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Outpatient treatment of imported uncomplicated *Plasmodium falciparum* malaria: results from a survey among TropNet and GeoSentinel experts for tropical medicine

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Abstract

Background: *Plasmodium falciparum* malaria (*P.f.* malaria) is frequently imported to non-endemic countries. Recommendations on outpatient treatment differ largely due to differences in country-level guidelines and even between tropical medicine referral centres within the same country.

Methods: This survey among experts from TropNet or GeoSentinel referral centres for tropical medicine outside malaria endemic areas investigated common practices in *P.f.* malaria management, selection criteria for outpatient management and diagnostic procedures as a first step for developing a future common and evidence-based approach.

Results: A total of 44 referral centres participated. Most of the centres are located in Europe ($n = 37$). Overall, 27 centres (61%) treat uncomplicated *P.f.* malaria patients as outpatients, of which eight centres (18%) reported treating $\geq$75% of patients on an outpatient basis. Seventeen centres (39%) reported treating patients only as inpatients. No single criterion stands out for the decision regarding outpatient treatment, but three groups of factors were identified: (i) clinical criteria including laboratory parameters, clinical condition and tolerance of oral medication; (ii) factors such as patient compliance, reachability by phone and support at home and (iii) patient origin and place of residence as a proxy for possible underlying semi-immunity. The threshold parasitaemia for outpatient treatment varied from 0.1 to 5% with a median of 2%. A median of 0.5% of outpatients were admitted during follow-up. During the last 10 years, 33 complications were reported by nine of the 27 centres and three deaths by one centre.

Conclusion: This study gives insight into the heterogeneous management of *P.f.* malaria patients outside endemic regions. Although there is no consensus among experts, the majority of centres includes outpatient treatment in their clinical routine. However, the lack of evidence-based criteria and established safety for this approach shows the need for prospective studies to define and evaluate criteria and practices for safe outpatient management.

Key words: Plasmodium falciparum, atoquavone-proguanil, mefloquine, tafenoquine, parasitaemia, sentinel surveillance, travellers

Introduction

Plasmodium falciparum malaria (*P.f.* malaria) is frequently diagnosed among international travellers and migrants in non-endemic countries; it is associated with high morbidity and in severe cases with high lethality.[1,2] National management recommendations for imported *P.f.* malaria in non-endemic countries differ significantly—if they exist at all. Even specialist referral centres for tropical medicine in a single country may have different approaches to management of *P.f.* malaria.[3]

Patients with uncomplicated *P.f.* malaria in malaria endemic countries are routinely managed as outpatients, whereas guidelines in malaria non-endemic countries mostly recommend inpatient management of all imported *P.f.* malaria cases regardless of parasitaemia or other clinical factors indicating severity.[4,5] Regarding complicated *P.f.* malaria—either in accordance to the World Health Organization (WHO) definition[6] or respective national definitions (see below)—this approach is reasonable and necessary. However, the option of outpatient treatment of uncomplicated *P.f.* malaria cases in malaria non-endemic countries is appealing to clinicians for several reasons: in contrast to a ≈3- to 4-day hospital stay, outpatient management poses no risk of hospital-associated complications/infections and may be associated with higher patient satisfaction in eligible patients.

A major difference between endemic areas and non-endemic areas is the concept of semi-immunity. People in endemic areas may acquire semi-immunity against malaria resulting in less severe acute malaria episodes, which in turn may render outpatient treatment safer. There is no unanimous definition of semi-immunity or of the duration of its persistence after leaving an endemic area. People originating from malaria-endemic areas who have lived outside these areas for a certain amount of time may preserve some of their semi-immunity. In case of return to endemic areas, these travellers—typically those known as visiting friends and relatives (VFRs)—show a different and often less severe clinical picture compared with patients who had never been infected before. This may allow different routine management of these patients.

