Behavioural aspects of travellers in their use of malaria presumptive treatment

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The use of stand-by treatment for malaria by travellers depends on their knowledge, attitudes and behaviour. We examined the behavioural aspects of a cohort of travellers from Switzerland to low-risk malarial areas who, on recruitment, were provided with a kit containing medication for stand-by treatment, guidelines on the diagnosis of malaria, and materials for collection of blood samples for later confirmation of malaria. All subjects were urged to seek medical advice at the first signs of possible malarial symptoms.

Illness (fever as the main indicator) was reported by 123 of the 1187 participants, often accompanied by shivering/chills (36.6%), headache (35.0%), gastrointestinal symptoms (69.9%), and myalgia and/or arthralgia (41.5%). Two-thirds of those ill failed to seek medical attention despite their symptoms and pretravel advice. Only 9 (7.3%) were actually beyond the reach of medical attention. The stand-by treatment was self-administered by 6 travellers, only one of whom had confirmed malaria. Two non-serious adverse events were reported. All users consulted a physician after administering the presumptive treatment. This stand-by approach is limited by inappropriate behaviour and poor malaria awareness among travellers. These negative factors can be mitigated by development of an improved kit containing a simple test for self-diagnosis.

Introduction

More than 10 000 travellers every year fall ill with malaria and the case fatality rate in infections due to *Plasmodium falciparum* varies between 0.4% and 8.7% (*1–3*). Both the World Health Organization (*4, 5*) and the U.S. Centers for Disease Control (*6*) recommend that in addition to, or sometimes instead of chemoprophylactic drugs, travellers to malaria-endemic areas may carry with them suitable medication for presumptive or stand-by treatment (SBT) for emergency use when malaria is suspected and medical help is unavailable. This alternative is envisaged primarily for travellers to remote malarious areas where access to diagnostic and therapeutic facilities is limited. The rationale behind this recommendation is that in areas of low transmission the risk of adverse events attributed to chemoprophylaxis (suppressive therapy) exceeds the benefit of avoided infections (*7*). Presumptive treatment can be life-saving since falciparum malaria in a non-immune traveller requires prompt treatment.

Knowledge of, attitudes towards and practices of stand-by treatment are poorly documented. There is some information on the use of presumptive therapy by travellers (*8*) and airline crews (*9, 10*). Data on associated problems such as treatment failures (*11*), inappropriate use for non-malarial fevers, and incidence of adverse events are scarce. There is very little information on the behavioural aspects of travellers who are prepared for stand-by treatment, including the geographic location, type and timing of symptoms, chronological sequence of events, availability of medical help, compliance, medical follow-up and final outcome. We therefore conducted a longitudinal study to elucidate the behavioural characteristics of travellers with regard to the use of malarial stand-by treatment. Volunteers were followed by questionnaire and serologically using blood samples from the fingertip.

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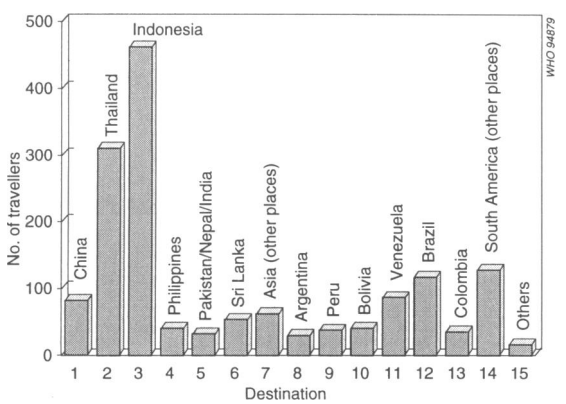
Materials and methods

Selection of subjects. All travellers, who could normally be recommended to carry stand-by treatment with them according to Swiss guidelines (*12*), were invited to take part in a cohort study at the Vaccination Centre of the Institute for Social and Preventive Medicine, University of Zurich, between March and November 1992. Their destinations were predominately areas of Central and South America or destinations in Asia (Fig. 1). The nature of the study was fully explained to each potential volunteer, who entered the study by giving written informed consent. Excluded from the study were pregnant or nursing women, persons with a history of allergy or severe reaction to components of the trial medication, and those with a history of epilepsy or psychiatric disorder. Long-term travellers (sojourns of more than six months) were excluded due to follow-up difficulties.

