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Shigellosis in Southeast Asia: A systematic review and meta-analysis

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ABSTRACT

Background: Southeast Asia is attractive for tourism. Unfortunately, travelers to this region are at risk of becoming infected with *Shigella*. We conducted a meta-analysis to provide updates on *Shigella* prevalence in Southeast Asia, along with their serogroups and serotypes.

Methods: We conducted a systematic search using PubMed, EMBASE, and Web of Science for peer-reviewed studies from 2000 to November 2022. We selected studies that detected *Shigella* in stools by culture or polymerase chain reaction (PCR). Two reviewers extracted the data using a standardized form and performed quality assessments using the Joanna Briggs Institute checklist. The random effects model was used to estimate the pooled prevalence of *Shigella*.

Results: During our search, we identified 4376 studies. 29 studies (from six Southeast Asian countries) were included in the systematic review, 21 each in the meta-analysis of the prevalence of *Shigella* (Sample size: 109545) and the prevalence of *Shigella* serogroups.

The pooled prevalence of *Shigella* was 4% (95% CI: 4–5%) among diarrhea cases. *Shigella sonnei* was the most abundant serogroup in Thailand (74%) and Vietnam (57%), whereas *Shigella flexneri* was dominant in Indonesia (72%) and Cambodia (71%). *Shigella dysenteriae and Shigella boydii* were uncommon (pooled prevalence of 1% each). The pooled prevalence of *Shigella* was 5% (95% CI: 4–6%) in children aged <5 years. The pooled prevalence showed a decreasing trend comparing data collected between 2000–2013 (5%; 95% CI: 4–6%) and between 2014–2022 (3%; 95% CI: 2–4%). *Shigella* prevalence was 6% in studies that included participants with mixed pathogens versus 3% in those without. *Shigella flexneri* serotype 2a was the most frequently isolated (33%), followed by 3a (21%), 1b (10%), 2b (3%), and 6 (3%).

Conclusions: This study provides compelling evidence for the development of effective *Shigella* vaccines for residents of endemic regions and travellers to these areas.

1. Introduction

International travelers to Southeast Asia are at elevated risk of being infected with multidrug-resistant *Shigella* species (hereafter *Shigella* spp. or *Shigella*) [1]. *Shigella* is a Gram-negative bacterium belonging to the family Enterobacteriaceae that cause shigellosis or bacillary dysentery [2]. There are four recognized *Shigella* spp. (*Shigella flexneri, Shigella sonnei, Shigella boydii, and Shigella dysenteriae*); however, *S. flexneri and S. sonnei* account for the bulk of shigellosis cases [3,4].

Shigella is highly communicable; shigellosis occurs when as few as 10 viable organisms [5] are ingested through contaminated water, food, or via direct fecal-oral contact [6,7]. *Shigella* infect people using various virulence factors including Shiga toxin (Stx, which is cytotoxic, neurotoxic and enterotoxic) [6], and a type III secretion system (T3SS) and cognate effector proteins, which are responsible for the most severe symptoms of shigellosis [8]. It was previously believed that only *S. dysenteriae* type 1 carries Stx-encoding genes. Nevertheless, novel strains of non-*S. dysenteriae* type 1 that contains Stx genes have been identified in Haiti and the Dominican Republic, and among international travelers [9,10].

Acute diarrhea (watery, mucoid, or bloody), tenesmus, stomach discomfort, nausea, and vomiting are the most typical symptoms of

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shigellosis [2]. Shigellosis can become fatal if left untreated, especially in young children [11]. Additionally, shigellosis has been linked to sequelae like post-infectious irritable bowel syndrome (PI-IBS) in travelers [12,13] or cognitive decline and growth faltering in young children [14,15].

The *Shigella* spp. are common causes of traveler's diarrhea (TD) in international travelers [13]. *Shigella* spp. may be responsible for approximately 10% of TD (6–12%) [12]. Between 2012 and 2014, a study in Nepal reported that 8% of TD was caused by *Shigella* spp., of which 78% and 39% of isolates were resistant to ciprofloxacin and azithromycin, respectively [16]. Indeed, several studies of travelers have found travel-associated *Shigella* infections in returned travelers and men who have sex with men (MSM). For example, a recent study from the United Kingdom (UK) reported an outbreak of extensively drug-resistant *S. sonnei* among MSM, some of which were linked to travel abroad [17]. In another investigation, patients from the UK were shown to have imported ciprofloxacin-resistant *Shigella* due to travel [18]. A case of acalculous cholecystitis linked to *Shigella* was described in an Australian traveler returning from Vietnam [19]. Moreover, a significant number of travelers returning to the Netherlands (from Asia) [20], USA, and Germany (from the tropics) have been infected with *Shigella* [21,22]. Travel-associated multidrug-resistant *Shigella* in Orthodox Jewish communities has also been reported [23], as well as ciprofloxacin-resistant *S. sonnei* in Irish travelers [24].

In impoverished Southeast Asian populations, the *Shigella* spp. are also among the most typical causes of diarrhea, especially in children under the age of five [11,25]. The distribution of *Shigella* in Southeast Asia is shifting. For instance, *S. sonnei* that used to predominate in developed countries appears to be replacing *S. flexneri* in areas of Southeast Asia where economies have been improved [26–28].

Because Southeast Asia is an attractive destination for international travelers (not only for sightseeing, but also for medical tourism [29–31]) and given the likelihood that travelers to this region can develop TD due to *Shigella*, it is crucial to provide them with evidence-based data related to *Shigella*. In addition, *Shigella* spp. in Southeast Asia are becoming increasingly multidrug-resistant [32,33]. For instance, *S. sonnei* and *S. flexneri* have been found to be resistant to many contemporary antibiotics, including trimethoprim [34], azithromycin [35], quinolones (such as ciprofloxacin) [34,36], and third-generation cephalosporins (such as ceftriaxone) [34,37]. These findings were confirmed by a recent study, which found that Southeast Asia has the highest prevalence (83.4%) of multidrug-resistant *Shigella* spp. [33]. However, it should be noted that as Southeast Asia lacks sufficient diagnostic and drug-susceptibility testing capacity [38,39], selection bias may apply to this estimated prevalence.

Thus, the objective of this meta-analysis was to determine how common *Shigella* species are in Southeast Asia. The goal is to gain a better understanding of the disease burden currently present in Southeast Asia and advocate for effective *Shigella* vaccines development. There are now various vaccination candidates being evaluated [7], but licensed *Shigella* vaccines are not yet available. Hence, visitors to locations where *Shigella* is endemic should be familiar with strategies for preventing *Shigella* infections, such as good hand hygiene, drinking clean water, and eating safe food.

2. Material and methods

2.1. Study design

We conducted a systematic review and meta-analysis following the guidance from the preferred reporting items for a systematic review and meta-analysis (PRISMA) [40]. We focused on Southeast Asian countries which is known as the Association of Southeast Asian Nations (ASEAN). It comprises eleven countries: Brunei Darussalam (Brunei), Cambodia, Indonesia, Lao People's Democratic Republic (Laos), Malaysia, Myanmar, the Philippines, Singapore, Thailand, East Timor (Timor-Leste), and Vietnam [41].

This review is registered in the international prospective register of systematic reviews (PROSPERO; registration number: CRD42022357044).

2.2. Search strategy

In this study, three electronic databases (PubMed, EMBASE, and Web of Science) were searched (without language restriction) for articles published from January 2000 to 14 November 2022. The search methodology employed in this review was the same as that used in our previous systematic review and meta-analysis on *Shigella* in South Asia [2]. Search strategy keywords included: "*Shigella*" or "shigellosis" or "bacillary dysentery" or "dysentery." These keywords were combined with the names of each country of Southeast Asia (see supplementary material, Table S1). We also manually searched the reference lists of included articles to identify additional studies. Retrieved articles were imported to Endnote software X9 (Clarivate, Philadelphia, USA), where duplicate articles were removed.

2.3. Selection criteria

On the basis of selection criteria in our previous systematic review and meta-analysis [2], the eligible criteria for inclusion were as follows: (1) the study must have been conducted on people infected with *Shigella* and living in Southeast Asia (population); (2) the study must have assessed the presence of *Shigella* spp. in stool using culture or polymerase chain reaction (PCR) (exposure); (3) a study without a mandatory comparison group (comparison); (4) the study must have reported the number of participants testing positive for *Shigella* (outcomes); and (5) original cohort, case-control, and cross-sectional peer-reviewed studies (study design).

We excluded studies conducted outside of Southeast Asia, studies connected to outbreaks, abstracts from conferences, commentaries, editorials, letters to editors, case reports, and review papers. Additionally, we disregarded studies with a sample size of fewer than 50 participants.

To select studies, firstly two reviewers (BAM and KK) independently screened the titles and abstracts of articles that were retrieved from the search. Then, potentially relevant articles were reviewed in full. Reasons for exclusion were recorded, and disagreements were resolved through consensus.

