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Malaria Standby Emergency Treatment (SBET) for Travelers Visiting Malaria Endemic Areas: a Systematic Review and Meta-Analysis

Running title: Malaria SBET Systematic Review and Meta-Analysis

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RT and BG: Conceptualization, literature review, data collection, statistical analysis, writing and review of final manuscript.

JE: Methodology guidance, development of search vocabulary, review of final manuscript.

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1. Abstract

Background:

Malaria prevention methods for travelers to low or moderate malaria risk areas varies and remains controversial. Standby Emergency Treatment (SBET) for malaria is one possible strategy increasingly recommended since 1988 with little evidence on its effectiveness or how it is truly being used.

Methods:

A systematic review and meta-analysis were performed based on a structured search in Embase, Medline, PubMed, Cochrane, and Web of Science on September 7, 2018. The primary outcome was the overall prevalence of SBET use in travelers, and secondary outcomes were the proportion carrying SBET, the response to fever (use of SBET, health facility attendance, use of malaria rapid diagnostic test [mRDT]), adverse events to SBET, and the proportion using SBET incorrectly (incorrect dosage/duration). The pooled SBET use prevalence was analyzed using a random-effects model. A descriptive summary was done to present secondary outcomes. The study protocol was registered with PROSPERO CRD42018103703.

Results:

11 studies were eligible for inclusion among the 1027 titles identified by our search. The studies included 7/11 prospective cohort studies that recruited pre-travel clinic attendees in Europe, and 4/11 cross-sectional studies, of which 3 recruited travelers at airports before their return home from South-East-Asia and Africa, and 1 from an employee registry including long-term travelers. The overall pooled prevalence of SBET use among the 26’403 travelers was 2.5% (95%CI 1.1%-4.3%; range 0.4%-10.8%). There was significant variation in the proportion of travelers carrying SBET medication (40%-100%), the proportion of travelers

with appropriate response to fever (23%-100%), adverse events (0%-33%) and incorrect dosage/duration of SBET (0%-100%).

Conclusions:

Adherence to the proposed recommendations for SBET use, notably the response to fever, was poor. If the use of SBET is to be pursued, modifications to the current SBET strategy should be considered, such as better selection of travelers at higher risk for malaria, and the potential addition of mRDTs.

2. Introduction

The number of international travelers to countries at risk of malaria transmission is estimated to be more than 125 million per year (1). The importance of proper preventive measures against malaria is emphasized by a case fatality rate of malaria among international travelers to be around 1% (2, 3). While chemoprophylaxis remains the standard preventive measure for international travel to countries at high-risk of malaria transmission, preventive measures for travelers to low or moderate-risk areas, most notably the use of standby emergency treatment (SBET), remains controversial (4-6).

SBET is defined as the self-administration of anti-malarial drugs in emergency situations as a life-saving measure when malaria is suspected (7). The World Health Organization (WHO) (1) proposes the use of SBET among:

a) travelers staying in remote locations unable to seek medical attention within 24 hours of the onset of fever,

b) travelers in some occupational groups making frequent short stops to countries or areas with malaria risk over a prolonged period of time

c) short-term travelers spending ≥ one week in certain remote rural areas where there is very low risk of infection.

Areas of low to moderate risk of malaria infection is difficult to define (8), some defining it as an annual incidence of malaria in the indigenous population of less than 10 per 1000 individuals, or between 1-10 per 100 000 travelers (9, 10), while others use a combination of various surveillance data (11, 12).

Those in favor of SBET argue that malaria can be lethal if not treated promptly, could reduce the need for daily or weekly chemoprophylaxis, and the rise of counterfeit drugs justifies that

travelers carry their own supply of malaria medication. Furthermore, travelers to low or moderate risk areas often prefer the use of SBET as opposed to other prevention strategies (13). The use of SBET has been proposed to be used as a treatment in combination with chemoprophylaxis (11, 12) or as a stand-alone treatment in specific circumstances (1). Opponents of SBET propose daily chemoprophylaxis for low or moderate malaria endemic areas because of the potential fast progression to severe disease even when treated promptly, and question as well travelers' capabilities to respond appropriately to the SBET recommendations. Others argue that mosquito protection is sufficient for such areas given the easy access to health facilities in touristic areas, the risk of neglecting other lethal diseases when using SBET, and the wasted resources of unused anti-malarial drugs (4, 14).