Materials. Each volunteer was provided with a kit containing the stand-by treatment which, as recommended by Swiss experts in 1992, was the triple combination called Fansimef (mefloquine 250 mg, sulfadoxine 500 mg, and pyrimethamine 25 mg). A single administration of three Fansimef tablets was the recommended dose for persons with a body weight >45 kg in cases of suspected malaria. The front of the kit contained concise information on how to recognize malarial symptoms and what procedure to follow if the condition were suspected. Appropriate use of the medication was defined as a single dose of 3 tablets of Fansimef administered if all of the following were applicable:

— the traveller was unwell with fever (37 °C on two readings taken at least 2 hours apart) with or without headache and/or myalgia;

Fig. 1. **Number of travellers and their destinations.** More than one destination is possible.



— at least 6 days had elapsed since the traveller entered the endemic area; and

— medical attention was unavailable within 12 hours of the illness. After this presumptive treatment it was stressed as imperative that the traveller should visit a physician as soon as possible to confirm the presumptive diagnosis.

A thermometer in a protective case was also provided, together with material (cotton swabs and lancets) for sampling fingerprick blood (50 µl) and chromatography paper that was clearly demarcated into three imprinted circles: one each to contain the blood droplet on recruitment, when malarial infection is suspected but before medication is administered, and after return to Switzerland irrespective of whether malarial treatment had been administered. This last sample was to be collected at least four weeks after the return date to ensure that any malarial cases occurring in this time frame were included in the study. Thus, each volunteer provided at least two blood samples, by fingerprick, which were spotted directly onto the chromatography paper.

Each volunteer also received a questionnaire concerned with the following:

— data on the traveller and his/her destination and type of sojourn;

— data in cases of illness with fever;

— data when presumptive treatment was administered; and

— data on medical consultations, malaria tests and differential diagnoses.

A stamped addressed envelope was provided for return of the questionnaire, the chromatography paper blood samples, and unused medication. In addition, a postcard was included in the kit (to be retained by the traveller for six months after return) in case malarial symptoms or delayed adverse events appeared later than one month after return. Written reminders were mailed to those who failed to return the questionnaires and blood samples as instructed.

Analysis of blood samples. The blood samples, eluted from the chromatography paper, were analysed using enzyme-linked immunosorbent assay (ELISA) for the presence of IgM and IgG antibodies to the synthetic peptide (NANP)50, which represents the immunodominant central repeat region of the major surface protein of *P. falciparum* sporozoites. Earlier work (*13*) suggests good sensitivity with this method but to ensure complete detection, the paper samples were later re-tested using the polymerase chain reaction (PCR) (*14–16*). PCR amplification was carried out on a polymorphic region of the major merozoite surface protein 1 (MSP1) of both *P. falciparum* and

P. vivax (*17, 18*). Cases of malaria were included only if confirmed by a positive ELISA or a positive PCR, or microscopically from blood smears obtained by the physician consulted when malaria was suspected. Persons who were treated presumptively but remained unconfirmed were considered to be non-malarial cases.

Statistical analysis. Data were analysed using the SPSSPC software package. The relationship between use of stand-by treatment and other variables was analysed using the chi-squared test and testing Kendall's τ coefficient. Significance was defined as $P<0.05$.

Results

A total of 1572 volunteers (approximately half of all who received stand-by treatment at the vaccinating centre in the specified period) were recruited, of which 1187 (76%) were evaluated. The remaining volunteers (24%) failed to return their questionnaires despite reminders or were lost to follow-up. The demographic data are shown in Table 1. The duration of the travellers' sojourn varied from less than one week to periods of up to six months. The volunteers were exposed for 4918 weeks in the low-risk malaria endemic areas. A total of 123 subjects (10.4%) reported that they had been ill with fever during their trip or in the month after return. Additionally, 14.2% were ill without fever or had some form of minor accident, and 73.5% of all participants regarded themselves as healthy throughout the entire sojourn. The relationship between the traveller's sex and incidence of illness was not significant ($P=0.12$). Younger travellers (aged ≤30 years) tended to classify themselves as ill more often than older travellers. This difference was significant ($P<0.01$). The first group, those reporting illness with fever, were further investigated since fever was one of the prerequisites for presumptive malarial treatment. Symptoms, concomitant with the fever, which could be ascribed to malaria included shivering/chills (36.6%), headache (35.0%), gastrointestinal symptoms (69.9%), and myalgia and/or arthralgia (41.5%) (Fig. 2).

Behaviour in response to illness. In reply to the question: "When did you first suspect malarial infection?", 7 (5.6%) of the 123 persons with fever suspected malaria before day six of their trip while 41 (33.3%) contacted a physician within the specified time-frame of 12 hours (including 12 (9.8%) who contacted a doctor but could not obtain a consultation within 12 hours). A total of 82 travellers (66.6%) failed to seek medical attention despite their symptoms. This category included 9 persons (7.3%) who did not consult a physician as they were out of reach of medical attention.

