Vector-Borne Diseases & Treatment

Chapter 2

Stand-by Emergency Treatment (SBET) for Malaria

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Abstract

Background: Stand-by emergency treatment (SBET) is a strategy that aims to reduce the importation of malaria cases and their impact in terms of medical complications and health care costs. Some epidemiological studies have been focused on SBET use, but results were controversial. Therefore, a systematic review has been done to provide updated information.

Methods: A systematic research of scientific databases was performed to find studies reporting data not only on the use of SBET among travellers, but also whether its use was accurate and it was safe.

Results: Of 934 titles and abstracts screened, 7 articles were included in the systematic review synthesis, with significant heterogeneity between them. The number of SBET users among travellers was quite low (2.8%) and not accurate (30%), considering that some of them did not carry SBET medications while travelling abroad (36.8%).

Conclusions: The systematic review highlighted a sub-optimal adherence to pre-travel recommendations on SBET use among travellers, and fostered further studies to assess the cost-effectiveness and safety of this strategy.

1. Background

Malaria is an arthropod-borne disease transmitted by Anopheles spp. and caused by multiple *Plasmodium* species, occurring in Africa, Asia and America [1].

Malaria represents a relevant global health problem focused mainly on developing countries and travellers moving to endemic zones [2]. Every year, approximately 10,000 imported cases are diagnosed among travellers, which are associated with increased morbidity, mortality, and health care costs [3,4]. Mosquito-bite prevention is a basic strategy to protect against malaria (repellent use and sleeping under a mosquito net), whereas chemoprophylaxis represents an effective additional recommendation. Chemoprophylaxis is not always recommended; it depends on malaria attack rates, the main types of *Plasmodium* present while travelling, and the extent of travel.

However, chemoprophylaxis adherence and safety are questionable in some specific conditions. This is why the World Health Organization (WHO) in 1988 developed some recommendations to provide stand-by emergency treatment (SBET) among travellers. SBET was recommended as self-medication in case travellers were experiencing unexplained fever occurring seven or more days after visiting any malaria-endemic area and medical attention were unavailable in the first 24 hours after the onset of symptoms [5]. SBET was considered a curative course of anti-malarial drugs while travelling abroad to low- or moderate-risk areas or for those who did not declare specific itineraries of travel [6]. SBET was first adopted by Switzerland and, lately, several national guidelines of travel medicine have supported its use among travellers.

Nevertheless, recent reports cast doubts on the feasibility and the effectiveness of SBET itself [7-10]. This study aimed to review primary research investigating SBET use among travellers systematically.

2. Methods

2.1. Literature search

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements were followed while reporting findings of the presented systematic review [11,12]. A systematic search strategy was applied to an examination of PubMed, Embase, SCOPUS, Web of Science, Europe PMC, WHOLIS and LILACS databases, with the following terms: “malaria” and one among “emergency treatment”, “presumptive treatment”, “stand-by emergency treatment”, and “SBET” (both as MeSH terms and free-text keywords). Efforts to incorporate all available studies and grey literature also included manually cross-referencing bibliographies from full-

text articles assessed for eligibility, hand-searching abstracts from scientific congresses and meetings and surveillance reports. Observational studies on travellers' compliance towards malaria chemoprophylaxis that reported data on SBET separately were included. Reports in English, Spanish, Italian, Portuguese, and French were considered for inclusion in this analysis. No restriction in articles' time of publishing was considered. The literature extraction was conducted from June 2017 to December 2017, with one updated on 15 April 2018.

2.2. Screening, selection criteria and quality assessment

Selection criteria used for screening titles and abstracts were as follows: (1) original studies; (2) those including traveller populations and reporting data on the use of SBET for preventing malaria cases; (3) those addressing findings on the number of SBET users (main outcome) and the sequential steps of its use (number of travellers prescribed SBET, number of travellers who carried drugs while travelling abroad, number of travellers who experienced fever during the travel, number of SBET users, number of SBET users who experienced drug adverse effects, number of SBET users seeking medical attention after drug intake and confirmations of malaria diagnosis); and (4) those whose full text was accessible.