2.4. Data extraction

To minimize errors in data extraction, we designed a standardized data extraction sheet using Microsoft Excel 2019 (Version 2204, Microsoft Corp., Albuquerque, NM, USA). From each eligible study, extracted data included: the first author's name, year of publication and data collection, study site and area of residence (urban, rural or mixed), study design, age group, laboratory methods of *Shigella* spp. confirmation (culture; PCR; or both), sample size, number of participants testing positive for *Shigella*, the prevalence of *Shigella* and serotypes, the prevalence of mixed infections with *Shigella*, and the season of *Shigella* isolation. We also recorded information required to assess the quality of individual studies. Two independent reviewers (BAM and KK) extracted data. Any disagreements were resolved through consensus. We also consulted a third investigator (AO) in cases of disagreement.

2.5. Study quality

Two reviewers independently assessed the quality of the studies (BAM and KK) using a modified Joanna Briggs Institute (JBI) checklist for prevalence studies [42]. The modified JBI checklist contains eight questions that were weighted as follows: 1 = we answered "yes" to the question; 2 = we answered "no" to the question; 3 = the question was answered with "unclear" or "not applicable" [42].

2.6. Data analysis

All analyses were conducted in Stata (version 16, StataCorp LP, College Station, TX, USA) using the metaprop command [43]. For the meta-analyses, random-effects models were used to estimate the prevalence of *Shigella* in Southeast Asia. Studies were stratified into three groups: (1) studies that examined the prevalence of *Shigella*, (2) those that assessed the prevalence of *Shigella* serogroups (*S. flexneri, S. sonnei, S. boydii, and S. dysenteriae*), and (3) those that evaluated the prevalence of *S. flexneri* serotypes (1b, 2a, 2b, 3a, and 6). For case-control studies, only data from subgroups of patients were included in the meta-analyses.

We evaluated the degree of heterogeneity using the I^2 statistics (I^2 of >50% was considered to indicate considerable heterogeneity) [44].

Furthermore, we carried out subgroup analyses to explore sources of heterogeneity. The following variables were selected as potential sources of heterogeneity: age group (children under 5 years old versus all ages) and year of data collection (2000–2013 versus 2014–2022). We also performed sensitivity analyses by excluding studies that had reported mixed pathogens and studies identified as outliers.

3. Results

3.1. Search results

After the titles and abstracts of articles retrieved from the search (n = 4376) were screened, 48 articles were eligible for the full-text review (Appendix 1). Of these, 19 were excluded because they did not meet our eligibility criteria (Table S2), and 29 articles from six southeast Asian countries met the eligibility criteria and were included in the systematic review (Table S3). 21 of these articles were included in the meta-analysis of prevalence of *Shigella* in Southeast Asia (Table S4) and 21 in the meta-analysis of prevalence of *Shigella* spp. serogroups (Table S5). Nine studies were included in the meta-analysis of *S. flexneri* serotypes (Table S6).

3.2. Study characteristics

Details of the study characteristics are displayed in Table S3. The studies were published in English between 2003 and 2021.

Of the 29 included studies, Vietnam had the highest number of studies (14 studies) [45–58], followed by Thailand (8 studies) [55,59–65], Indonesia (4 studies) [55,66–68], Cambodia (3 studies) [69–71], and one study each was from Laos [72] and Malaysia [73]. One study was conducted in three countries (Indonesia, Thailand, and Vietnam) [55]. No study from Brunei, Myanmar, the Philippines, Singapore, and Timor-Leste met the eligibility criteria.

The reviewed studies included both children and adults: 13 (44.8%; 13/29) studies were carried out in children [45–49,52–54,56,57,61,69,74] and the remaining 16 studies (55.2%; 16/29) were from both adults and children (Table S3). Nine studies (31.0%; 9/29) exclusively included children under 5 years old [45–49,53,57,61,74]. Shigellosis was also reported to be common among patients over 60 years of age [58,66].

Sample sizes ranged from 72 to 186007. The methodological assessment with JBI checklist (graphic and tabular summaries) are displayed in Appendix 2 and Table S7. We found that all studies were hospital-based surveillance, thus they were less likely to be representative of the target population. However, 6 (20.7%; 6/29) studies clearly stated that the community was also involved [48,50,55,62–64].

Shigellosis cases occurred throughout the year; however, they were more frequent during the warm and rainy seasons, which vary by area. For example, increased shigellosis cases were observed in the rainy months in Kon Tum province in Vietnam (between May and October) [51], in Nha Trang in Vietnam (between September and November) [50,58], in Ho Chi Minh City in Vietnam (between May and September) [53,54], in Thailand (between July and August) [60,63,65], in the northeastern region of Jakarta in Indonesia (between February and April) [66], and the northeastern region of Malaysia (during the pre-monsoon: May to August; and during the rainy season: between November and December) [73].

There were twelve (41.4%; 12/29) studies that included participants with enteric mixed pathogens in the stool; however, only four studies described their types, namely rotavirus [57], enterotoxigenic *Bacteroides fragilis* [57], *Salmonella* [68], *Vibrio cholerae* [66], enteroinvasive *Echerischia coli*, sapovirus, plesiomonas and astrovirus [65].

The reviewed studies showed the presence of multidrug resistance *Shigella* strains against first- and second line antibiotics [47,52–55,70,71], including resistant *Shigella* expressing extended-spectrum beta--lactamases (ESBLs) [52,53,70,71].

By eyeballing the data of the reviewed studies, we found that the prevalence of *Shigella* ranged from 1% to 46% (Table S4). Two studies conducted in Vietnam were identified as outliers; they reported *Shigella* prevalence of 25% [47] and 46% [58].

3.3. Meta-analysis

3.3.1. Prevalence of Shigella

A total of 29 data points (21 studies) covering 113,211 stool tests were available for estimating the prevalence of *Shigella* in the Southeast Asian countries included in this study (Table S4). *Shigella* prevalence was estimated to be 6% (95% CI: 5–7%) (Appendix 3) among cases with diarrhea. After removing two outliers (that reported prevalence of 25% [47] and 46% [58]), we found that the pooled prevalence slightly decreased to 4% (95% CI: 4–5%) (Fig. 1), with heterogeneity ($I^2 = 98.7$; $p < 0.01$).

By restricting the analysis to children aged ≤5 years, the pooled prevalence slightly increased to 5% (95% CI: 4–6%) (Appendix 4).

Furthermore, a comparison of the pooled prevalence over two time periods revealed a declining trend: 5% (95% CI: 4–6%) in data collected between 2000 and 2013, and 3% (95% CI: 2–4%) in data collected between 2014 and 2022 (Appendix 5).

Additionally, in studies with patients who had mixed pathogens, the pooled prevalence of *Shigella* was two times higher (6%; 95% CI: 4–7%) than in studies with *Shigella* alone (and those where mixed pathogens information was not reported) (3%; 95% CI: 2–4%), which was slightly close to the overall estimate (4%) (Appendix 6).

3.3.2. Prevalence of Shigella serogroups

The prevalence of *Shigella* serogroups was estimated using 21 studies (with 23 data points and a sample of 6102 stool samples) (Table S5).

The overall prevalence of *S. sonnei* was 54% (95% CI: 42–67%) (Fig. 2). We found that *S. sonnei* replaced *S. flexneri* as the most prevalent species in Thailand (74%) and Vietnam (57%). The only study for Malaysia reported 50% of *S. sonnei* [73].

The overall prevalence of *S. flexneri* was 45% (95% CI: 33–58%) (Fig. 3). *S. flexneri* remains dominant in Indonesia (71%) and Cambodia (71%).

Furthermore, we found that *S. boydii* (Appendix 7) and *S. dysenteriae* (Appendix 8) were uncommon (pooled prevalence of 1% each).

3.3.3. Prevalence of Shigella flexneri serotypes

We included nine studies (analyzing 3368 isolates) in the meta-analysis of *S. flexneri* serotypes (Table S6).

The dominant *S. flexneri* serotypes were *S. flexneri* 2a (33%), followed by serotype 3a (21%), serotype 1b (10%), serotype 2b (3%), and serotype 6 (3%) (Fig. 4).