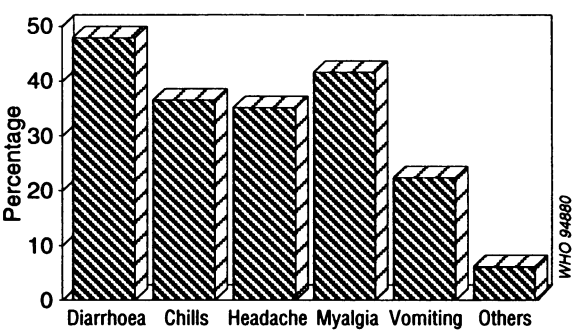
Of those who received medical attention, the time interval from onset of symptoms to medical consultation was in 95% of cases less than 4 days (range, 4 hours to 30 days; mean, 44 hours), and 59.1% of those who tried did manage to receive medical attention within 12 hours. The behaviour in reaction to perceived illness did not vary significantly with age or sex although there was a trend showing that women were more compliant with the issued instructions than men.

Table 1: **Demographic data on the 1187 participants in the study**

Characteristic	%	Characteristic	%
Age group (years):		*Duration of stay*:	
<20	1.2	≤1 week	5.6
20–29	47.4	2 weeks	17.4
30–39	26.4	3 weeks	29.7
40–49	12.0	4 weeks	27.5
50–59	8.1	~2 months	11.2
≥60	3.9	3–6 months	6.0
Unknown	1.0	Unknown	2.5
Sex:		*Place of stay*:[a]	
Male	50.4	Mainly in cities	23.3
Female	48.6	Mainly in towns/ tourist centres	48.2
Unknown	1.0	Villages/countryside	33.1
Type of trip:			
Tourist	64.5		
Adventure	21.9		
Business	1.9		
Visit family/friends	7.6		
Other	2.2		
Unknown	1.9		

[a] More than one answer possible.

Fig. 2. **Percentage distribution of symptoms in 123 patients with fever.** A patient could report more than one symptom.

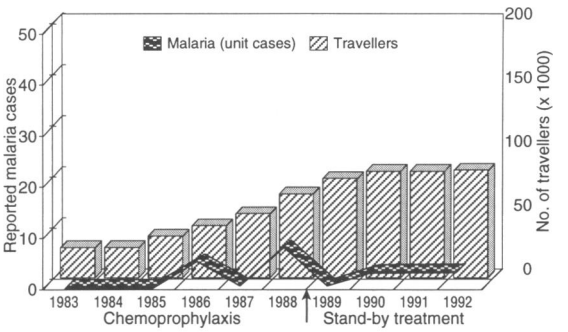


Influence of education. Those with higher education (university level) were less likely to consider themselves ill with fever and possible malarial symptoms than the other travellers ($P<0.01$). Those with a lower educational status were more correct in their behaviour and their reaction to illness ($P=0.01$). In general, the lower the level of education the greater the likelihood that the traveller would seek medical attention when ill.

Users of presumptive treatment. Only six persons, three women and three men, actually used the therapy for suspected malarial symptoms after the 6th day abroad. This accounts for 0.5% of the complete study population and also for a small proportion (4.6%) of those in the "ill with fever" group. The characteristics of the six users are shown in Table 2. All users of the medication complied with the dosage instructions and administered the three Fansimef tablets as a single dose. Two travellers self-administered their medication back home in Switzerland on the advice of their doctor. The time required for fever clearance ranged from 1 to 3 days. All users consulted a doctor after the administration of the medication to check the presumptive diagnosis; in some cases, medication other than the antimalarial agents was prescribed. Only one of the users actually had a malarial infection (confirmed by blood smear).

Adverse events. Subjective adverse events were experienced by two of the six Fansimef users: one case of subjectively severe dizziness resulting in 2 days incapacitation (bed rest required) was reported. The other event was insomnia, lasting for two nights.