SBET was first prescribed in Swiss travelers in 1988 (15) and progressively adopted by other countries around the globe. As malaria risk worldwide continues to decline (16), more travel destinations will become low to moderate malaria risk areas, thus possibly increasing the prescription of SBET as already seen (17, 18). While SBET has been prescribed for over 30 years now, we have little evidence on how it is truly used nor how effective it is in travelers around the world. The goal of this systematic review and meta-analysis is to better understand how SBET is currently used among travelers to malaria endemic countries, and notably how travelers apply SBET recommendations, with the aim of reassessing the relevance of SBET as a preventive strategy.

3. Methods

Methods of this analysis were specified in advanced and published in a protocol on PROSPERO on September 6, 2018, CRD42018103703 (19). This systematic review followed

the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplementary Material S1 for PRISMA checklist) (20).

Search strategy

We searched the following five databases for relevant articles: Embase.com, Medline Ovid SP, PubMed, Cochrane Library Wiley, and Web of Science – Core collection on September 7, 2018. The search performed combined three terms: malaria; self-treatment/standby emergency treatment; and traveler (see Supplementary Material S2 for full details on search strategies). Reference lists of retained articles were also reviewed.

Eligibility criteria

We included prospective cohort and cross-sectional studies that documented primary data on the number of travelers using malaria SBET out of the number prescribed or carrying SBET. No language, or publication date restrictions were imposed.

The study population included all adult and children travelers from non-endemic malaria countries to malaria endemic countries. Travelers included short and long-term travelers, workers, employees, volunteers, military personnel or expatriates visiting a malaria endemic countries.

The primary outcome was SBET use prevalence, defined as the number of travelers using SBET out of the number carrying SBET. In prospective observational studies in which the number of travelers carrying SBET was not documented, we used the number of malaria SBET prescribed.

Secondary outcomes included when available, the proportion of travelers carrying SBET among those that were prescribed SBET, the number of SBET carriers with appropriate response to fever (ingesting SBET, using mRDT and/or seeking a health professional), the

number of adverse events related to SBET use, and the number of SBET users with inappropriate SBET use (incorrect dose, incorrect duration). Given the expected limitation of data available for these outcomes and the heterogeneity of studies, a meta-analysis was not done for secondary outcomes, but rather we focused on describing the results of the individual studies.

Study selection, data collection and analysis

The two reviewers (RT, BG) independently scanned the titles and abstracts of studies identified in the computerized search to exclude publications that clearly did not meet the inclusion criteria. Independent full text review was also performed by both authors based on the review inclusion/exclusion criteria. Translations for the full-text review were undertaken for 4 studies in German and one in Chinese. We contacted authors to clarify information or to retrieve missing information when needed (8/11 studies). The data, as defined by the protocol, was extracted by one review author in a piloted form and the second author checked the extracted data. All disagreements were resolved by consensus.

The two reviewers (RT and BG) independently assessed the methodological quality of the included papers using a modified version of the Newcastle-Ottawa Scale (mNOS) checklist (21). In the modified version (Supplementary Material S3) the items relating to controls, comparability, and presence of outcome at start of study were eliminated due to the nature of the type of studies included.

Data for the meta-analysis were analyzed using STATA version 15.1. Stabilizing the variance of individual studies was performed using the Freeman-Turkey Double Arcsine Transformation (22). Due to the expected differences between study population characteristics, a random-effect model using the method of DerSimonian & Laird was applied to pool SBET use prevalence (23). Data for the primary outcome was presented using a forest

plot of SBET use prevalences. Heterogeneity was evaluated by measuring the variation between studies using the I^2 statistic, and explored using a funnel plot and Egger's test to assess for small-study effects.