4. Discussion

This study documents shigellosis in Southeast Asian countries. In our meta-analysis, we estimated that the prevalence of *Shigella* spp. in

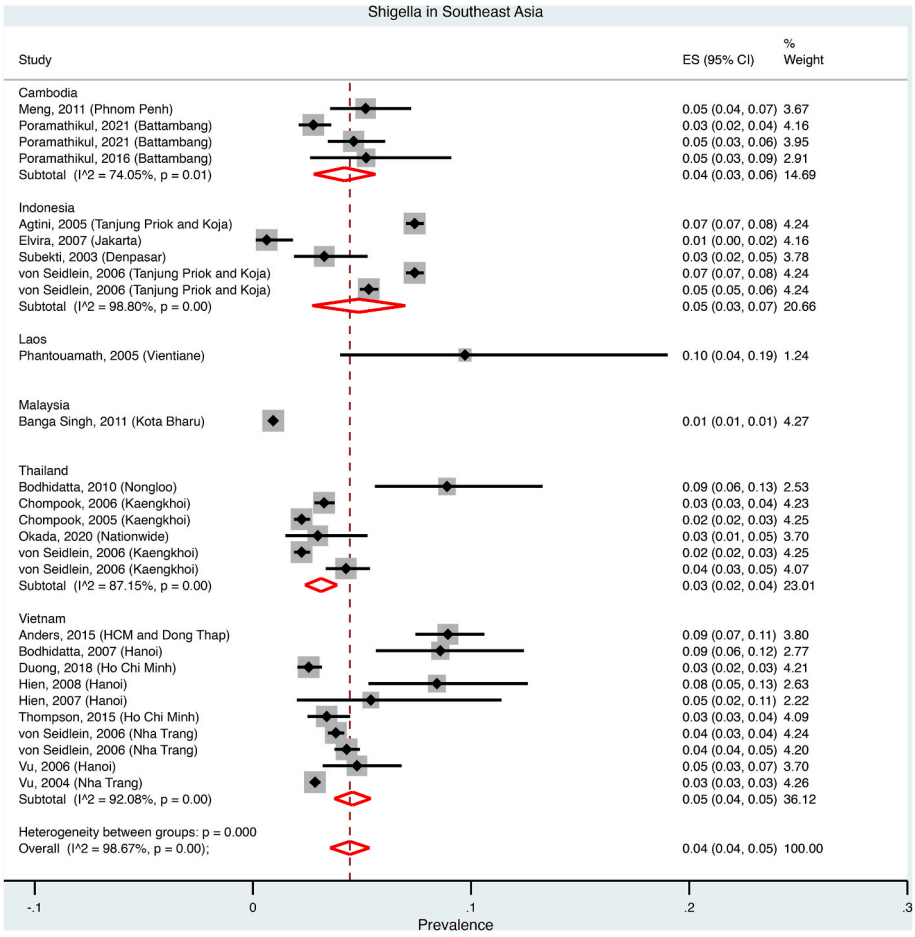

Fig. 1. Pooled prevalence of *Shigella* species in Southeast Asia, overall and by country (Vietnam, Thailand, Indonesia, Cambodia, Laos and Malaysia). ES = effect size; CI = confidence interval.

Southeast Asian countries is 4% among diarrhea cases. Compared with the estimated prevalence of *Shigella* in South Asian countries (7%) [2] and that reported for Ethiopia (6.6%) [75], the estimated prevalence of *Shigella* is lower in Southeast Asia.

The estimated prevalence of *Shigella* (4%) found in this study is slightly higher than that reported by Salleh et *al.* in 2022 in Southeast Asia (2.9%) [33]. The prevalence, however, dropped to 3%, close to the data by Salleh et al. [33], when our meta-analysis was restricted to recent studies published between 2014 and 2022. However, the present investigation included 21 studies with 109545 samples in the meta-analysis, whereas the study by Salleh et *al.* was limited to four studies with a sample size of 7748 [33]. Thus, the current study provides more comprehensive and accurate information on *Shigella* species in Southeast Asian countries.

While there was significant variability by age, presence of mixed pathogens, and period of data collection, our findings indicate that people living in Southeast Asia are highly exposed to *Shigella.* In Southeast Asia, *Shigella* endemicity is partly due to the lack of adequate sanitation in some parts of the region, despite significant progress in providing adequate water, sanitation, and hygiene (WASH) [76]. Of note is that transmission of *Shigella* has been associated with untreated wastewater used for irrigation in agriculture and proximity to a river in Vietnam [48,50], and flies in the kitchen area in Thailand [62]. International travellers to this region should be aware of these inadequate WASH provisions.

Due to the elevated *Shigella* prevalence in Southeast Asia, travellers from high income countries to Southeast Asia and deployed military personnel may be at an increased risk of contracting *Shigella* infections or TD caused by *Shigella*. Indeed, the estimated prevalence (4%) among diarrhea cases is within the range of 2–13% for TD due to *Shigella* found among international visitors to Southeast Asia [9].

The prevalence of TD caused by *Shigella* in international travellers bound to Southeast Asia had previously been estimated to be 2.17% [77], 3% (in visitor to Thailand) [78], and 3.8% (in US military and civilian travellers) [79]. Moreover, *Shigella* has been implicated in TD in 6.6% in US deployed military and 5.5 in civilian travellers [80]. According to a recent review, *Shigella* spp. are detected in 5–18% of stool samples collected from patients who suffer from TD [81]. Considering that shigellosis can result in substantial economic losses (such as time and productivity losses) and chronic sequelae (such as PI-IBS) [12,13], international travelers to Southeast Asia need to be alerted about health risks and counselled accordingly on risk reduction. They should also be counselled on TD management including dehydration prophylaxis: for example, adequate fluid intake [82,83] and oral rehydration salts. If a traveler is returning home with acute diarrhea, physicians should trace back their travel history and consider the possibility of a bacterial infection (including shigellosis) in the differential diagnosis.

Given the seasonal dynamics of shigellosis, i.e., prevalent in the hot and rainy seasons, we can expect the risk of TD due to *Shigella* to increase during the summer and monsoon seasons in travellers to Southeast Asia. This is plausible because when it is hot, most bacteria, such as *Shigella*, grow and multiply faster [84,85]. Furthermore, water demands are affected during rainy seasons (by floods and cyclones), especially for rural communities [86]. This observation suggests that travellers should take extra precautions during the hot and rainy seasons when visiting high-risk areas. Policymakers in endemic countries should take climatic

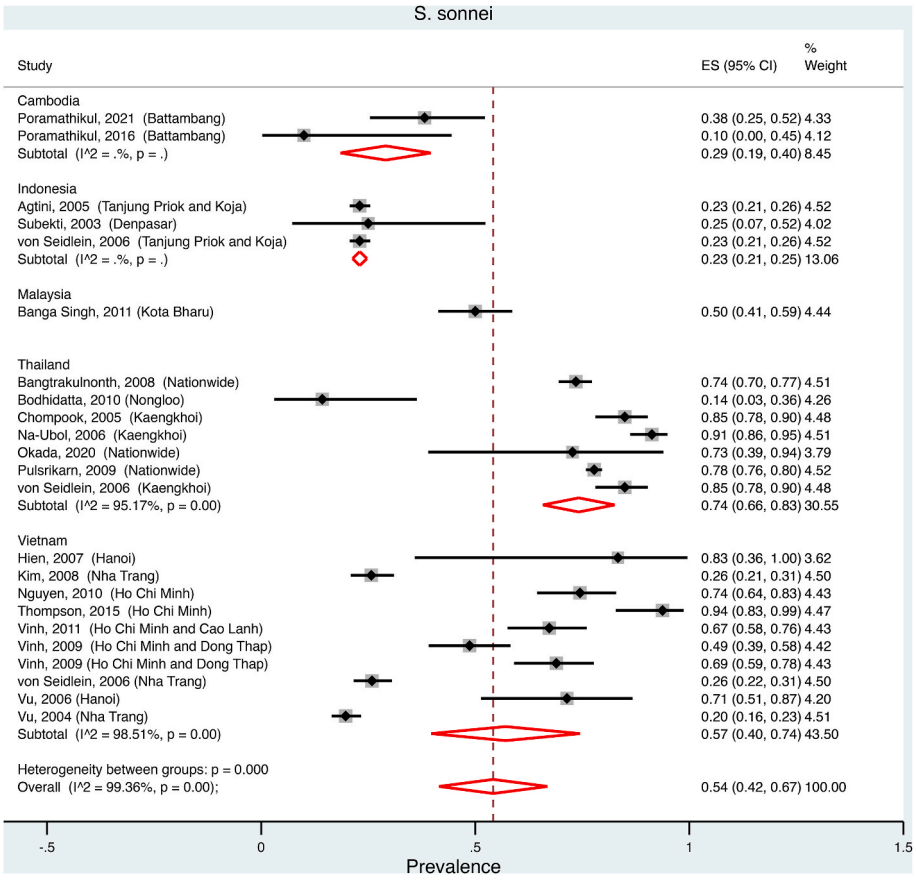

Fig. 2. Pooled prevalence of *Shigella sonnei* in Southeast Asia, overall and by country (Vietnam, Thailand, Indonesia, Cambodia, and Malaysia).
ES = effect size; CI = confidence interval.

factors into consideration to prevent transmission during these seasons. Of note, the observation that *Shigella* was mostly isolated during the warm and rainy seasons does not imply that the risk of developing TD due to *Shigella* is nullified during other seasons because the reviewed studies showed that *Shigella* was isolated throughout the year in Southeast Asia. Indeed, TD did not show any seasonal dynamics in a study conducted in Thailand [87,88].

Several studies have reported the occurrence of *Shigella* as a co-pathogen in stool samples from patients with shigellosis [89,90]. Similarly, in our study, a high number of mixed pathogens was observed among patients with shigellosis (a pooled prevalence of 6%), in agreement with the results published in our previous study on *Shigella* in South Asia where we found that studies including participants with mixed pathogen showed a high prevalence of 10% [2]. Recently, in a cross-sectional study designed to elucidate the role of *Shigella* in TD, one study found a high prevalence (75%; 15/20) of *Shigella* as co-pathogen in travellers with TD [91].

