Thermophilic *Campylobacter* - Neglected Foodborne Pathogens in Cambodia, Laos and Vietnam

Abstract

Thermophilic *Campylobacter* are the most common bacterial cause of gastroenteritis in humans worldwide. Poultry and poultry products are the main sources for human infections. Epidemiological data concerning campylobacteriosis in Asia are limited. Overall, it is difficult to accurately assess the burden of *Campylobacter* infections. South-East Asia including Cambodia, Laos and Vietnam is known as a hotspot for emerging diseases. Campylobacteriosis is a problem of public health concern in these countries, hence. Epidemiological data are scarce. This is influenced by the limited number of laboratory facilities and lack of equipment and awareness in physicians and veterinarians resulting in the lack of surveys.

This review lists articles and reports on *Campylobacter* and campylobacteriosis in these developing third world countries. Subjects are prevalence of thermophilic *Campylobacter* in humans, animals and food and their resistance to several antibiotics.

Keywords: *Campylobacter*; Cambodia; Laos; Vietnam; Antibiotic resistance

Review Article

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Highlights

This review gives an overview about articles and reports on *Campylobacter* and campylobacteriosis in Cambodia, Laos and Vietnam. The knowledge about these objects is limited for the three countries. One topic in the literature is prevalence of thermophilic *Campylobacter* in humans and their relation to diarrhea. In Vietnam a prevalence rate up to 11% was reported. In Cambodia and Laos it was ever higher. Especially, children under five years of age were affected. Animals and food as source for human infections play an important role. Carriage of *Campylobacter* by different animal species and contamination rate of meat are generally high and can reach more than 70%. Resistance to antibiotics is of public health concern. High rates of resistance to nalidixic acid, erythromycin, tetracycline and ciprofloxacin were detected reaching sometimes 100% of isolates.

Introduction

Zoonoses are diseases and infections which can be transmitted from animals to humans or *vice versa.* Over 200 pathogens are recognized as zoonotic agents and classified as foodborne and non-foodborne agents. Zoonotic foodborne pathogens may cause human diseases after uptake of contaminated food or water. Several of these microorganisms can be found in the intestinal tract of healthy food-producing animals e. g. thermophilic *Campylobacter* species.

Thermophilic *Campylobacter* species are the most common bacterial cause of gastroenteritis in humans worldwide. Incidence and prevalence of campylobacteriosis have increased in both, developed and developing countries, over the last 10 years [1]. A dramatic increase in the number of reported cases was recognized in Australia, Europe, and North America. In the United States, an incidence of 14.3 campylobacteriosis cases per 100.000 inhabitants was reported for the period between 1996 and 2012 [2]. In Quebec, Canada an annual incidence of 35.2 cases per 100,000 persons was reported [3]. In Europe, *Campylobacter* has become the most frequently reported bacterial pathogen causing gastrointestinal infections in humans since 2005. In 2013, 214,779 confirmed cases were reported by the member states of the European Union (EU) which correlated with a notification rate of 64.8 per 100,000 inhabitants [4]. Hence, the number of fatal cases was very low with 0.05%. Data from African countries are limited and indicate that *Campylobacter* infections are most prevalent in children. In a study in Malawi, 14% of non-diarrheic children and 28% children with diarrhea were PCR positive for *C. jejuni* and *C. coli* [5]. *C. jejuni* and *C. coli* were also found to be endemic in children in Madagascar and Kenya [6,7]. Epidemiological data concerning campylobacteriosis in Asia are limited. A study from China reported that 5% of diarrheic patients were PCR positive for *C. jejuni*. The highest prevalence was detected in the cohort of children younger than 7 years [8]. Also in Japan and India *Campylobacter* infections occur quite frequently [9,10]. Overall, it is difficult to accurately assess the burden of *Campylobacter* infections in Asia owing to insufficient epidemiological data [1].

International travel, consumption of undercooked chicken and products thereof, environmental exposure, and direct contact with farm animals were recognized as risk factors for human campylobacteriosis [11]. The most important sources of foodborne campylobacteriosis are consumption of contaminated food, especially poultry products, unpasteurized milk and water. Broilers are the main source for thermophilic *campylobacters* to humans [12]. Studies in Switzerland estimated that 71% of human cases were caused by uptake of contaminated chicken meat [13,14]. The UK Food Standards Agency found 72.9% of fresh retail chicken *Campylobacter* positive with nearly 20% being highly contaminated [15]. Besides broilers, turkeys and ducks, and also cattle and pigs serve as reservoirs of thermophilic *Campylobacter*. *Campylobacter* contaminated water was responsible for outbreaks of human campylobacteriosis, but also for transmission within animal populations [1].