Records that met the following criteria were excluded: (1) studies without defined objectives or outcome measures, (2) those referring to SBET without providing additional information on the aforementioned consecutive steps of the use of SBET, (3) those examining presumptive treatment (not SBET) administered by health care professionals, (4) including populations (p.e., immigrants and expatriates) other than travellers. Assessment of titles, abstracts, and full texts for relevant articles was conducted by the authors, using a pre-determined form. Possible disagreements were resolved by group discussion until consensus was reached. A similar strategy was followed to evaluate the methodological quality of included studies, using an adapted version of the Newcastle-Ottawa Scale (NOS) [13]. For the purpose of this review, studies achieving a NOS score of 7 or greater were considered high-quality studies. Finally, those studies including only travellers for professional reasons were differentiated from those recruiting all type of travellers.

2.3. Data extraction and analysis

Baseline characteristics of included studies were extracted: first author's last name, country and year of publication, study type, sample size, description of outcomes of interests. Prevalence rates were calculated by extracting raw proportions with 95% confidence intervals (CI). Following the strategy built by Higgins and Thompson [14], *I2* statistics was performed to assess heterogeneity across the included studies, with a value of *I2* higher than 50% considered to represent substantial statistical heterogeneity. *P* value was set at ≤ 0.05. Probability of publication bias was also considered and evaluated by Begg's rank correlation test, funnel plot [15] and Egger's asymmetry test [16].

Subgroup analyses, with stratifications according to study design and NOS quality assessment, were performed. Sensitivity analysis was also applied to examine the effect of the removal of studies on the pooled estimates provided from meta-analytic models.

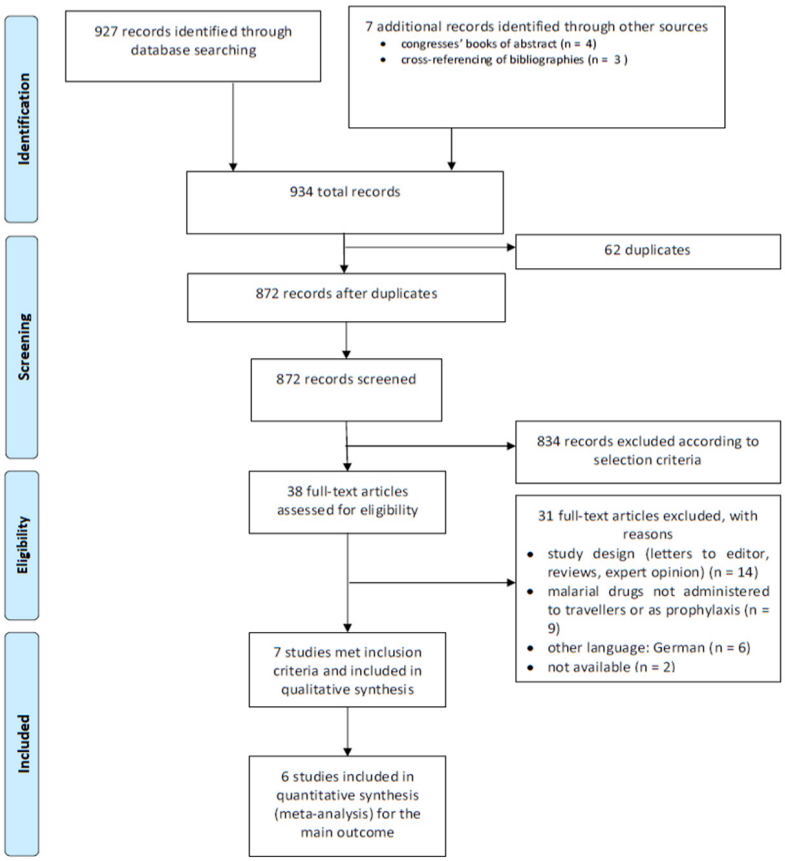
Data were analysed with Stata, version 12 statistical software, and a random-effects meta-analysis model, using the *metaprop* command was used to produce pooled prevalence estimates [17,18]. Forest plots were built using Review Manager, version 5.3 [19].

3. Results

3.1. Study identification

A total of 934 titles and abstracts of all articles were screened (**Figure 1**). After full-text examination, 7 articles were included in the systematic review, according to inclusion and exclusion criteria.

Figure 1: PRISMA flow chart of the included studies selection process.



The majority of studies (see **Table 1**) were done as cohort studies among European travellers (Switzerland, Germany, Netherlands, Spain) for tourism purpose after year 2000. The majority of evaluated studies (90%) were of good methodological quality (NOS >=5). A meta-analysis was recently published by the authors of this chapter [14], so we included its results and conclusions.