Shigellosis was more prevalent in children under five years of age, consistent with the literature [92,93]. Pediatric international travellers are also at an increased risk of TD [83,94,95]. Indeed, travel-associated shigellosis has also been reported to be high in children below the age of five years [96]. This suggest that when *Shigella* vaccines become available these two groups (young children travelling to - and living in - endemic countries) should be considered among the most priority groups.

Most importantly, our study confirms that *S. sonnei* has replaced *S. flexneri* as the predominant species in nations with developing economy like Vietnam, and Thailand. Nonetheless, *S. flexneri* remains the predominant serogroup in some Southeast Asian countries such as Indonesia and Cambodia, and in South Asian countries such as India and Bangladesh [2]. In fact, regardless of the region visited, *S. sonnei* is the most common species detected in recorded episodes of TD caused by *Shigella* [9,96–100].

In our study, we found that the most endemic species were *S. sonnei* and *S. flexneri* serotypes 2a, 3a, 1b, 2b, and serotype 6. We previously reported similar findings regarding shigellosis in South Asia [2]. Our observation is consistent with findings that claim that to produce a protective immunity of 40%–50% against shigellosis, effective *Shigella* vaccines need at the very least comprise *S. sonnei* and *S. flexneri* 2a [101]. *Shigella* vaccines are especially needed for children living in endemic countries [102], and travelers from high-income countries, like tourists, people living with HIV, families travelling with young children, charity workers, missionaries, business travelers, and expatriates travelling to Shigella-endemic areas, as well as the military stationed there [2,79,92,103,104]. Furthermore, MSM may also benefit from *Shigella* vaccines, as they are at higher risk of exposure [2,17]. Indeed, by developing an effective *Shigella* vaccine, we can mitigate short and long-term effects of *Shigella* [101], prevent antibiotics abuse to help avert the spread of antimicrobial resistance [104–108], as well as reduce healthcare costs [2,103].

Of concern are recent reports from Southeast Asia indicating an increasing patients infected with drug-resistant *Shigella* strains [47,52–55,70,71]. Excessive use of antibiotics or abusive use of antibiotics could explain in part these antibiotics resistance. Indeed, resistant strains of *Shigella* spp. has also been isolated in international travelles after visiting Southeast Asia [1,9,109–111].

This reaffirms that for prophylaxis, an effective *Shigella* vaccine would likely reduce the use of antibiotics in travellers and people in endemic countries in Southeast Asia.

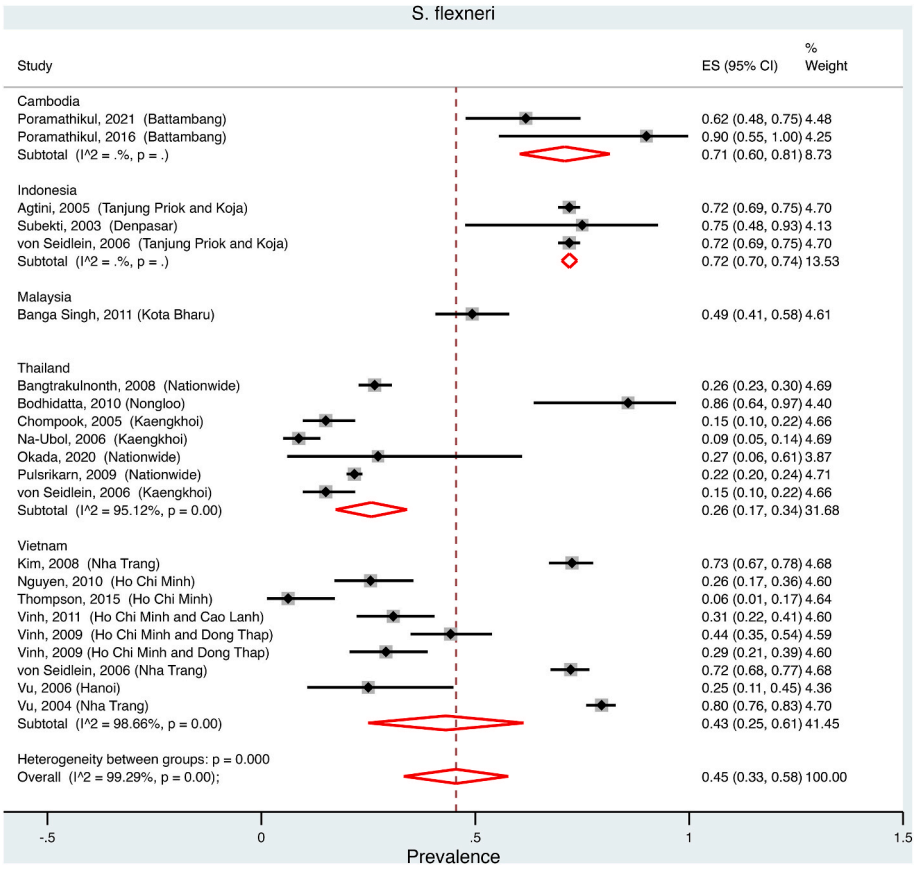

Fig. 3. Pooled prevalence of *Shigella flexneri* in Southeast Asia, overall and by country (Vietnam, Thailand, Indonesia, Cambodia, and Malaysia).
ES = effect size; CI = confidence interval.

4.1. Limitations

It is important to acknowledge the limitations of our study. First, for the following three reasons, it is likely that the estimated prevalence of *Shigella* (4%) identified among diarrhea cases is underestimated.

(1) the use of stool culture to isolate *Shigella* in most (93%; 25/27 data points) of the reviewed studies. This reflects current clinical practice to confirm shigellosis. Culture of bacteria is a less sensitive method, which results in lower estimations and is not widely available in several Shigella-endemic areas [106,108].
(2) Only patients who sought treatment were included in our study. Our estimates do not include those who self-medicate (which is a common practice in many Asian countries [112]) or do not seek medical attention, as well as those who are asymptomatic carriers of *Shigella*. One study carried out in Laos reported that the prevalence of *Shigella* in asymptomatic carriers was 6.2% (9/145) [72]. Because only patients with diarrhea were included in the meta-analysis, the estimated prevalence of 4% should not be generalized to the general population.
(3) We were also limited by lack of published data in the Philippines, Bhutan, Myanmar, Timor-Leste, and Singapore. Thus, the estimated prevalence might not be generalizable to other Southeast Asian countries that did not have any studies that evaluated *Shigella* prevalence. However, *Shigella* might be a rising issue in Brunei, and likely to be endemic in the Philippines, Myanmar [113], Singapore, but published epidemiological data are scarce. The lack of data should not serve as barriers to prevention or advocate for *Shigella* vaccines. Indeed, TD cases due to *Shigella* have been reported following travel to the Philippines [98], and Singapore [99]. As such, we recommend continued surveillance studies and implementation of consistent reporting in these countries lacking epidemiological data. This is because of the shifting epidemiology in *Shigella* species and the emerging antimicrobial strain of *Shigella*.

Studies of surveillance could help to develop evidence-based prevention strategies or recommendations for travellers to prevent TD. Yet, it is difficult to prevent TD for travellers who cannot cook or arrange clean drinking water for themselves [88].

Second, the lack of stratification for travellers could lead to some challenges in utilizing etiology from non-travellers and applying it to travellers' situations. However, this limitation was mitigated by expanding our discussion to travellers' situations and by emphasizing the need for *Shigella* vaccines for travellers and the military.

Despite the above limitations, our study contributes to studies on *Shigella* distribution. This study partially fills the knowledge gap on *Shigella* serogroups and serotypes distribution in Southeast Asia. A throughout understanding of the serotypes distribution of *Shigella* in different geographical regions provide insights into planning *Shigella* vaccine development or trials and assists in policy decisions [114].

5. Conclusions

This study was conducted to update the burden of shigellosis in Southeast Asia, a hotspot for multidrug-resistant *Shigella* transmission and an attractive destination for medical tourism, vacation, and a region with US military deployment. We found that shigellosis remain prevalent in Southeast Asia (estimated pooled prevalence of 4% among cases with diarrhea), with substantial difference between age, period of data collection, and presence of mixed pathogens (prevalence of 6%).