Referral centres for tropical medicine often apply centre-based guidelines or standard operating procedures in *P.f.* malaria patients with differing recommendations regarding outpatient treatment. Furthermore, national guidelines on management of *P.f.* malaria are not harmonized.[3] Some national guidelines in Europe, however, give clinicians the option of outpatient management in uncomplicated *P.f.* malaria patients. For example, the French guideline offers an option of outpatient treatment, whereas the UK guideline mentions this option more cautiously and the German guideline like most others excludes this option.[5,7,8] The American Centers for Disease Control and Prevention guideline recommends the admission of uncomplicated *P.f.* malaria patients to monitor clinical and parasitological response.[4] A position paper by the European Society of Clinical Microbiology and Infectious Diseases considers outpatient treatment within very strict limits.[9]

Several retrospective or observational studies on different malaria cohorts in Europe show that uncomplicated *P.f.* malaria patients have been treated safely as outpatients with an overall low mortality.[3,10,11] Furthermore, small studies have investigated treating imported *P.f.* malaria patients as outpatients prospectively using centre or in-house criteria for patient selection.[12–14] These studies support the general feasibility of outpatient treatment. However, these studies were conducted in the era of mefloquine and quinine treatment[12,14] or used atovaquone-proguanil as primary treatment.[13] Artemisinin combination therapies (ACTs) now offer new and unprecedented options for safer outpatient treatment, due to their rapid action and relatively low potential for adverse drug reactions. Their use in this context has not been evaluated prospectively so far.

Given the lack of safety and efficacy data in industrialized countries, outpatient treatment of uncomplicated *P.f.* malaria in non-endemic areas is still a field of intense scientific and clinical debate, and the lack of evidence in form of prospective studies using ACTs leads to uncertainty in guideline development.

To address this issue, this study investigated common practices in *P.f.* malaria management, selection criteria for outpatient management and diagnostic procedures performed at referral centres for tropical medicine outside malaria endemic areas. A survey among travel and tropical medicine experts working at these centres was conducted in order to give an overview of current practices, approaches and experiences. The information presented is intended to support the development of a multi-centre expert consensus for criteria on outpatient treatment, ideally as the first step towards a formal prospective evaluation of these criteria in multi-centre research protocols.

Methods

The study was designed as an expert survey using a password-protected web-based questionnaire on the TropNet website (see Supplementary Material for the full questionnaire). Experts were defined as senior specialists in tropical medicine working at either TropNet (European Network for Tropical Medicine and Travel Health, www.tropnet.eu) or GeoSentinel (Global Surveillance Network of the International Society of Travel Medicine, https://www.istm.org/geosentinel) sites with clinical responsibility for the management of *P.f.* malaria patients. Network centres were informed about the survey via internal communication and asked for voluntary participation.

The main endpoints were (i) information on whether *P.f.* malaria patients are routinely managed as outpatients and (ii) the basis on which the decision for outpatient treatment is made.

Furthermore, centres were asked specific questions regarding their management of *P.f.* malaria patients and concerning malaria in general such as defining the 'ideal *P.f.* malaria outpatient' or giving a definition for malaria semi-immunity. Furthermore, the questionnaire presented hypothetical *P.f.* malaria cases in order to obtain information on real-life clinical decision-making. In addition, centres were asked to estimate their annual numbers of *P.f.* malaria patients including the estimated percentage of outpatients and complication rates.

Depending on the response, we defined centres either as centres performing outpatient or inpatient treatment: 'outpatient centres' (OPC) or as centres which only performed inpatient treatment as 'inpatient centres' (IPC). Questions regarding outpatient malaria management practices were thus aimed at centres already performing such management; IPCs, however, were asked what management strategies they would consider if they performed outpatient therapy.

This study was designed as a survey among experts and did not ask for individual patient data; informed consent and ethical review were therefore not required. Patient numbers were estimates provided by the respective centre survey respondent. Completed questionnaires were electronically transmitted to the study coordinators. Data were analysed using JMP Vers. 13.2 (SAS Institute Inc., NC, USA). Statistical testing was carried out using the χ^2 test and Fisher's exact test, as appropriate regarding categorical data. Continuous data were analysed using the Mann–Whitney U-Test.

Results

Participating centres

Forty-four referral centres for tropical medicine took part in this survey. The majority of centres was located in Europe ($n = 37$). Five centres were located in North America and one centre each in South Africa and New Zealand.

Overall, 27 centres (61%) treated some *P.f.* malaria patients as outpatients (OPCs) and 17 centres (39%) reported treating patients exclusively as inpatients (IPCs). Table 1 shows the number of participating centres per country including the number of centres per country performing outpatient treatment; furthermore, the total number of patients per country is given as estimated by the respondents. Overall, there were no geographical differences in outpatient treatment practices. In most countries with several participating centres, there is no harmonized national practice. In countries with a guideline suggesting inpatient treatment only, such as Spain, Italy and Germany, about half of the centres nevertheless use the option of outpatient treatment.