South-East Asia is known as a hotspot for emerging diseases. Part of the region is former French Indochina including Cambodia (Kingdom of Cambodia), Laos (Lao People´s Democratic Republic) and Vietnam (Socialist Republic of Vietnam) with a shared history since the 19th century. All three countries are developing third world countries suffering the aftermath of the Vietnam War. Campylobacteriosis is a problem of public health concern in these countries, hence. Epidemiological data are scarce. This may be caused by the limited number of laboratory facilities and lack of equipment and awareness in physicians and veterinarians resulting in the lack of surveys. A recent review of foodborne bacterial and parasitic zoonosis in Vietnam summarized a number of studies on thermophilic *Campylobacter* infections [16] but no data on the prevalence of campylobacteriosis are available for Laos and Cambodia.

Therefore, in this review we summarize literature on *Campylobacter* affecting human and animal populations, their prevalence as foodborne pathogen and the resistance to antibiotics in these countries from 1971 to 2016. We delineate knowledge and capability gaps, which will foster new research and surveillance programs. This will help to tackle the impact on public health that is caused by *Campylobacter* infections in the respective countries.

Methods and Research Data

Information presented in this review was collected by searching published studies on database including CABDIRECT, Science Direct, Pubmed and Google with keywords "*Campylobacter* and Vietnam", "*Campylobacter* and Laos", "*Campylobacter* and Cambodia". The searched publications were reviewed and relevant information was retrieved. All Articles or studies provided information on prevalence of thermophilic *Campylobacter* in humans, animals or food and/or information on antibiotic resistance in these bacteria. All articles and studies were in relation to South-East Asian countries of Cambodia, Laos and/or Vietnam.

Results and Discussion

Articles on *Campylobacter* in Cambodia, Laos and Vietnam

Thirty one publications were retrievable in Pubmed and other database concerning *Campylobacter* in Cambodia, Laos and Vietnam between 1971 and 2016. Nineteen articles were related to Vietnam, 3 articles to Laos and 9 articles to Cambodia. Eleven articles were related to antibiotic resistance but most of the papers dealt with investigations of the prevalence of *Campylobacter* in humans, animals and food.

Campylobacter in humans

An overview about papers concerning *Campylobacter* in humans in Vietnam, Laos and Cambodia is given in Table 1. The main source of human campylobacteriosis is the consumption of chicken meat, but meat of other species can also be contaminated with *Campylobacter*. Identification of thermophilic *campylobacters* was carried out by cultivation in combination with biochemical methods. Only recently, identification and differentiation by PCR assays was introduced. Detection rates ranged between 0 and 12% depending on country and the method of detection. *C. jejuni* was detected more often than *C. coli*. Children under 5 years of age are most frequently affected. The risk of infections seems to be correlated with undernutrition, poor hygiene, keeping of animals in the house, manure and wet litter in house yards and contaminated drinking water [17]. In Cambodia, 12% of 681 human faecal samples were tested positive by PCR assays [18]. Rates for Vietnam and Laos were below 5%. In an investigation in children with and without diarrhea in Ho Chi Minh City, Vietnam, 2.2% of stool samples were positive, but in the control group without diarrhea 2.6% samples were also found positive [19]. A similar result was reported from Cambodia. In Phnom Penh 4.7% *C. jejuni* and 1.5% *C. coli* were detected in diseased children at an age under 5 years and 6.2% *C. jejuni* and 2.4% *C. coli* in the control group [20]. It seems that *Campylobacter* is widespread in the population, but the mere presence of the bacteria in the gut is not inevitable related to clinical symptoms of campylobacteriosis.

In a detailed study from Cambodia, Osbjer et al. [18] could not detect *Campylobacter* in 681 stool samples by cultivation of frozen samples [18]. Hence, 66 *C. jejuni* and 16 *C. coli* were identified by multiplex PCR. In the group of children up to 15 years, *Campylobacter* was detected in 18.8% of the samples whereas only 7% to 8% of those of male and female group over 15 years were *C.* positive. Risk factors for human campylobacteriosis were slaughtering of domestic animals, allowance of animal access to sleeping and food preparation areas and eating of undercooked meat [17].