S. sonnei has replaced *S. flexneri* as the prevalent serotypes in most

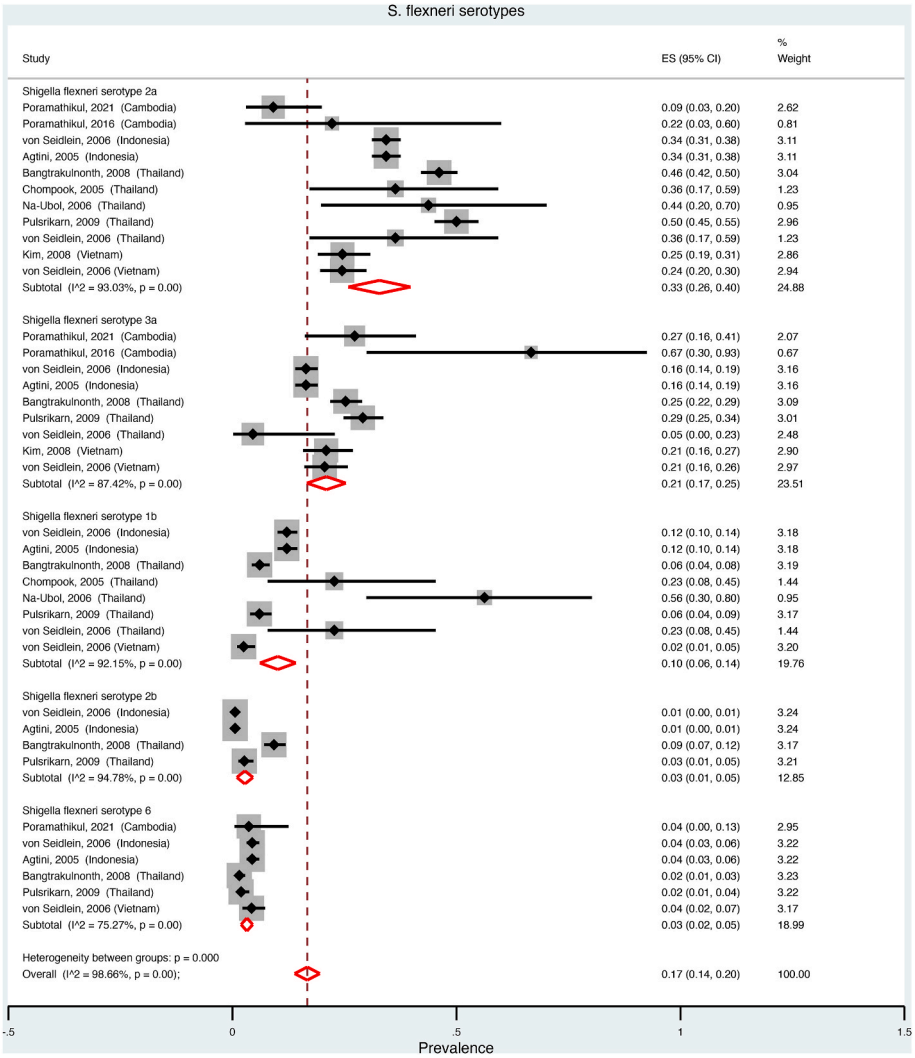

Fig. 4. Pooled prevalence of *Shigella flexneri* serotypes.
ES = effect size; CI = confidence interval.

regions in Vietnam and Thailand. However, *S. flexneri* remains prevalent in countries like Indonesia and Cambodia.

Several reviewed studies confirmed the emergence of multidrug-resistants *Shigella* strains, including those expressing ESBLs, which pose a major threat to public health in Southeast Asia and travellers to this region.

The findings of the reviewed studies have some implications for the practice of travel medicine. Firstly, our data justify that pretravel counseling should be encouraged to raise awareness of shigellosis risk among travellers for better preparedness. Secondly, healthcare professionals are being reminded to consider shigellosis in the differential diagnosis when a traveler returns home with acute diarrhea. In addition, there is a possibility that certain antimicrobials, such as cephalosporins and fluoroquinolones, might not be effective in treating returning travelers with multidrug-resistant *Shigella*, and that precautions should be taken when using these drugs.

Integrated control efforts to reduce the burden of shigellosis in Southeast Asia include improved WASH, hygiene education, poverty reduction, improved laboratory diagnostic resources, and behavioural changes (such as open defecation), to name a few. The most effective strategy to prevent shigellosis would be vaccination. Licensed *Shigella* vaccine that provide long-term protection against *Shigella* spp. are still not available. Our findings provide a powerful argument to recommend the development of effective *Shigella* vaccines for people living in endemic regions, travellers, and the military personnel on deployment in endemic regions.

Author contributions

All authors contributed significantly to this study.

BAM, KK and SIM: study conception and its design; BAM and KK: literature search, data collection, analysis and interpretation; BAM: wrote the first draft of the manuscript; KK and DM: Commented on an early version of the manuscript; KK, DM, AO, JK, SD and SIM: revised the manuscript for important academic content. SIM: supervised this work.

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Institutional review board statement

No ethical approval was necessary for this study because this study is a review.

Informed consent statement

Not applicable for this study because this study is a review.

Declaration of competing interest

The authors declare no conflict of interest.

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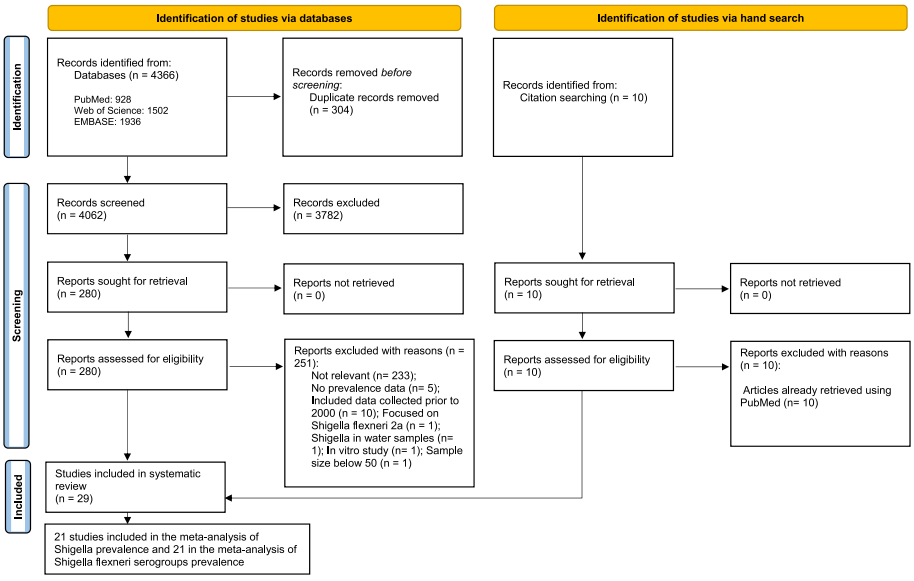
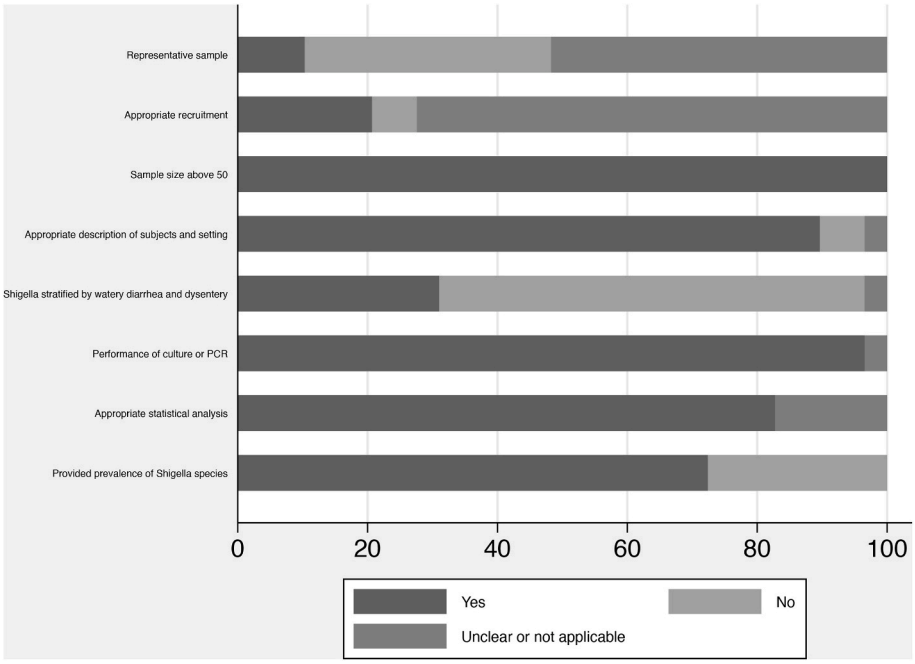
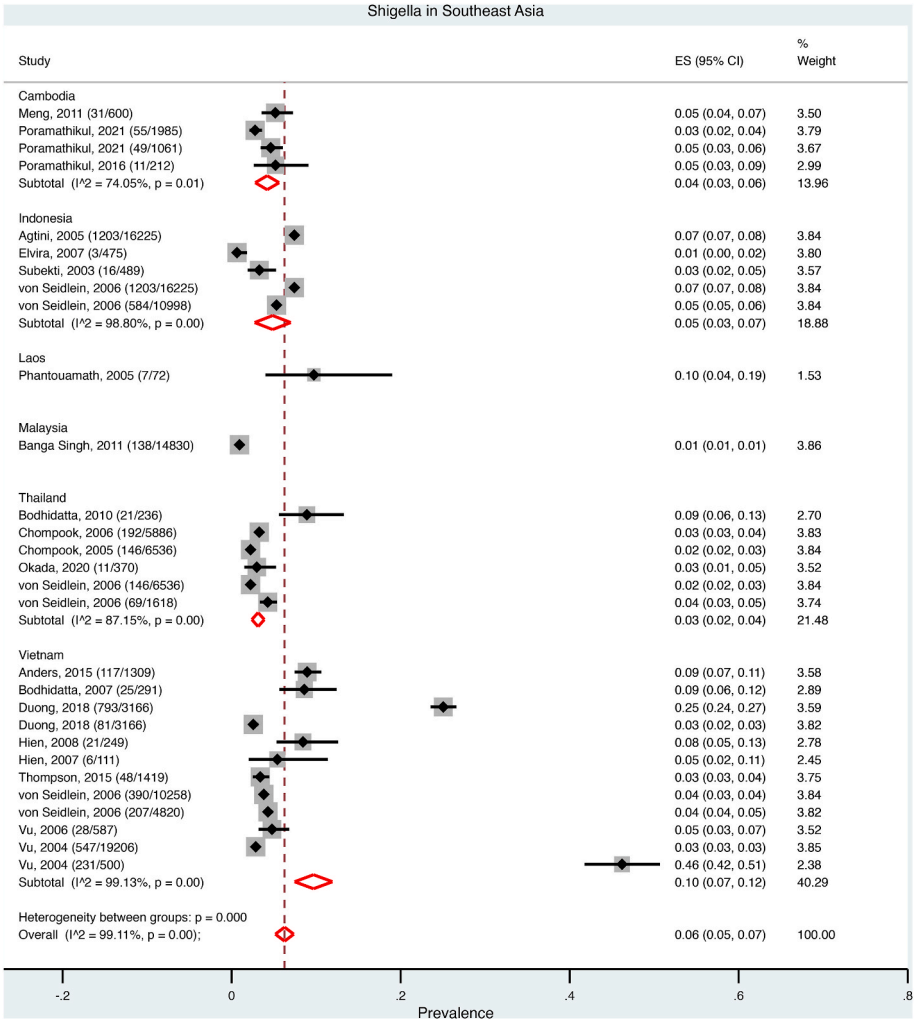
Appendix A. Supplementary data