Fig. 3. **Imported malaria cases from Thailand among Swiss travellers, 1983–92, using chemoprophylaxis (till 1988) and stand-by treatment (from 1989).**



Discussion

The participants in this study all travelled to classified low-risk areas where the probability of contacting a malarial infection during a limited time period is minimal. The soundness of the antimalarial strategy adopted by the Swiss (i.e., no chemoprophylaxis, but prepared for stand-by treatment) during travel to low-risk areas is demonstrated by the fact that the number of imported malaria cases from areas, such as Thailand, has not increased since this strategy was introduced in the autumn of 1988 (Fig. 3). There are, however, problems inherent in the strategy as shown in our study. Diagnosis of malaria is difficult, even for medical professionals and it is likely that trav-

Table 2: **Characteristics of six travellers who used stand-by treatment for presumptive malaria**

	Age/sex (years)	Area of use	Symptoms	Onset of symptoms	Physician consulted	Diagnosis	Fever clearance in:
User 1	26/F	Colombia	Fever, headache, myalgia, diarrhoea, vomiting	Day 17	Out of reach	Gastritis	3 days
User 2	38/M	Switzerland (returned from Malaysia)	Fever, headache, chills, myalgia	Day 24	Yes	Malaria (confirmed by microscopy)	3 days
User 3	28/F	Hong Kong (on arrival from Indonesia)	Fever, headache, chills, myalgia	Day 20	Yes	Viral infection	2 days
User 4	58/M	Switzerland (on return from Indonesia)	Fever, diarrhoea, vomiting	>Day 7	Yes	Amoebiasis	2 days
User 5	28/M	Sarawak (Malaysia)	Fever, shivering, myalgia, headache, diarrhoea, vomiting	Day 17	Yes (twice)	Viral fever (dengue fever)	1 day
User 6	29/F	Nepal	Fever, diarrhoea, headache, vomiting, shivering, myalgia	Day 6	Yes	Viral infection	1 day

ellers may mistake influenza or some other febrile illness for malaria and use the stand-by treatment. In this study, 123 persons (10.4%) judged their own clinical symptoms, with "malaria" as one possible diagnosis. Six persons used the stand-by treatment (0.5% of the entire cohort or 5% of those with possible malarial symptoms), but only one had confirmed malaria. On the other hand, some persons with typical malaria symptoms (82 (66.6%) of those ill) often hesitate to use the treatment—and a few of them may really have malaria. Thus, while wrong use of stand-by treatment may lead to serious adverse effects, failure to use it could result in death due to malaria.

The efficacy of the medication as a stand-by treatment cannot be assessed from this study, but travellers to areas of multiple-drug resistance (such as the border areas of Thailand) should be aware that the use of emergency malarial treatment in such areas could act as a short-term febrifuge and symptom suppressant without a cure, so that prompt medical attention is always imperative (*8*).

The inappropriate use of stand-by treatment may expose persons without malaria to a significant drug risk. With mefloquine, for example, which is often used alone as a stand-by treatment, the incidence of psychiatric events in prophylaxis is rare (approx. 1 in 13 000), but neurotoxicity is approximately sixty times more probable after treatment than with prophylactic use (*19*). Another drug for presumptive therapy, halofantrine, has been associated with electrocardiographic changes, namely prolongation of the QTc interval (*20–23*). In our study, none of the users experienced a serious adverse event; the adverse events reported were probably due to the mefloquine component of Fansimef. Such events have been reported elsewhere (*24–26*).

The behaviour of travellers is unpredictable. Tourists despite being made aware of the urgency of malarial treatment in this study, as elsewhere (*27*), waited for their symptoms to resolve spontaneously. This was contrary to the prescribed advice. The majority of travellers to Asia and South America can consult a physician if they suspect malaria; only 9 (7.3%) of those with fever in our study considered themselves out of reach of medical attention. Stress should thus be placed on seeking medical attention locally, whenever possible in case of illness. The importance of immediate follow-up consultation after stand-by treatment should also be underlined to determine the accuracy of the presumptive diagnosis, the need for alternative antimalarials in cases of non-efficacy of this treatment, and other treatment in cases of erroneous self-diagnosis.

Instructions to travellers should be given orally and in writing, including details of the type and severity of possible malarial symptoms and the circumstances in which the use of stand-by treatment can be considered. A possible future development is a kit which will enable the traveller to test a blood droplet for possible malarial infection using a simple diagnostic technique such as the rapid manual test "*para*Sight-F", an antigen capture test which is simple to perform and provides a definitive answer (88.9% sensitivity) in approximately ten minutes (*28*).[a] Such a test, appropriately simplified for use by travellers, would reduce the risk of a wrong diagnosis of malaria and enhance the strategy of presumptive treatment. Self-diagnosis of other frequently occurring illnesses among travellers (e.g., diarrhoea) is comparatively easier because the symptomatology can be clearly defined, but in malaria the clinical symptoms are often mild and atypical. Provision of a diagnostic test would increase the cost of the SBT strategy. A small additional charge may be acceptable compared with the overall cost of travel to distant places.