Campylobacter in animals and meat

In an investigation from the Mekong delta, Vietnam, the prevalence of *Campylobacter* in faeces of chickens, ducks and pigs was reported to be 31.9%, 23.9%, and 53.7%, respectively [21]. Similar results were found in Cambodia [18]. In 41.3% of swab and faeces samples of chickens, ducks, pigs and cattle *Campylobacter* was detected by multiplex PCR. 56.1% of chicken and 23.8% of duck samples were positive. 72.2% of pigs but only 5.3% of cattle samples were tested positive for *C. jejuni* and *C. coli*, respectively. *C. jejuni* was the dominant species in chickens and ducks, *C. coli* was more prevalent in pigs. The low prevalence rate of *Campylobacter* in cattle (5.3%) was similar to that in buffaloes in Laos i. e. 2% [22]. A remarkable difference was observed

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between cultivation and PCR assays. In contrast to 352 samples that were assessed to be positive by PCR assays (41.3%) only 106 samples were identified as *Campylobacter* positive by cultivation (12.4%). Cultivation of *Campylobacter* is difficult at least under field conditions because of their sensitivity to oxygen and changes in temperature.

Contamination rates of poultry products with thermophilic *Campylobacter* were determined to be between 15% and 35% in Vietnam (Table 2). Schwan, 2010 found 76.0% of swabs of chickens positive for *Campylobacter,* but none of the investigated meat samples was contaminated [23]. In Phnom Penh, Cambodia, was shown that 80.9% of poultry carcasses were contaminated [24]. The result was obtained by cultivation of *Campylobacter*. A lower contamination rate of 35.0% was reported for poultry products from markets in the capital of Cambodia [25]. *C. jejuni* (44.4%), *C. coli* (36.5%), *C. lari* (15.9%) and *C. upsaliensis* (3.2%) were identified among 63 *Campylobacter* isolates.

Table 1: Studies concerning presence of thermophilic *Campylobacter* in humans

Country	Region	Group	Method	Result	Reference
Vietnam	Red River	1,655 children under 5 years (one year of investigation)	Cultivation	150 *C. jejuni* and *C. coli* (43.2%) from 347 cultures isolated from 2,160 cases of diarrhoea	36
Vietnam	Hanoi	83 children under 3 years with persistent diarrhoea		No *Campylobacter*	37
Vietnam	Hanoi	291 children under 5 years with acute diarrhoea (one year of investigation)	Cultivation, enzyme immunoassay	4% *Campylobacter* positive stool samples	38
Vietnam	Ho Chi Minh City, southern Vietnam	1,309 stool samples of children up to 12 months with diarrhoea	Real-time PCR	152 *Campylobacter* positive (11.6%)	39
Vietnam	Ho Chi Minh City	1,419 stool samples of children under 5 years with diarrhoea	Cultivation	6 *Campylobacter* positive in 293 norovirus positive samples	40
Vietnam	Da Nang	987 U. S. Marines		No *Campylobacter*	41
Vietnam	Ho Chi Minh City	1,419 children with and 609 without diarrhoea over a one-year period	Cultivation	31 *Campylobacter* sp. in stools of diarrheal cases (2.2%) and 16 in samples without diarrhea (2.6%)	19
Vietnam	Hanoi	636 adults observed for 18 months	Cultivation	0.6 % of stool samples *Campylobacter* positive	42
Laos	Vientiane	880 patients with diarrhea in an 11 months period	Cultivation	2.4% *C. jejuni* and 2.0% *C. coli*	43
Laos	Vientiane	70 patients with diarrhoea in a 13 months period (most of them < 5 years)	Cultivation	2.9% *C. jejuni*	44
Cambodia	Thai-Cambodian border	65 stool specimen from children younger 2 years	Cultivation, latex agglu-tination test	16% *Campylobacter* positive	45
Cambodia	Thai-Cambodian border	487 children with diarrhoea under 5 years	Cultivation	107 out of 487 *Campylobacter* positive (22.0%)	46
Cambodia	Phnom Penh	600 children under 5 years with diarrhea and 578 children without diarrhoea	Cultivation	4.7% *C. jejuni* and 1.5% *C. coli* in diseased children; 6.2% *C. jejuni* and 2.4% *C. coli* in control group	20
Cambodia	No information	25 *C. jejuni* from children under 5 years	Multiplex PCR	Detection of capsule type	47
Cambodia	Villages in 3 provinces	681 stool samples	Cultivation, multiplex PCR	No *C.* detection by cultivation; 12% *Campylobacter* positive in PCR	17,18

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Table 2: Studies concerning presence of thermophilic *Campylobacter* in animals and meat.