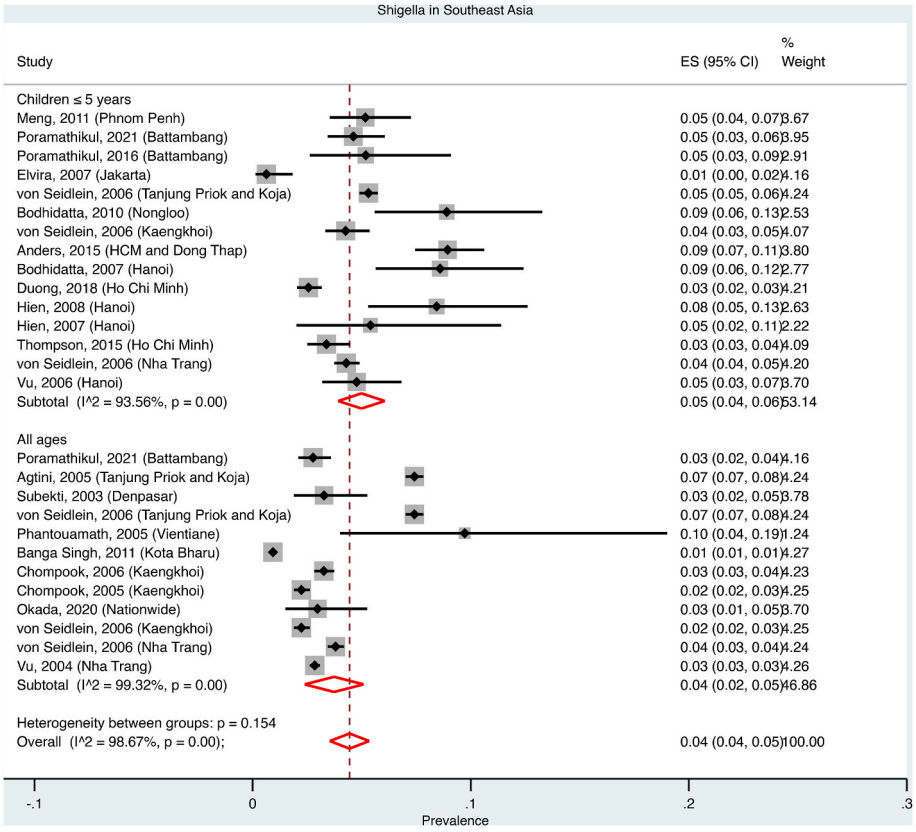
Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2023.102554.