There was no association between the annual number of cases treated per centre (as a surrogate of experience) and the practice of outpatient treatment. The percentage of patients managed as outpatients differs widely between centres (Table S1 available as Supplementary data at *JTM* online). Of the 27 OPCs, eight (29%) managed over 75% of patients as outpatients, whereas six centres (22%) only treated 1–5% as outpatients. IPCs were asked if outpatient management was an option and how many patients would be under consideration for outpatient treatment. Only four centres (of 17) would not consider outpatient treatment at all. The majority would, however, consider only 10% or less of patients as suitable for outpatient management. Again, treating higher numbers of malaria patients was not associated with the increased consideration of outpatient treatment.

Table 1. Centres per country with patient numbers

Country	Proportion of centres with outpatient treatment	Total annual patient numbers*
Italy	3/7	245
Spain	3/6	163
Germany	2/4	145
Switzerland	4/4	110
France	3/3	220
USA	2/3	37
Canada	2/2	27
Czech Republic	0/2	*5*
Denmark	0/2	20
UK	2/2	40
Portugal	1/1	10
Belgium	1/1	40
Finland	0/1	20
Ireland	1/1	10
The Netherlands	1/1	*5*
New Zealand	0/1	1
Norway	0/1	*5*
Sweden	1/1	40
South Africa	1/1	10

*Sum of estimated patient numbers of all participating centres per country.

When questioned whether applicable national guidelines exist with the option of outpatient treatment, 18 centres answered yes (41%), while 26 (59%) answered no.

Criteria for outpatient treatment. Centres were asked which patient population(s) were mainly treated as outpatients or which population would be considered to be suitable for outpatient treatment by IPCs (Table S2 available as Supplementary data at *JTM* online).

VFR patients and other so-called 'semi-immune patients' were treated or respectively considered as the major outpatient treatment population, whereas returning short-term travellers were considered least suitable for outpatient treatment. There were no significant differences in the classification of travellers suitable for outpatient treatment between OPCs and IPCs.

Workup of P.f. malaria patients. The diagnostic workup of *P.f.* malaria patients in general was surveyed in order to obtain an overview of which diagnostic procedures are applied by the different centres and on which potential selection criteria for outpatient management decisions could be based. All centres but one ($n = 43$) performed parasite counts (the centre in South Africa treats short-term traveller patients from malaria non-endemic regions in the field, performs a rapid test based on immunochromatographic detection of histidine-rich-protein-2 (HRP-2) and is therefore not included in this specific analysis). Additionally, full blood count, creatinine levels and transaminases levels were done by all centres; other tests/exams were performed in the following percentages of centres: in 91% bilirubin, 79% lactate dehydrogenase (LDH), 65% C-reactive protein, 53% ECG,

Table 2. Clinical criteria applied to decide on outpatient treatment

	All centres N = 43*	OPCs N = 27	IPCs N = 16*	*P*-value
Absence of criteria for severe malaria (WHO Criteria)	43 (100%)	27 (100%)	16 (100%)	n.a.
Compliance	37 (86%)	23 (85.1%)	14 (87.5%)	1
Accessibility/Distance to Treatment-Centre	32 (74.4%)	21 (77.7%)	11 (68.7%)	0.72
Support by friends/relatives	32 (74.4%)	21 (77.7%)	11 (68.7%)	0.72
Patient can be reached by phone	33 (76.7%)	20 (74%)	13 (81.3%)	0.72
Normal X-ray	13 (30.2%)	6 (22.2%)	7 (43.7%)	0.14
Semi immunity	22 (51.1%)	13 (48.1%)	9 (56.2%)	0.6
Fever < 38.5°C	12 (27.9%)	6 (22.2%)	6 (37.5%)	0.28
Not vomiting repeatedly	39 (90.7%)	26 (96.3%)	13 (81.3%)	0.13
No insurance	4 (9.3%)	4 (14.8%)	0 (0%)	0.27

OPC: centre with outpatient treatment; IPC: centre with inpatient treatment only.
*one centre did not provide answers.

42% Chest X-ray, 26% procalcitonin, 23% blood gas analysis and 16% abdominal sonography. Further testing by free text entry indicated the performance of blood glucose and lactate measurement (if not included in the blood gas analysis).

Clinical criteria for outpatient treatment. Centres were asked which clinical criteria are applied to decide on outpatient treatment or, in case of a centre without outpatient treatment, which criteria they would deem important for this decision; the questionnaire provided pre-specified criteria; additional criteria could be given in Table 2.