Country	Region	Group	Method	Result	Reference
Vietnam	Hanoi	177 samples of raw food (poultry, pork, beef meat, fish, vegetables) from canteens	Cultivation	28.3% of poultry samples were contaminated with *C. jejuni*	48
Vietnam	Hanoi	100 samples from chicken breast	Cultivation	31.0% were positive for *Campylobacter*	49
Vietnam	Ho Chi Minh City	319 broiler carcasses	Cultivation	35.1% were positive for *Campylobacter*	50
Vietnam	Mekong delta	96 samples of chicken meat and 96 cloacal swabs from 20 farms	Cultivation, PCR	No *Campylobacter* from meat; 76.0 % of swab samples were *Campylobacter* positive	23
Vietnam	Ho Chi Minh City	150 chicken neck-skins	Cultivation	15.3% *Campylobacter* positive	51
Vietnam	Mekong delta	634 faecal samples from pigs, chickens, ducks	Cultivation, PCR	Animal level prevalence of *Campylobacter* was 31.9%, 23.9% and 53.7% for chickens, ducks and pigs	21
Vietnam	Hanoi	9 *Campylobacter* isolates from chicken and pork meat	Cultivation, PCR	Genotyping by PCR-based methods	29
Laos	Vientiane	82 caecum samples from cattle; 184 caecum samples and 100 bile samples from buffaloes	Cultivation	4 *Campylobacter* isolates from buffaloes	22
Cambodia	Phnom Penh	152 poultry carcasses	Cultivation	123 carcasses were positive for *Campylobacter*	24
Cambodia	Phnom Penh and peri-urban areas	180 samples from markets	Cultivation	63 samples (35.0%) positive for *Campylobacter* (28 *C. jejuni*, 23 *C. coli*, 10 *C. lari*, 2 *C. upsaliensis*)	25
Cambodia	Kampong Thom[a)]	36 monkeys (*Macaca fascicularis*)	Cultivation, PCR	36.1% were *Campylobacter* positive	26
Cambodia	Villages in 3 provinces	753 livestock samples	Cultivation, PCR	342 samples tested positive for *Campylobacter* (42.5%)	17
Cambodia	Villages in 3 provinces	853 livestock samples (cloacal swabs and faeces from chickens, ducks, pigs and cattle)	Cultivation, MALDI-TOF-MS, PCR	*Campylobacter* detected in 106 samples by cultivation and in 352 samples by PCR (41.3%)	18

[a)]kept in Japan

In a study concerning the prevalence of thermophilic *Campylobacter* in cynomolgus monkeys (*Macaca fascicularis*) kept in captivity and semi-free-range outdoor areas in Japan, these bacteria were detected in 36% of animals of a group imported from Cambodia, but not in animals from Vietnam [26]. Table 2 gives an overview about reports on *Campylobacter* in animals and meat in the three Southeast Asian countries.

Antibiotic resistance of *Campylobacter*

Information on antibiotic resistance of thermophilic *Campylobacter* isolates is very limited in Vietnam and Cambodia, and no was published data about antimicrobial susceptibility of *campylobacter*s in Laos were found. Disc diffusion, agar dilution and broth microdilution test were methods for determination of antibiotic resistance of *Campylobacter*. *Campylobacter* isolates were highly resistant to nalidixic acid (58% up to 100%; Table 3) with one exception of 7% [27]. Resistance to ciprofloxacin was in the range from 7% up to 100% (Table 3). Resistance rates to erythromycin were found between 0% and 100% depending on country, source or method of investigation.