A subgroup analysis was predetermined to explore heterogeneity using the following categories: short versus long-term travelers, by study design, by period of study (last year), by type of recruitment, by use of mRDT, and by mNOS. Due to the small number of studies (less than ten studies per subgroup category), subgroup analysis was not done, as recommended by the Cochrane handbook for systematic reviews (24).

4. Results

Study selection and characteristics

The search identified 1847 studies, for which 1027 remained after adjusting for duplicates. 53 studies were included for full text review, including 8 from cross references of the final studies. 11 studies were identified for inclusion in the meta-analysis (15, 25-34). See flow diagram Figure 1.

Among the 11 studies included, 7/11 were prospective cohort studies, and 4/11 were cross-sectional studies. Five studies included a study period between 1985 and 1995, two studies between 1996 and 2006, and four between 2007 and 2017 (Table 1). Publication dates ranged from 1990 to 2017 (median, 2000).

The included studies involved 26'403 travelers carrying SBET, of which 65% were from the Steffen et al. cross-sectional study published in 1990 (26). 9/11 studies included mostly short-term travelers (<3 months), with two studies that included mostly long-term travelers; Roukens et al. studied long-term international oilfield service employees (31), and Berthod et

al. long-term travelers (69%), travelers to remote areas (57%), humanitarian workers (11%), short-stay frequent travelers (4%), and travelers not willing to take malaria chemoprophylaxis (10%) for whom SBET was proposed together with mRDTs (32). Among the cross-sectional studies, three recruited travelers from Europe (25, 26, 30) and North America (25) at airports before flying back from their travel destination, while all the prospective cohort studies only included travelers recruited from their pre-travel consultations in Europe [Sweden (27), Germany (28, 29, 33), Switzerland (15, 32) and Spain (34)].

TABLE 1

The quality assessment using the mNOS found two studies that received 3/4 stars, four studies received 2/4 stars, four studies received 1/4, and one study received 0/4 stars (Supplementary Material S4). The major source of bias in all studies, came from the assessment of outcomes, as they were all self-reported, and ascertainment of exposure, as most were written self-reports.

Primary outcome: SBET use prevalence

The overall pooled SBET use prevalence of the 26'403 SBET carriers in 11 studies was 2.5% (95%CI 1.1%-4.3%). We detected significant heterogeneity within the studies (I^2 = 97.2%; Chi^2 = 357.41, df = 10) (Figure 2). A notable outlier that had a significantly higher SBET use prevalence included the Roukens et al. study, which enrolled international oilfield service employees who were mostly stationed for a long period in low to high malaria risk areas, a completely different population compared to the other studies (31). When excluding this study, the overall pooled SBET use prevalence of the remaining 10 studies dropped to 1.8% (95% CI 0.8%-3.2%) with a slight reduction in heterogeneity (I^2 = 95.8%). A funnel plot was drawn to explore this heterogeneity which did not find any evidence of a small study bias, confirmed by the Egger's test (p=0.53) (Sup. Mat. S5).

Figure 2: Forest plot of SBET use prevalence using a random-effects model

Secondary outcomes: SBET carriage, response to fever, adverse events due to SBET, incorrect dosage/duration of SBET

The data on the proportion of travelers carrying SBET out of those receiving a SBET prescription were available in 6/11 studies (table 2). All travelers carried the prescribed malaria medication for SBET in studies which either provided the drug as part of the study (15), provided the medication from the employer (31), or by ensuring SBET medication was bought when paying for the travel consultation immediately after the consultation (32). In the other studies, travelers had to buy their medication from a pharmacy after their travel consultation, with proportions as low as 38% (34) to as high as 72.6% (33). In the Ropers et al. cross-sectional study, they found that 65.9% (85/129) carried SBET medication out of those who were prescribed SBET, however overall 216 carried SBET medication, meaning 131 carried SBET without a SBET prescription, possibly acquiring SBET medication from a previous trip or from a friend/family member (30).