Table 1: Overview of studies included in the systematic review

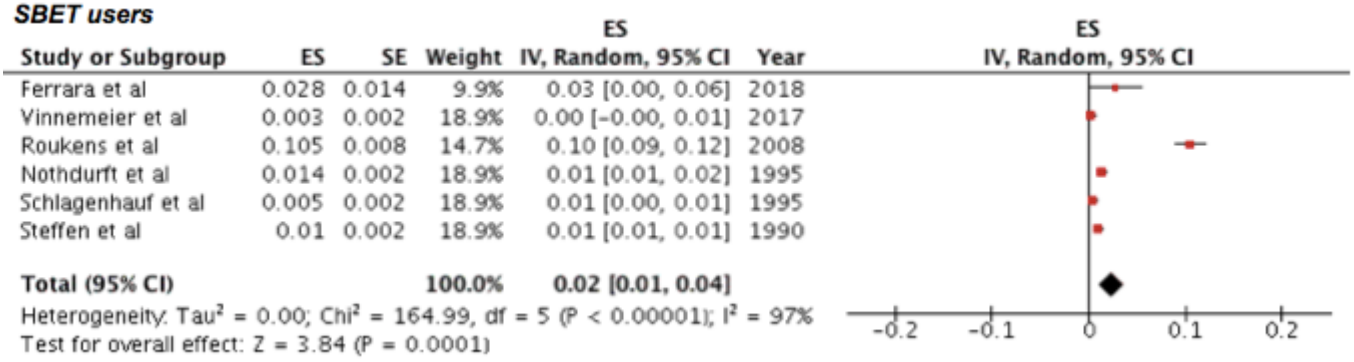
First author and year of publication		**Sample** *N*	**Proportion with fever** *N (%)*	**SBET users** *N (%)*	**Proportion of SBET users seeking medical care** *N (%)*	**Proportion of SBET users experiencing AEs** *N (%)*	**Confirmed malaria cases** *N (%)*
Ferrara, 2018[7]	**Total**	**145**					
	Not carrying SBET	61	NR	4 (10.8%)	0 (0%)	1 (0.3%)	0 (0%)
	Study design and sampling period	*Cohort study* - 2017 (12 months)		***Travel destination***	Worldwide	***Prescribed antimalarial drugs***	Atovaquone/ proguanil
Vinnemeier, 2017[8]	**Total**	**714**					
	Not carrying SBET	203	130 (18.2%)	2 (0.4%)	1 (50%)	NR	0 (0%)
	Study design and sampling period	*Cohort study* – 2013-14 (14 months)		***Travel destination***	Asia	***Prescribed antimalarial drugs***	Atovaquone/ proguanil
Roukens, 2008[18]	**Total**	**1645**					
	Not carrying SBET	NR	NR	172 (8.6%) *	NR	NR	NR
	Study design and sampling period	*Cross-sectional study* – 2007 (3 months)		***Travel destination***	Worldwide	***Prescribed antimalarial drugs***	Artemether/ lumefantrine
Kimura, 2006[17]	**Total**	**NR**					
	Not carrying SBET	**NA**	NA	9	6 (66.7%)	NR	NR
	Study design and sampling period	*Cross-sectional study* – 2003-4 (2 months)		***Travel destination***	Sub-Saharan Africa and Asia	***Prescribed antimalarial drugs***	Chloroquine (alone ore in combination)
Nothdurft, 1995[16]	**Total**	**2867**					
	Not carrying SBET	NR	232 (8.1%)	40 (17.2%)	23 (57.5%)	6 (15.0%)	4 (10.0%)
	Study design and sampling period	*Cohort study* – 1993 (12 months)		***Travel destination***	Worldwide	***Prescribed antimalarial drugs***	Chloroquine Halofrantrine Mefloquine
Schlagenhauf, 1995[19]	**Total**	**1187**					
	Not carrying SBET	NR	123 (10.4%)	6 (0.5%)	6 (100%)	2 (33.3%)	1 (16.7%)
	Study design and sampling period	*Cohort study* – 1992 (9 months)		***Travel destination***	South-America and Asia	***Prescribed antimalarial drugs***	Mefloquine Pyrimethamine
Steffen, 1990[15]	**Total**	**2075**					
	Not carrying SBET	NR	NR	21 (1%)	NR	NR	NR
	Study design and sampling period	*Cohort study* – 1984 (12 months)		***Travel destination***	Worldwide	***Prescribed antimalarial drugs***	Pyrimethamine