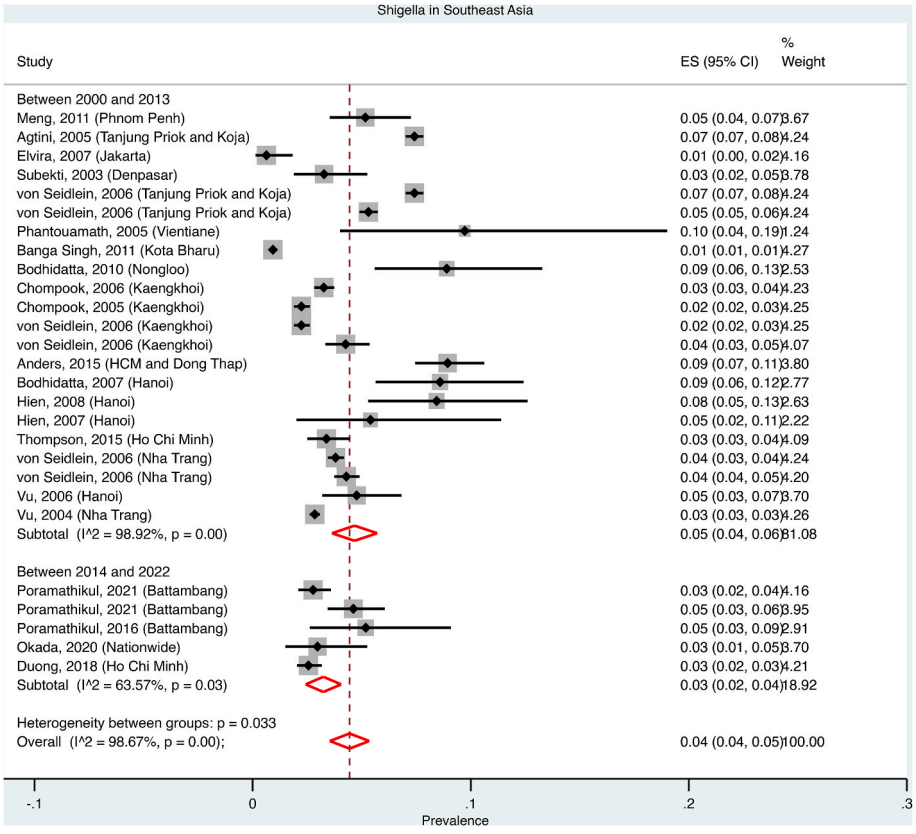
Appendix 1. PRISMA Study selection

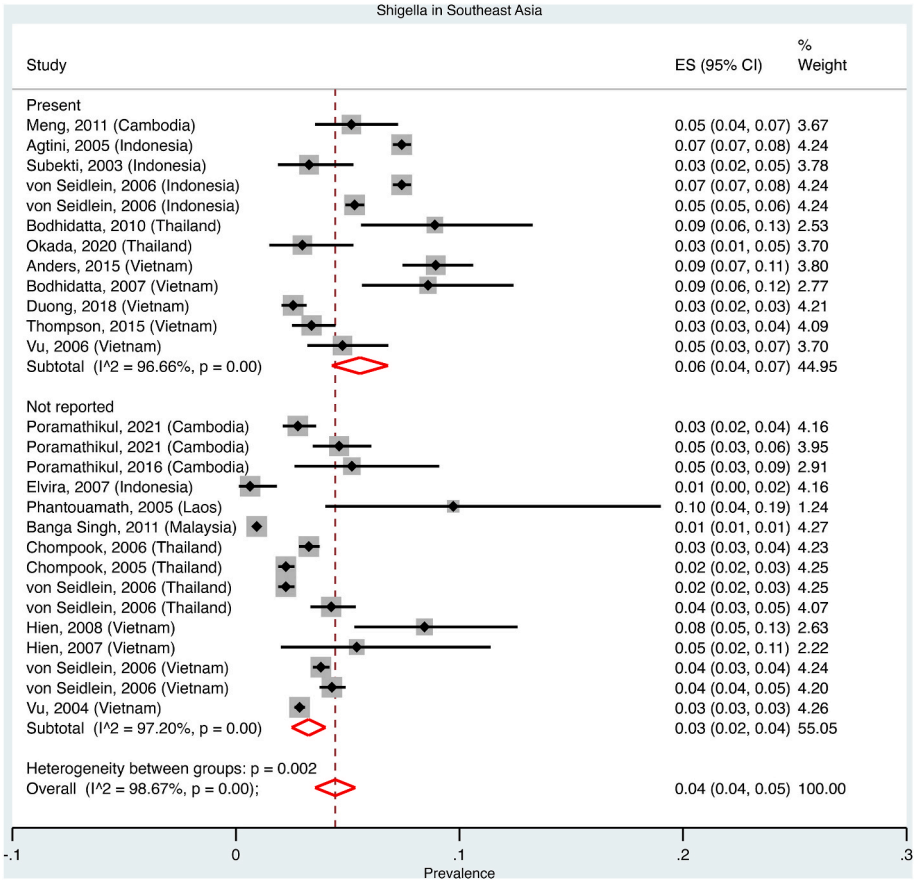


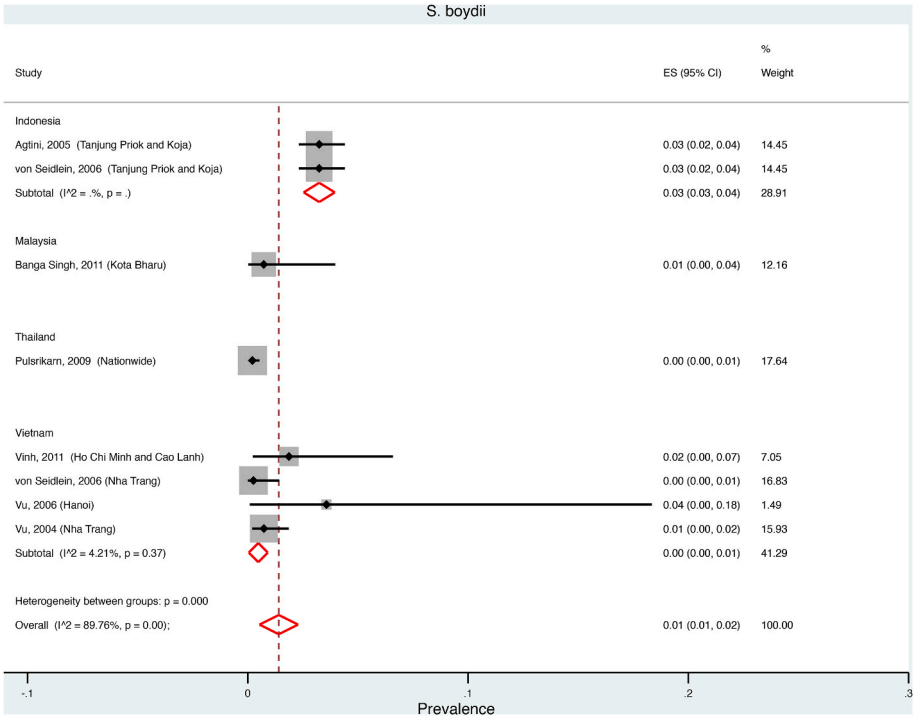


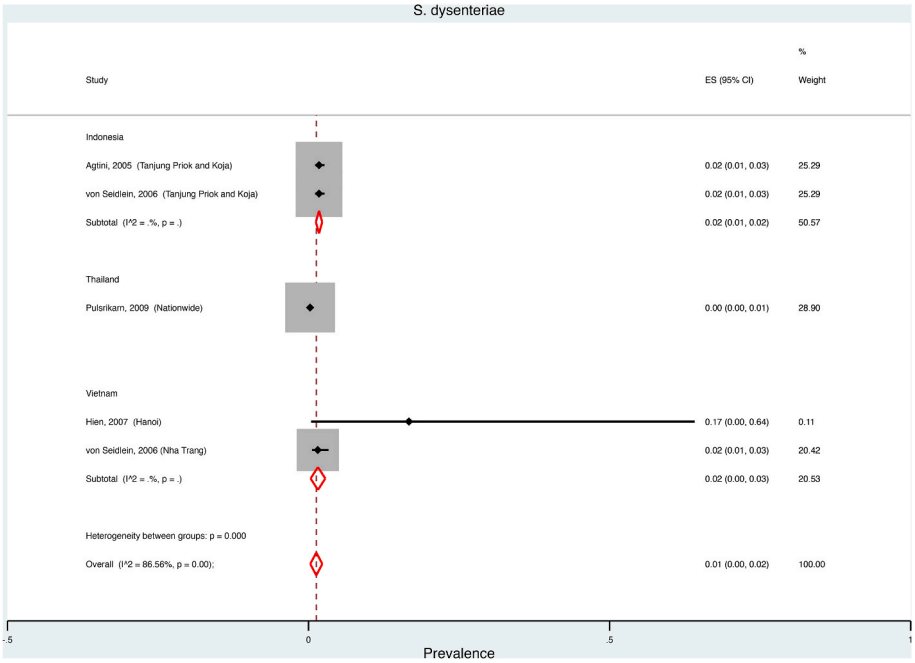

Shigella in Southeast Asia
Study
ES (95% CI)
% Weight
Cambodia
Meng, 2011 (31/600) 0.05 (0.04, 0.07) 3.50
Poramathikul, 2021 (55/1985) 0.03 (0.02, 0.04) 3.79
Poramathikul, 2021 (49/1061) 0.05 (0.03, 0.06) 3.67
Poramathikul, 2016 (11/212) 0.05 (0.03, 0.09) 2.99
Subtotal (I^2 = 74.05%, p = 0.01) 0.04 (0.03, 0.06) 13.96
Indonesia
Agtini, 2005 (1203/16225) 0.07 (0.07, 0.08) 3.84
Elvira, 2007 (3/475) 0.01 (0.00, 0.02) 3.80
Subekti, 2003 (16/489) 0.03 (0.02, 0.05) 3.57
von Seidlein, 2006 (1203/16225) 0.07 (0.07, 0.08) 3.84
von Seidlein, 2006 (584/10998) 0.05 (0.05, 0.06) 3.84
Subtotal (I^2 = 98.80%, p = 0.00) 0.05 (0.03, 0.07) 18.88
Laos
Phantouamath, 2005 (7/72) 0.10 (0.04, 0.19) 1.53
Malaysia
Banga Singh, 2011 (138/14830) 0.01 (0.01, 0.01) 3.86
Thailand
Bodhidatta, 2010 (21/236) 0.09 (0.06, 0.13) 2.70
Chompook, 2006 (192/5886) 0.03 (0.03, 0.04) 3.83
Chompook, 2005 (146/6536) 0.02 (0.02, 0.03) 3.84
Okada, 2020 (11/370) 0.03 (0.01, 0.05) 3.52
von Seidlein, 2006 (146/6536) 0.02 (0.02, 0.03) 3.84
von Seidlein, 2006 (69/1618) 0.04 (0.03, 0.05) 3.74
Subtotal (I^2 = 87.15%, p = 0.00) 0.03 (0.02, 0.04) 21.48
Vietnam
Anders, 2015 (117/1309) 0.09 (0.07, 0.11) 3.58
Bodhidatta, 2007 (25/291) 0.09 (0.06, 0.12) 2.89
Duong, 2018 (793/3166) 0.25 (0.24, 0.27) 3.59
Duong, 2018 (81/3166) 0.03 (0.02, 0.03) 3.82
Hien, 2008 (21/249) 0.08 (0.05, 0.13) 2.78
Hien, 2007 (6/111) 0.05 (0.02, 0.11) 2.45
Thompson, 2015 (48/1419) 0.03 (0.03, 0.04) 3.75
von Seidlein, 2006 (390/10258) 0.04 (0.03, 0.04) 3.84
von Seidlein, 2006 (207/4820) 0.04 (0.04, 0.05) 3.82
Vu, 2006 (28/587) 0.05 (0.03, 0.07) 3.52
Vu, 2004 (547/19206) 0.03 (0.03, 0.03) 3.85
Vu, 2004 (231/500) 0.46 (0.42, 0.51) 2.38
Subtotal (I^2 = 99.13%, p = 0.00) 0.10 (0.07, 0.12) 40.29
Heterogeneity between groups: p = 0.000
Overall (I^2 = 99.11%, p = 0.00); 0.06 (0.05, 0.07) 100.00
-.2
0
.2
.4
.6
.8
Prevalence