Seven studies provided information on the proportion of SBET carriers experiencing fever, varying between 4.6% - 23% (table 2). Among available information on attitude in those with fever, 2-100% used SBET when febrile, 0-79.9% consulted a health facility, and among the two studies in which travelers were provided mRDT, 50.4% and 57.1% used mRDT when febrile. Appropriate response to fever, defined as using SBET, consulting a health facility or using mRDT in the case of fever, varied between 23% to 100%. Among travelers using SBET, those consulting a health facility thereafter varied; 23/50 in the Nothdurft et al. study (28), 6/6 in Schlagenhauf et al. study (15), 94/178 in the Roukens et al. study (authors personal communication), 1/5 in the Berthod et al. study (32), and 0/4 in the Ferrara et al study (34). While according to our definition we considered that 23% (23/100) had

appropriate response to fever in the Vinnemeier et al. study, the authors of the study found that only 16% (16/100) had an appropriate response to fever, as they did not count 6 health facility visits by travelers that were not within the advised 24 hour period, and two who used SBET but did not apply the correct dosage/duration (33). Although disaggregated data was not available for the Roukens et al. study, there were already 79.9% (303/379) who had an appropriate response to fever by consulting a health facility, without considering SBET or mRDT use.

Two studies found that 87.5% (35/40) and 100% (2/2) travelers used SBET incorrectly, defined as ingesting the wrong dosage or duration of SBET medication (28, 33), while in three other studies there were no travelers that used SBET incorrectly (15, 32, 34).

Adverse events to SBET were documented in 6 studies with a proportion between 0 – 33.3% of SBET users. The majority of adverse events occurred in the older studies in which pyrimethamine, sulfadoxine, mefloquine, halofantrine, or chloroquine were used for SBET (15, 26, 28), all malaria medication that were no longer used in the more recent studies (32-34).

TABLE 2

5. Discussion

In this systematic review and meta-analysis of 11 studies describing SBET use in travelers to malaria endemic areas, the pooled overall SBET use prevalence among those who carried SBET was 2.5% (95% CI 1.1% - 4.3%). When eliminating the Roukens et al. study which included a very different study population, the overall pooled prevalence was 1.8% (95% CI 0.8%-3.2%).

A similar systematic review and meta-analysis was recently published without previous publication of the protocol. It included only seven studies for the primary outcome despite

using similar inclusion criteria, resulting in a similar SBET use prevalence of 2% (95% CI 1-3%) (35). Among the secondary outcomes analyzed, we included three more studies on the reporting of fever, two more studies reporting on the correct dosage/duration of SBET, one more study reporting adverse events, and additional analysis on the proportion of SBET use among travelers with fever. Our findings are in line with this previous meta-analysis but provide supplementary data for primary and secondary outcomes.

The SBET use prevalence of 2.5%, corresponds to a number needed to carry (NNC) SBET of 40 for every SBET used (NNC 56 when excluding the Roukens et al. study). As such, it seems like a reasonable number for a preventive measure against a potentially lethal disease. However when considering a SBET use prevalence of 2.5% for travel destinations where malaria incidence should be less than 0.001%, it becomes clear that SBET is mostly used for non-malarial infections (10). In fact Nothdurft et al. and Schlagenhauf et al. found that only 10.8% (4/37) and 16.7% (1/6) of SBET users actually had malaria (15, 28). Extrapolating this to our initial calculation (NNC 40), the number needed to carry becomes 240 to 370 for every SBET used for a real malaria infection. Considerably lower than the estimated NNC of 200’000 for travelers to Southeast Asia by Behrens (4). Moreover, in order to assess the relevance of SBET as a preventive strategy, the number needed to prescribe may be a better indicator than the number needed to carry, as it better assesses the intervention (prescription of SBET). The number needed to prescribe thus would vary between 370 to 981 for every SBET used for malaria. Despite this, the SBET approach without the use of mRDT, is expected to be used in the case of non-malarial febrile illnesses, as such it is not surprising that the NNP or NNC for the treatment of malaria to be so high.