Steffen et al. [15] prescribed pyrimethamine as SBET to 2,075 airline crews, but only 1% (n = 1) took it, and no adverse events (AEs) were described. Five years later, Schlagenhauf et al. [6] also prescribed pyrimethamine or mefloquine as SBET to 1,187 travellers, but even they presented some criteria to take SBET (fever in 10% of cases); only 0.5% of travellers and 5% (n = 6/123) of symptomatic travellers were SBET users presenting some adverse events in 1 of each 3 SBET users (n = 2/6), and one malaria case was diagnosed. In the same year, Nothdurft [16] obtained similar results (prescribed SBET to 2,867 travellers, but SBET users were 1.4% of travellers who presented fever in 8.1% (n = 232/2867) of cases; 4 cases were diagnosed with malaria) with other antimalarial drugs prescribed (chloroquine, halofantrine or mefloquine), which could explain different side-effect rates of SBET described (15%). In Japan, Kimura et al. [17] described among nine SBET users (with chloroquine alone or in combination) that 6 of them sought medical care, so 30% of them took SBET appropriately, and no malaria was diagnosed among them. The study that reported higher SBET user rates was Roukens et al. [18], with 10.5% (172 among 1,645 travellers travelling worldwide) and higher malaria attack rates, with 3% of travellers (n = 46), maybe due to the type of antimalarial drugs prescribed (artemether, lumefantrine). Finally, the last two studies, Vinnemeier et al. [8] and Ferrara et al. [7] reported that malaria cases were diagnosed; they found different SBET user rates (0.4% and 2.8%, respectively) with the same antimalarial drugs prescribed (atovaquone/proguanil) and different percentages of travellers carrying SBET while travelling abroad (71.6% and 58%, respectively), probably linked to different national health services and travelling to different areas.

3.2. Number of SBET users and subgroup analysis

Overall, a total of 8,633 travellers entered the quantitative synthesis and, of those, 245 (2.8%) used SBET (see **Figure 2**).

Figure 2: Forests plot of pooled estimates of SBET users



SBET: stand-by emergency treatment for malaria; *ES*: effect estimate; *SE*: standard error; *CI*: confidence interval; IV: inverse variance; *df*: degrees of freedom.

The overall pooled effect estimate (ES) of SBET users in the studied population was 0.02 (95% CI, 0.01–0.04), with no publication bias (Egger's test p-value = 0.113), even sig-

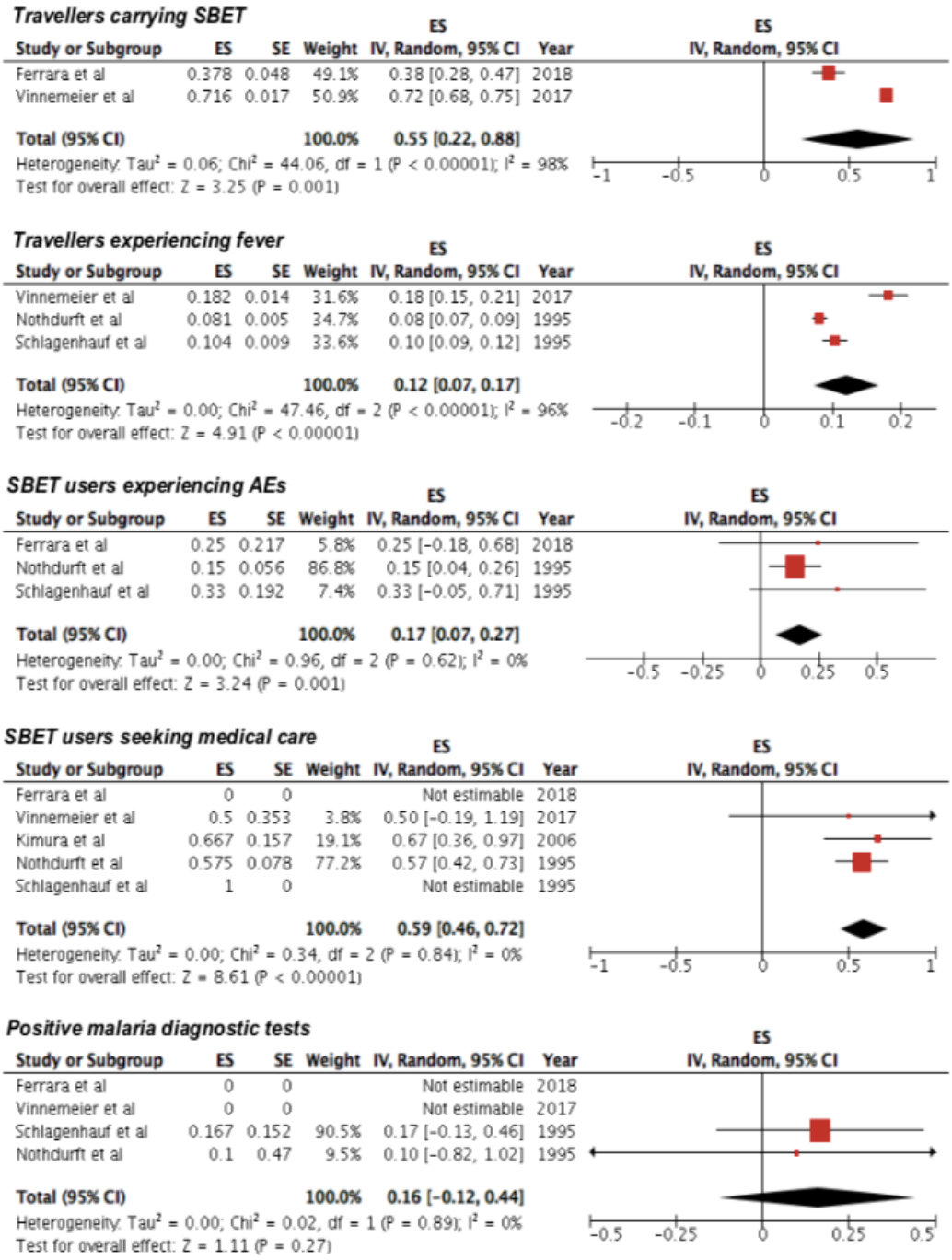
nificant heterogeneity (I2 = 97%, p <0.01) and asymmetry was described [14], mainly due to the Roukens et al. study [18]. A subgroup analysis according to NOS scores and study designs was performed, and no considerable changes were detected [14].