In one report, no difference was found in the prevalence of resistance to several antibiotics between different host species [21]. The resistance profiles were identical for *C. jejuni* and *C. coli* isolates. Generally, the resistance rate of in *C. coli* isolates is higher than that of *C. jejuni*. Remarkable was resistance to chloramphenicol with up to 25% in some reports, because use of chloramphenicol is banned in animal breeding in Europe for more than 20 years, but it is still often used in many third world countries [28]. *C. coli* isolates were resistant to ciprofloxacin, nalidixic acid, streptomycin and tetracycline [29].

Resistance rates of Cambodian *campylobacter*s from chicken to ciprofloxacin reached 90.0% for *C. lari* isolates and was lower for *C. jejuni* and *C. coli* with 60.7% and 52.2%, respectively [25]. *C. coli* (30.4%) showed a higher resistance rate to erythromycin in comparison to *C. jejuni* (17.9%). Resistance to tetracycline varied around 50% whereupon *C. coli* showed the highest value (56.5%). *Campylobacter* isolated from faeces of monkeys were 100% sensitive to erythromycin and chloramphenicol [26]. Archawakulathep et al. [30] 2014 gave a good overview of perspectives on antimicrobial resistance in livestock and livestock products in ASEAN countries [30].

Table 3: Studies concerning antibiotic resistance of thermophilic *Campylobacter* of different origin.

Country	Region	Source	Number of Isolates Method of Investigation	Resistance Rate to	Reference
Vietnam	-	Human	88 isolates; MIC agar-plate dilution test	NA: 7% CIP: 7% AZM: 0%	27
Vietnam	Hanoi	Human		CIP: 27%	38
Vietnam	Mekong delta	Chicken	22 *C. jejuni* and 6 *C. coli*; Broth microdilution test	NA: 64% [b)]; 100% [c)] ERY: 0%[b)]; 33% [c)] CIP: 64% [b)]; 100% [c)] GEN: 9% [b)]; 33% [c)] STR: 14% [b)]; 50% [c)] TET: 68% [b)]; 83% [c)]	23
Vietnam	Ho Chi Minh City	Chicken	20 chicken neck-skin samples; Disc diffusion test	AMP: 40% ERY: 25% NA: 95% CIP: 95%	51
Vietnam	Mekong delta	Chicken, ducks, pigs	202 *Campylobacter* isolates (*C. jejuni* and *C. coli*); Disc diffusion method	ERY: 100% SXT: 99% NA: 92% CIP: 20.8% CHL: < 10%	21
Vietnam	Ho Chi Minh City	Human	66 *Campylobacter* isolates from children with diarrhea; 16 isolates from non-diarrheal control; E-test using disc diffusion	AMP: 26.3% CIP: 80.0% CHL: 1.5% NA: 84.8% ERY: 7.8% CIP: 68.7% [a)] NA: 62.5% [a)] CHL: 18.7% [a)]	19
Vietnam	Hanoi	Chicken and pig meat	9 *Campylobacter* isolates (8 *C. jejuni* and 1 *C. coli*); Broth microdilution test	CIP: 62.5% [b)] NA: 87.5% [b)] STR: 62.5% [b)] TET: 75.0% [b)] CHL: 25.0% [b)] ERY: 25.0% [b)] GEN: 25.0% [b)]	29
Cambodia	Phnom Penh	Poultry carcasses	139 *Campylobacter* isolates (*C. jejuni, C. coli, C. lari*); Disc diffusion method	CIP: 25.9% ERY: 4.3% GEN: 1.4% NA: 58.3%	24
Cambodia	Phnom Penh	Human	23 *C. coli* and 64 *C. jejuni* isolates; Disc diffusion method	NA: 34% [b)]; 57% [c)] ERY: 2% [b)]; 9% [c)] CIP: 31% [b)]; 57% [c)] AMP: 14% [b)]; 22% [c)] GEN: 0% [b)]; 17% [c)] SXT: 75% [b)]; 87% [c)] TET: 27% [b)]; 44% [c)]	20

Cambodia	Phnom Penh and peri-urban areas	Poultry, carcasses, environment	63 *Campylobacter* isolates (*C. jejuni; C. coli; C. lari, C. upsaliensis*) from markets; Agar dilution method	CIP: 61.9% ERY: 22.2% TET: 50.8%	25
Cambodia	Kampong Thom [d)]	Cynomolgus monkeys	15 *Campylobacter* isolates; Agar dilution method	CIP: 100% [b)]; 100%[c)] STR: 0% [b)]; 44% [c)] GEN: 0% [b)]; 44% [c)] TET: 13% [b)]; 78% [c)]	26