Among the secondary outcomes analyzed, there was missing data for a number of variables in most studies. A high proportion of travelers were found not to adhere to the recommendations for SBET use. The first barrier to appropriate SBET use, arose before travel even begun, in

which three studies describing a considerable number of travelers who did not buy and carry the SBET medication prescribed to them (65.9%, 72.6%, 37.8%) (30, 33, 34). Two other studies not included in this analysis (did not fill inclusion criteria) found that only 61.4%, and 83% carried their prescribed SBET medication (36, 37). Proportions as low as 37.8% of travelers who bought their SBET medication, may suggest different views on the risk of malaria among travelers from different countries, and differences in pre-travel advice. Non-adherence to medical advice in regards to malaria prevention however is not new, and has been found to be low for chemoprophylaxis use and mosquito bite prevention despite good knowledge of the risk of malaria (38-40).

Poor adherence to the recommendations in case of fever when carrying SBET occurred frequently. WHO guidelines recommend that travelers consult a physician immediately if a fever occurs, and only if it is impossible to consult a physician or establish a diagnosis (with mRDT for example) within 24 hours, they should ingest SBET and then consult medical care thereafter (1). Only in the Roukens et al. study did more than half of the febrile travelers consult a health facility, while the second highest proportion of travelers consulting when febrile was found in the Berthod et al. study which also equipped travelers with mRDTs (31, 32). In the remaining studies that did not use mRDTs, travelers seeking a health facility ranged between 0-33%. Although the association between mRDT use and health facility consultation is limited by severe heterogeneity and small sample size, it may be explained by travelers wanting to consult a health facility due to confirmation of malaria with a positive mRDT, or by encouraging travelers to pursue with further investigations in the case of a negative mRDT. Among those seeking health care, not all did so within the recommended 24 hour limit as demonstrated in the Vinnemeier et al. study in which only 14/20 sought health care within this 24 hour limit (33). Schlagenhauf et al. found that while 66.6% (82/123) failed to seek medical attention, only 7.3% (9/123) were out of reach (15), similar to a Japanese

study on SBET use, which found that only 11% (1/9) of SBET users were out of reach from a health facility (41). As such, many travelers may have taken SBET despite being in proximity of a health facility. Additionally, among those taking SBET, not all sought health care after use, and several took an incorrect dosage schedule of SBET. While the overconsumption of antimalarials may not be associated to a significant number of adverse events, as demonstrated in the more recent SBET use studies, the false reassurance of taking SBET and not consulting may lead to serious complications and delay in diagnosis for other diseases mimicking the symptoms of malaria (42, 43). One retrospective analysis on imported malaria in France found that the use of SBET was associated to a 3.4 times higher odds of presenting severe malaria (44). Finally, some travelers did not adhere to any of the recommendations and did not seek health care or take SBET. In certain cases however, travelers were able to provide good reasons for their actions (symptoms lasting a few hours, incubation period too short) (28, 32) with good outcomes, suggesting that the proposed recommendations to fever response may not be appropriate in certain situations.

Despite poor adherence to SBET use recommendations, there are some studies that provide optimism. Roukens et al. demonstrated a high rate of medical attendance in case of fever that may be attributed to a formal training employees received on the risks and preventive methods against malaria and the presence of a 24 hour a day “Malaria hot line” (31). While such training is unrealistic for most pre-travel consultations, it may demonstrate the potential for more in-depth pre-travel counselling. Furthermore, the use of mRDT may limit the overconsumption of SBET as demonstrated by Berthod et al. who found a low SBET use prevalence despite including travelers at a higher risk of malaria. The prescription of mRDT however must be accompanied with proper training including written instructions and even a blank run in order to avoid inappropriate procedures and misinterpretation of results (45-47).