Our results showed only one case of confirmed malaria in a population of 1572 travellers, which is similar to previously reported attack rates for low-risk areas (*8*). The intervention costs incurred with the single malaria case in this study were approximately Sw.fr. 44 000 (approximately US$ 32 000) (i.e., 1572 times the cost of the kit (Sw.fr. 23), plus 41 visits to doctors (Sw.fr. 169 each) and six additional follow-up visits). The visits are at Swiss prices, which in developing countries would cost less. The benefits of this intervention strategy are the prevention of malarial complications. The approximate costs incurred in various outcomes of malarial infections, including death, have previously been estimated by Dinkel et al. (*29*). The addition of a simple diagnostic kit to the stand-by treatment would increase the intervention cost but would reduce the potential for misdiagnosis and inappropriate treatment. Travel to areas with greater malaria attack rates and the possibility of carrying the kit on more than one trip (prolonged expiry dates) would enhance the cost-effectiveness of this development.

In summary, the advantages of the stand-by treatment approach are the avoidance of side-effects associated with chemoprophylaxis and the life-saving potential of having presumptive therapy for falciparum infections. One constraint is the wide range of clinical presentations of malaria which makes it difficult to define simple guidelines with

[a] **Peyron F et al.** Assessment of a rapid manual test for the diagnosis of *Plasmodium falciparum* malaria (Poster). In: *Proceedings of the 3rd Conference on International Travel Medicine, 26–29 April 1993, Paris.*

accurate indications for the safe and appropriate use of antimalarial drugs by travellers. As the diagnosis of malaria is unlikely to be correct, stand-by treatment is more often overused or underused than used correctly. Incorrect use may actually be dangerous (*30*). Travellers should be encouraged to use adequate anti-mosquito measures and to visit a local physician if symptoms occur. Education of the travelling public and increasing their understanding of malaria prevention and cure are top priorities. In addition, there is an urgent need for development of a kit containing a test for rapid self-diagnosis by evaluation of a blood droplet. The aim therefore should be refinement of the strategy with the addition of a test for self-diagnosis.

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Résumé

Aspects comportementaux de l'utilisation du traitement présomptif du paludisme par les voyageurs

Les connaissances, les attitudes et les pratiques des voyageurs en ce qui concerne le traitement de réserve (SBT) du paludisme sont mal documentées. Cette étude examine le comportement d'une cohorte de voyageurs en provenance de Suisse et se rendant dans des régions d'endémie palustre à faible risque, qui avaient adopté les mesures antimoustiques comme stratégie de prévention du paludisme et qui avaient emporté un traitement de réserve à utiliser en cas de besoin.

Les sujets ont été recrutés entre mars et novembre 1992; il leur a été distribué un nécessaire contenant un traitement médicamenteux de réserve (méfloquine, sulfadoxine et pyriméthamine), un thermomètre médical, des informations sur le diagnostic du paludisme, et un matériel de prélèvement de sang capillaire au bout du doigt en vue de la confirmation ultérieure de l'infection. Tous ces sujets ont été instamment invités à consulter un médecin dès les premiers symptômes pouvant évoquer un paludisme. Sur les 1187 participants, 123 ont signalé une maladie (la fièvre étant le principal indicateur), avec frissons (36,6%), céphalées (35%), troubles digestifs (69,9%), myalgies et/ou arthralgies (41,5%). Les deux tiers des sujets tombés malades n'ont pas consulté de médecin, malgré leurs symptômes et les conseils reçus; seuls 9 d'entre eux (7,3%) étaient réellement hors de portée de tout traitement médical. Six voyageurs ont pris leur traitement de réserve, mais un seul était atteint de paludisme confirmé. Tous les utilisateurs ont consulté un médecin après la prise du traitement préventif, et deux réactions indésirables sans gravité ont été signalées.

La stratégie du traitement antipaludique de réserve permet d'éviter les effets indésirables associés à la chimioprophylaxie et a l'avantage d'utiliser des médicaments capables de sauver le malade en cas d'infection à *falciparum*. Il est toutefois peu probable que le diagnostic de paludisme soit correct, et le traitement de réserve est plus souvent sur- ou sous-utilisé que correctement utilisé. Cette stratégie est donc limitée par le comportement des voyageurs, le manque de connaissances concernant le paludisme et la difficulté de savoir s'il faut prendre ou non le traitement. Une solution possible pourrait être de mettre au point un nécessaire qui permettrait au voyageur de faire lui-même, au moyen d'une technique simple, le diagnostic de paludisme sur une goutte de sang prélevée au bout du doigt.

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