NA: Nalidixic Acid; CIP: Ciprofloxacin; AZM: Azithromycin; AMP: Ampicillin; ERY: Erythromycin; SXT: Sulfamethoxazole-Trimethoprim; CHL: Chloramphenicol; STR: Streptomycin; TET: Tetracycline; GEN: Gentamicin

[a)]control group; [b)]*C. jejuni*; [c)]*C. coli*; [d)]kept in Japan

Consequence of finding of fluoroquinolone in imported basa catfish from Vietnam was the stop of sale of 350 tons of seafood in the US by the U. S. Food and Drug Administration (FDA) in 2005 [31]. Motivation was the emerging of resistance to enrofloxacin in *Campylobacter* caused by treatment of chickens and turkeys with this antimicrobial agent in poultry production and the risk for human health.

Other Topics

Recently, five genomes of *Campylobacter jejuni* isolates from Vietnam were sequenced. Some of these isolates had a cluster of genes of the type-6 secretion system (T6SS) which play roles in pathogen-pathogen and host-pathogen interactions. T6SS is associated with virulence, cell adhesion and cytotoxicity toward erythrocytes. Using the marker gene *hcp* (haemolysin co-regulated protein) the T6SS was detected in more than 70 % of Vietnamese human and chicken isolates [32].

Another study gave a detailed characterization of Vietnamese *Campylobacter* isolates [29]. Investigations concerning genotyping and antimicrobial resistance of *Campylobacter* isolates were carried out using *fla*A typing, MLST and DNA microarray assays. Resistance of *Campylobacter* to several antibiotics was determined phenotypically and by molecular biological methods. A limitation was the low number of isolates. In a study concerning the regional risks and seasonality in travel-associated campylobacteriosis in East Asia including Cambodia, Laos and Vietnam the risk was estimated to be 386 infections per 100,000 Swedish travelers per year. This is the highest value in the world apart from the Indian subcontinent with 1,253 cases per 100,000 travelers per year [33].

In an evaluation study of gastrointestinal pathogens in stool samples from diarrheic patients the usefulness of a multipanel pathogen identification system was shown. It represented a sensitive, specific and easy approach as an alternative to classical detection methods [34].

Conclusion

Little information about *Campylobacter* was reported in the past in the three South East Asian countries of Cambodia, Laos and Vietnam. Often, investigations were related to human infections especially in children of young age in big cities like Hanoi, Vientiane, Phnom Penh or Ho Chi Minh City. Knowledge about the prevalence of *Campylobacter* in humans and poultry and the antibiotic resistance is much better in Vietnam than in Laos or Cambodia. However, there exist no data about the prevalence of *Campylobacter* in milk or water sources, although *Campylobacter* contamination in both could be a risk for humans. Moreover, the common habit of consumption of unpasteurized milk in children under 5 year of age underlines the relevance of this potential route of transmission in these countries. However, food safety awareness and concepts are existing [35]. Surveillance and collaborative research within the South East Asian countries can clarify the epidemiology of foodborne infections like campylobacteriosis in humans. It can be also important for control of bacterial contamination in livestock and food of animal origin.

Prerequisite of improvement of food safety and as a consequence of human health is the introduction of modern diagnostics. PCR assays are rapid, reliable and comparably cheap, but especially in Laos molecular techniques are practically not in use yet and there is a substantial lack of laboratory infrastructure and equipment in all three countries. An increasing problem is antibiotic resistance in bacteria like *Campylobacter.* In the EU, antibiotic use of antibiotics as growth promotors in food animals was completely banned several years ago. National monitoring and control programmes for antimicrobial resistance in foodborne pathogens have not been established in ASEAN countries yet [30,36-51]. Limited data on the amount of antibiotics used in the farming industry exist, because there is no effective control, policy or regulation. In summary, national surveillance programs and international collaborations are needed to address the substantial gaps in knowledge about the epidemiology of campylobacteriosis in developing countries such as Cambodia, Laos and Vietnam. Establishment of at least one National Reference Laboratory with modern equipment and well trained personnel in each country is recommended.

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Conflict of Interest

No competing financial interests exist.

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