The first and main limitation of this meta-analysis is the heterogeneity of the studies. They include studies with different populations (origin, travel duration and destination), study design, recruitment methods, study periods (associated with changing malaria epidemiology), and use of mRDT. SBET was also used very differently, some as a stand-alone preventative method and others in combination with chemoprophylaxis in high risk areas. While these differences were expected, exploration of this heterogeneity was not possible due to the low number of studies. The quality of the studies varied, with significant bias as defined by the mNOS due to the self-reported nature of SBET use studies. .

In conclusion, SBET use was higher than expected given the estimated risk of malaria in the destination countries of travelers, however much lower than expected given the number with fever who did not consult a health facility. Adherence to the proposed recommendations for SBET use, notably the response to fever, was poor. If the use of SBET is to be pursued, modifications must be considered to reflect its current limitations, including better selection of travelers at higher risk for malaria, emphasis on the importance of consulting a health facilities, and the potential addition of mRDTs.

6. Figures Legend

Figure 1:

Title: Flow diagram of study selection

Subheading: SBET: Malaria Standby Emergency Treatment

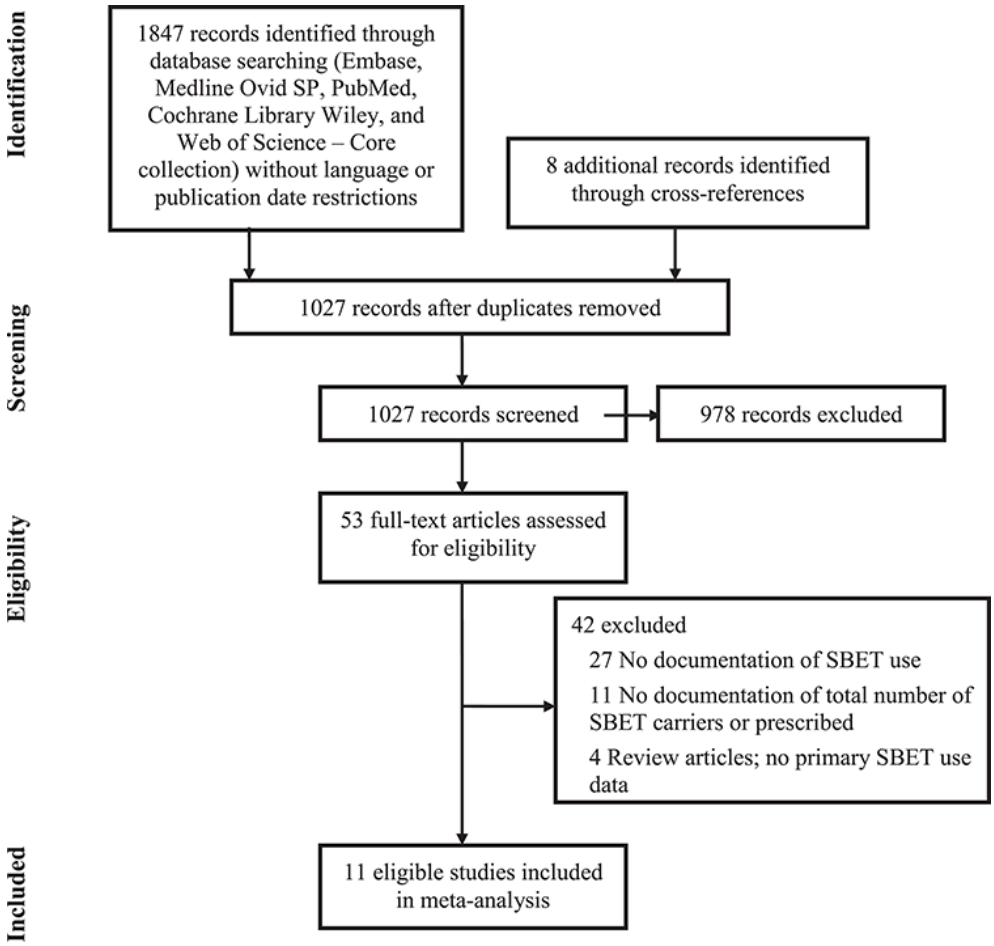

Figure 2:

Title: SBET use prevalence among travelers using a random-effects model

Subheading: SBET: Malaria Standby Emergency Treatment; CI: Confidence interval; ES: Effect size = SBET use prevalence in percentage

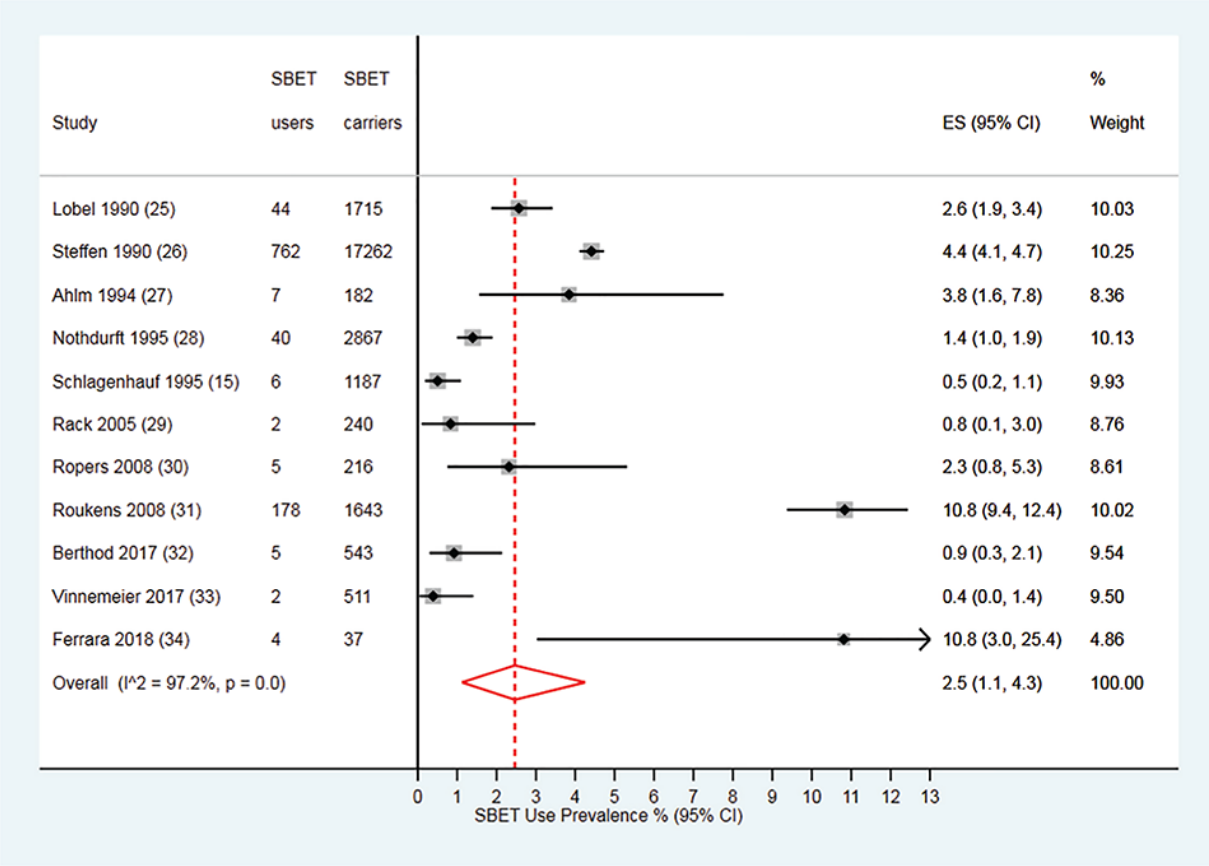

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Table 1: Study characteristics