Shigella in Southeast Asia
Study
ES (95% CI)
% Weight
Children ≤ 5 years
Meng, 2011 (Phnom Penh) 0.05 (0.04, 0.07) 3.67
Poramathikul, 2021 (Battambang) 0.05 (0.03, 0.06) 3.95
Poramathikul, 2016 (Battambang) 0.05 (0.03, 0.09) 2.91
Elvira, 2007 (Jakarta) 0.01 (0.00, 0.02) 4.16
von Seidlein, 2006 (Tanjung Priok and Koja) 0.05 (0.05, 0.06) 4.24
Bodhidatta, 2010 (Nongloo) 0.09 (0.06, 0.13) 2.53
von Seidlein, 2006 (Kaengkhoi) 0.04 (0.03, 0.05) 4.07
Anders, 2015 (HCM and Dong Thap) 0.09 (0.07, 0.11) 3.80
Bodhidatta, 2007 (Hanoi) 0.09 (0.06, 0.12) 2.77
Duong, 2018 (Ho Chi Minh) 0.03 (0.02, 0.03) 4.21
Hien, 2008 (Hanoi) 0.08 (0.05, 0.13) 2.63
Hien, 2007 (Hanoi) 0.05 (0.02, 0.11) 2.22
Thompson, 2015 (Ho Chi Minh) 0.03 (0.03, 0.04) 4.09
von Seidlein, 2006 (Nha Trang) 0.04 (0.04, 0.05) 4.20
Vu, 2006 (Hanoi) 0.05 (0.03, 0.07) 3.70
Subtotal (I^2 = 93.56%, p = 0.00) 0.05 (0.04, 0.06) 53.14
All ages
Poramathikul, 2021 (Battambang) 0.03 (0.02, 0.04) 4.16
Agtini, 2005 (Tanjung Priok and Koja) 0.07 (0.07, 0.08) 4.24
Subekti, 2003 (Denpasar) 0.03 (0.02, 0.05) 3.78
von Seidlein, 2006 (Tanjung Priok and Koja) 0.07 (0.07, 0.08) 4.24
Phantouamath, 2005 (Vientiane) 0.10 (0.04, 0.19) 1.24
Banga Singh, 2011 (Kota Bharu) 0.01 (0.01, 0.01) 4.27
Chompook, 2006 (Kaengkhoi) 0.03 (0.03, 0.04) 4.23
Chompook, 2005 (Kaengkhoi) 0.02 (0.02, 0.03) 4.25
Okada, 2020 (Nationwide) 0.03 (0.01, 0.05) 3.70
von Seidlein, 2006 (Kaengkhoi) 0.02 (0.02, 0.03) 4.25
von Seidlein, 2006 (Nha Trang) 0.04 (0.03, 0.04) 4.24
Vu, 2004 (Nha Trang) 0.03 (0.03, 0.03) 4.26
Subtotal (I^2 = 99.32%, p = 0.00) 0.04 (0.02, 0.05) 46.86
Heterogeneity between groups: p = 0.154
Overall (I^2 = 98.67%, p = 0.00); 0.04 (0.04, 0.05) 100.00
-.1
0
.1
.2
.3
Prevalence


Shigella in Southeast Asia
Study
ES (95% CI)
% Weight
Between 2000 and 2013
Meng, 2011 (Phnom Penh) 0.05 (0.04, 0.07) 3.67
Agtini, 2005 (Tanjung Priok and Koja) 0.07 (0.07, 0.08) 4.24
Elvira, 2007 (Jakarta) 0.01 (0.00, 0.02) 4.16
Subekti, 2003 (Denpasar) 0.03 (0.02, 0.05) 3.78
von Seidlein, 2006 (Tanjung Priok and Koja) 0.07 (0.07, 0.08) 4.24
von Seidlein, 2006 (Tanjung Priok and Koja) 0.05 (0.05, 0.06) 4.24
Phantouamath, 2005 (Vientiane) 0.10 (0.04, 0.19) 1.24
Banga Singh, 2011 (Kota Bharu) 0.01 (0.01, 0.01) 4.27
Bodhidatta, 2010 (Nongloo) 0.09 (0.06, 0.13) 2.53
Chompook, 2006 (Kaengkhoi) 0.03 (0.03, 0.04) 4.23
Chompook, 2005 (Kaengkhoi) 0.02 (0.02, 0.03) 4.25
von Seidlein, 2006 (Kaengkhoi) 0.02 (0.02, 0.03) 4.25
von Seidlein, 2006 (Kaengkhoi) 0.04 (0.03, 0.05) 4.07
Anders, 2015 (HCM and Dong Thap) 0.09 (0.07, 0.11) 3.80
Bodhidatta, 2007 (Hanoi) 0.09 (0.06, 0.12) 2.77
Hien, 2008 (Hanoi) 0.08 (0.05, 0.13) 2.63
Hien, 2007 (Hanoi) 0.05 (0.02, 0.11) 2.22
Thompson, 2015 (Ho Chi Minh) 0.03 (0.03, 0.04) 4.09
von Seidlein, 2006 (Nha Trang) 0.04 (0.03, 0.04) 4.24
von Seidlein, 2006 (Nha Trang) 0.04 (0.04, 0.05) 4.20
Vu, 2006 (Hanoi) 0.05 (0.03, 0.07) 3.70
Vu, 2004 (Nha Trang) 0.03 (0.03, 0.03) 4.26
Subtotal (I^2 = 98.92%, p = 0.00) 0.05 (0.04, 0.06) 81.08
Between 2014 and 2022
Poramathikul, 2021 (Battambang) 0.03 (0.02, 0.04) 4.16
Poramathikul, 2021 (Battambang) 0.05 (0.03, 0.06) 3.95
Poramathikul, 2016 (Battambang) 0.05 (0.03, 0.09) 2.91
Okada, 2020 (Nationwide) 0.03 (0.01, 0.05) 3.70
Duong, 2018 (Ho Chi Minh) 0.03 (0.02, 0.03) 4.21
Subtotal (I^2 = 63.57%, p = 0.03) 0.03 (0.02, 0.04) 18.92
Heterogeneity between groups: p = 0.033
Overall (I^2 = 98.67%, p = 0.00); 0.04 (0.04, 0.05) 100.00
-.1
0
.1
.2
.3
Prevalence


Shigella in Southeast Asia
Study
ES (95% CI)
% Weight
Present
Meng, 2011 (Cambodia) 0.05 (0.04, 0.07) 3.67
Agtini, 2005 (Indonesia) 0.07 (0.07, 0.08) 4.24
Subekti, 2003 (Indonesia) 0.03 (0.02, 0.05) 3.78
von Seidlein, 2006 (Indonesia) 0.07 (0.07, 0.08) 4.24
von Seidlein, 2006 (Indonesia) 0.05 (0.05, 0.06) 4.24
Bodhidatta, 2010 (Thailand) 0.09 (0.06, 0.13) 2.53
Okada, 2020 (Thailand) 0.03 (0.01, 0.05) 3.70
Anders, 2015 (Vietnam) 0.09 (0.07, 0.11) 3.80
Bodhidatta, 2007 (Vietnam) 0.09 (0.06, 0.12) 2.77
Duong, 2018 (Vietnam) 0.03 (0.02, 0.03) 4.21
Thompson, 2015 (Vietnam) 0.03 (0.03, 0.04) 4.09
Vu, 2006 (Vietnam) 0.05 (0.03, 0.07) 3.70
Subtotal (I^2 = 96.66%, p = 0.00) 0.06 (0.04, 0.07) 44.95
Not reported
Poramathikul, 2021 (Cambodia) 0.03 (0.02, 0.04) 4.16
Poramathikul, 2021 (Cambodia) 0.05 (0.03, 0.06) 3.95
Poramathikul, 2016 (Cambodia) 0.05 (0.03, 0.09) 2.91
Elvira, 2007 (Indonesia) 0.01 (0.00, 0.02) 4.16
Phantouamath, 2005 (Laos) 0.10 (0.04, 0.19) 1.24
Banga Singh, 2011 (Malaysia) 0.01 (0.01, 0.01) 4.27
Chompook, 2006 (Thailand) 0.03 (0.03, 0.04) 4.23
Chompook, 2005 (Thailand) 0.02 (0.02, 0.03) 4.25
von Seidlein, 2006 (Thailand) 0.02 (0.02, 0.03) 4.25
von Seidlein, 2006 (Thailand) 0.04 (0.03, 0.05) 4.07
Hien, 2008 (Vietnam) 0.08 (0.05, 0.13) 2.63
Hien, 2007 (Vietnam) 0.05 (0.02, 0.11) 2.22
von Seidlein, 2006 (Vietnam) 0.04 (0.03, 0.04) 4.24
von Seidlein, 2006 (Vietnam) 0.04 (0.04, 0.05) 4.20
Vu, 2004 (Vietnam) 0.03 (0.03, 0.03) 4.26
Subtotal (I^2 = 97.20%, p = 0.00) 0.03 (0.02, 0.04) 55.05
Heterogeneity between groups: p = 0.002
Overall (I^2 = 98.67%, p = 0.00); 0.04 (0.04, 0.05) 100.00
-.1
0
.1
.2
.3
Prevalence


S. boydii
Study
ES (95% CI)
% Weight
Indonesia
Agtini, 2005 (Tanjung Priok and Koja) 0.03 (0.02, 0.04) 14.45
von Seidlein, 2006 (Tanjung Priok and Koja) 0.03 (0.02, 0.04) 14.45
Subtotal (I^2 = .%, p = .) 0.03 (0.03, 0.04) 28.91
Malaysia
Banga Singh, 2011 (Kota Bharu) 0.01 (0.00, 0.04) 12.16
Thailand
Pulsrikarn, 2009 (Nationwide) 0.00 (0.00, 0.01) 17.64
Vietnam
Vinh, 2011 (Ho Chi Minh and Cao Lanh) 0.02 (0.00, 0.07) 7.05
von Seidlein, 2006 (Nha Trang) 0.00 (0.00, 0.01) 16.83
Vu, 2006 (Hanoi) 0.04 (0.00, 0.18) 1.49
Vu, 2004 (Nha Trang) 0.01 (0.00, 0.02) 15.93
Subtotal (I^2 = 4.21%, p = 0.37) 0.00 (0.00, 0.01) 41.29
Heterogeneity between groups: p = 0.000
Overall (I^2 = 89.76%, p = 0.00); 0.01 (0.01, 0.02) 100.00
-.1
0
.1
.2
.3
Prevalence



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