To date, travellers do not use SBET very often when they travel to different malaria-endemic areas; the estimated global use rate of SBET is 2% (95% CI: 1–4).

3.3. Other outcome measures

Other measures were collected and evaluated according to clinical symptoms presented while travelling, as well as safety and adequacy of SBET use (see **Figure 3**).

Figure 3: Forests plot of pooled estimates for other outcomes of interest.



SBET: stand-by emergency treatment for malaria; *ES*: effect estimate; SE: standard error; *CI*: confidence interval; IV: inverse variance; df: degrees of freedom; AE: adverse effects of stand-by emergency treatment.

The number of travellers prescribed SBET who actually carried medications abroad was 55% (95% CI: 22–88), so about a half of the patients who are prescribed the SBET strategy to minimise risk of severe malaria buy the drugs and carry them abroad.

Twelve percent of travellers (95% CI: 7–17%) presented fever, but only 2% of them started to use SBET (2%, 95% CI: 1–4%). Among the SBET users, 17% (95% CI: 7–27%) presented some adverse events (AEs), 59% (95% CI: 46–72%) sought medical care and 18% presented confirmed malaria (95% CI: 5–32%).

Ferrara [7], Nothdurf [16] and Schlagenhauf [6] described the side-effects as follows: one case of general malaise and nausea was reported in an atovaquone/proguanil user [7]; a case of severe nausea and vomiting, one of persistent headache, and one of generalised seizure, nervousness, generalised confusion and vomiting in three mefloquine users, whereas unspecified AEs were reported in one chloroquine user and in two halofantrine users [16]; and severe dizziness and insomnia were respectively reported by two travellers that self-administered mefloquine/pyrimethamine [6].

4. Discussion

This systematic review suggests that the overall prevalence of travellers who use SBET is low; a considerable proportion of travellers do not carry SBET medications while travelling abroad, and the majority of SBET users do not consider the conditions required for correct SBET implementation. So, much more effort is required in travel clinics to empower travellers.

The main goal of the presented synthesis was to assess the prevalence of travellers prescribed SBET who used it during travel, resulting in a pooled estimate of 2.8%. However, Roukens et al. (2008) reported a higher prevalence of SBET users (10.5%), likely because it was a cross-sectional study that supposed a high heterogeneity and enrolled workers of a single oilfield company, who previously attended a specific malaria training programme and received a curative medical kit, with temperature strip and disease self-test, in addition to SBET drugs [18, 19].

All included studies found a level of adherence to medical advice on SBET use among travellers that was far from optimal. A relevant proportion of them, despite medical prescription and recommendations, did not even carry drugs while travelling abroad. This finding might be ascribed to travellers' perception that going to low-risk areas for malaria falsely reassured them of not being infected with the disease [20].