Reference	Year	Study design	Type of traveler[a]	Number of SBET carriers	Study period
Lobel et al. (25)	1990	Cross-sectional	Short-term travelers flying back from Kenya	1'715	1-21 September 1987
Steffen et al. (26)	1990	Cross-sectional	Short-term travelers flying back from Africa	17'262	April 1985 to July 1988
Ahlm et al. (27)	1994	Prospective cohort study	Short-term travelers with pre-travel consultation in Sweden	182	November 1990 to May 1991
Nothdurft et al. (28)	1995	Prospective cohort study	Short-term travelers with pre-travel consultation in Germany	2'867[b]	1993
Schlagenhauf et al. (15)	1995	Prospective cohort study	Short-term travelers with pre-travel consultation in Switzerland	1'187	March to November 1992
Rack et al. (29)	2005	Prospective cohort study	Short-term travelers with pre-travel consultation in Germany	240	July 2003 to June 2004
Ropers et al. (30)	2008	Cross-sectional	Short-term travelers flying back to Germany	216	March to April 2004

			from Kenya, Senegal and Thailand		
Roukens et al. (31)	2008	Cross-sectional	Long-term international oilfield service employees	1’643	July to September 2007
Berthod et al. (32)	2017	Prospective cohort study	Long-term travelers with pre-travel consultation in Switzerland	543	February 2012 to February 2017
Vinnemeier et al. (33)	2017	Prospective cohort study	Short-term travelers to southeast Asia with pre-travel consultation in Germany	511	October 2013 to November 2014
Ferrara et al. (34)	2018	Prospective cohort study	Short-term travelers with pre-travel consultation in Spain	37	January 2017 to December 2017

[a] Short- and long-term travelers were defined as the majority of the cohort travelling <3 months or >3 months respectively. [b] Presumption that all those who were prescribed SBET carried SBET

Table 2: Secondary outcomes

Reference	Number of SBET carriers	SBET carriers out of those prescribed SBET (n/N)	Number with fever	SBET users	SBET use among those febrile	Health facility use among those febrile	Used mRDT among those febrile	Appropriate response to fever[a]	Adverse events to SBET	Incorrect dosage or duration of SBET medication
Lobel et al. (25)	1 715	-	n/a	44	-	-	-	-	-	-
Steffen et al. (26)	17 262	-	n/a	762	-	-	-	-	16.1% (123/762)	-
Ahlm et al. (27)	182	-	n/a	7	-	-	-	-	-	-
Nothdurft et al. (28)	2 867[b]	-	8.1% (232/2867)	40	17.2% (40/232)	-	-	-	15% (6/40)	87.5% (35/40)
Schlagenhauf et al. (15)	1 187	100% (1187/1187)	10.4% (123/1187)	6	4.9% (6/123)	33.3% (41/123)	-	34.1% (42/123)	33.3% (2/6)	0% (0/6)

Rack et al. (29)	240	-	n/a	2	-	-	-	-	-	-
Ropers et al. (30)	216	65.9% (85/129)	4.6% (10/216)	5	30% (3/10)	-	-	-	-	-
Roukens et al. (31)	1 643	100% (1643/1643)	23% (379/1643[c])	178	20.3% (77/379[c])	79.9% (303/379 [c])	50.4% (191/379 [c])	-	-	-
Berthod et al. (32)	543	100% (543/543)	16.8% (91/543)	5	5.5% (5/91)	40% (36/91)	57.1% (52/91)	79.1% (72/91)	0% (0/50)	0% (0/5)
Vinnemeier et al. (33)	511	72.6% (511/714)	19.6% (100/511)	2	2% (2/100)	21% (21/100)	-	23% (23/100)	0% (0/2)	100% (2/2)
Ferrara et al. (34)	37	37.8% (37/98)	10.8% (4/37)	4	100% (4/4)	0% (0/4)	-	100% (4/4)	25% (1/4)	0% (0/2[d])

[a] Appropriate response being defined as using SBET, consulting a health facility, or using mRDT. [b] Presumed that all those who were prescribed SBET carried SBET. [c] Personal communication. [d] 2/4 no data available