
[n] Total number of diarrhoea patients who did not present with dysentery = number of patients aged < 60 months + number of patients ⩾ 60 months.
[o] All patients = sum of dysenteric and non-dysenteric patients = y + z.