Characteristics of subjects and studies did not find significant heterogeneity while assessing the number of SBET users who sought medical care following drug administration;

however, interesting is the presence of a consistent number of them not complying with this advice, with all but one research showing a prevalence greater than 50% of users, and one even of 100% [6,7]. This may be explained by the idea that taking a curative dose of antimalarial drugs, as in the SBET regimen, could be considered by users as an alternative for avoiding or delaying medical care, despite guidelines recommending immediate medical consulting after the administration of the emergency treatment [5, 6, 8].

Due to the considerable proportion of subjects travelling without SBET medications or not following the instructions regarding SBET use, it worth emphasising that traveller' behaviours and adherence to emergency treatment are far from satisfying. This casts doubts about the effectiveness of SBET itself, also considering that its success strongly depends on strict adherence to recommendations [21]. Overall, an incorrect self-administration regimen of SBET among travellers was evaluable in this synthesis, weakening the powerful arguments supporting the SBET strategy. However, despite this evidence, SBET prescription is steadily increasing, particularly in European countries [9,22]. In this regard, it is worth emphasising that six of the included studies in the quantitative analysis were conducted in Europe and the seventh in Japan, whereas SBET is commonly not recommended in the United States except as treatment in case of confirmed malaria diagnosis to prevent the use of counterfeit medications in some countries [23]. Again, the latest guidelines for malaria prevention in travellers from the United Kingdom (2017) recommend SBET as support to chemoprophylaxis, intending it not as a replacement for chemoprophylaxis itself. These guidelines also enforce the advice of the Advisory Committee on Malaria Prevention for areas at low risk for malaria transmission, which recommends no prevention strategies other than mosquito-bite avoidance measures and seeking medical advice as soon as symptoms develop [24].

As well, SBET feasibility copes with the economic evaluation of its own impact as alternative approaches for malaria prevention; indeed, the previous cursory analysis led by Vinnemeier and colleagues resulted in an unfavourable balance of the over-prescription of SBET if weighed against the actual number of people travelling to areas at low risk for malaria, as well as when it is balanced against the low number of cases of imported malaria to be potentially prevented on an annual basis [8].

The scarcity of safety analyses of SBET, including the lack of data regarding the risk of severe adverse effects to which users are exposed, weakens the effectiveness of this strategy too [6].

Briefly, evidence available so far does not ensure the effectiveness of the SBET strategy, and choice of stand-by emergency treatment is not actually reliable for most travellers, due to their incorrect adherence to medical prescriptions and instructions. Yet, 30 years after SBET recommendations were launched by the WHO [5], its indications are still frowned on among

pre-travel health consultants, and its use is limited to certain contexts, although travellers' preferences are seen to be for SBET more than traditional chemoprophylaxis [7]. Underlying factors predicting practices of SBET use among travellers currently remain unknown, even though several behavioural drivers could be assumed, such as travellers' desire not to interrupt their holiday/travel or the possible communication barriers with non–English speaking physicians [25]. The complexity of the pre-travel consultation process may play a role in this respect. Its effectiveness strongly depends on relationship and communication between consultants and travellers, and the latter are often overwhelmed with too much information, without focusing the most relevant aspects for healthy and safe travel [26].

Some limitations must be considered in addressing the findings of this synthesis. The type of studies on the topic of interest weakens the systematic review and meta-analysis, because they differed in design and did not evaluate completely similar populations. Moreover, disparity in study sizes and other publication biases reflected high heterogeneity that could likely affect the meta-analysis. Therefore, the present results should be interpreted with caution. Finally, the outcomes were dissimilarly evaluated in the included research, thus preventing the synthesis of all data by meta-analysis. However, performing subgroup and sensitive analyses should mitigate all limitations.

5. Conclusions

The presented systematic review of observational studies assessing SBET use among travellers indicates that a minority of travellers receives a SBET prescription, and when it is prescribed, a vast majority of SBET users do not follow the recommendations regarding SBET in case of presumptive malaria symptoms correctly. Additional, large-scale studies are warranted to validate these findings, and further assessments of the cost-effectiveness and safety of SBET are needed to tackle the risk of malaria in travellers from non-endemic countries.

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7. Competing interests

Authors declare no competing interests.

8. Transparency declaration

All authors: nothing further to declare.

9. Author contributions

All authors conceived and designed this document and were involved in drafting, revis-

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