Absence of the 'WHO criteria for severe malaria' was unanimously important for outpatient treatment. Furthermore, treatment compliance and the absence of repeated vomiting were important for ≈90% of centres. Accessibility/distance to the treatment centre as well as support at home and possible contact via phone were important in 70%.

Laboratory criteria for outpatient treatment. Parasitaemia was found relevant by all centres; however, the range of maximum parasitaemia acceptable for outpatient treatment was wide, ranging from 0.1 to 5%. The median accepted parasitaemia was 2% in OPCs. IPCs would consider a median parasitaemia of 1% acceptable. Likewise, haemoglobin levels considered sufficient for outpatient therapy ranged from 5 to 12.5 g/dl (median 10 g/dl). Thrombocyte levels ranged from 15 000 to 140 000/µl with OPCs accepting slightly lower median levels of 62 500/µl, contrary to 100 000/µl considered by IPCs ($P = 0.07$). In general, OPCs considered more abnormal threshold values acceptable than IPCs. All surveyed laboratory parameters are shown in Table S3 (Supplementary data are available at *JTM* online). Again, values given by OPCs and IPCs are listed separately.

Model cases. Model cases were presented in order to obtain information on real-life clinical decisions made in different centres. Table 3 presents eight typical examples of patients with malaria and the recommended form of treatment with stratification between OPCs and IPCs. No statistically significant differences were observed in clinical decisions made between centre types.

Cases 'sick VFR #1' and 'sick tourist #1' are unanimously considered as inpatient cases. Both cases present with high parasitaemia with relevant malaria-associated laboratory findings. Looking at the other three 'VFR-cases', the option of outpatient treatment is more frequently considered. Cases 'asymptomatic VFR #1' and 'asymptomatic VFR #2' show the same clinical condition and differ only in laboratory values especially in parasitaemia of 2 vs 1% and haemoglobin of 9 vs 13 g/dl, respectively. These differences in laboratory values led to an increase for consideration for outpatient treatment from 42 to 93%.

Consideration of outpatient treatment among tourists is generally lower. In both 'asymptomatic tourist cases' rates for recommendation of outpatient treatment were lower than the corresponding asymptomatic VFR cases.

Concept of semi-immunity. We asked the centres to provide a definition for malaria semi-immunity. Forty-two centres provided answers, and nine centres did not give a clear definition (all answers are provided in the Supplementary Material). Centres gave very different definitions varying from 'VFR patients in general' to 'patients born and still living in an endemic area with no period of absence from such area for more than a few weeks in any year'.

Two approaches in defining semi-immunity were visible: in one perspective, the time outside an endemic area was applied without further definition of the time spent in the endemic country; the time ranged from only visiting a non-endemic country without defining the duration of the visit up to 10 years outside the endemic country. In the second approach, the time spent in an endemic area was seen as important regardless of the time outside that region; the time defined ranged from 'childhood' over 'born and raised' to '>10 years' or permanently living in an endemic region. In summary, approaches to the definition showed great variability.

Treatment of outpatient P.f. malaria. Centres with outpatient treatment were asked for their first-line antimalarial treatment of outpatients. The majority of centres ($n = 17/27$, 58%) uses artemether/lumefantrine. Ten centres (34%) use dihydroartemisinin/piperaquine and two (8%) centres use atovaquone/proguanil as first-line medication. Second-line medication included mainly atovaquone/proguanil ($n = 19/27$, 65%) and oral quinine ($n = 3/27$, 10%).

Follow-up, complications and readmission to hospital. Twenty-six of the 27 centres practicing outpatient treatment systematically

Table 3. Model cases

Model case	All centres $n = 43$		OPCs $n = 27$		IPCs $n = 16$*	
	Admission	Outpatient	Admission	Outpatient	Admission	Outpatient
'Sick VFR #1': Migrant from sub-Saharan Africa, living in Europe since 5 years, was VFRs, no prophylaxis feels ill, fully conscious, parasitaemia: 7%, Hb 8.5 g/dl, thrombocytes: 80/nl, creatinine: 1.4 mg/dl	43	0	27	0	16	0
'Sick VFR #2': Migrant from sub-Saharan Africa, living in Europe since 5 years, was VFRs, no prophylaxis, feels well after paracetamol, fully conscious, parasitaemia: 4%, Hb 9 g/dl, thrombocytes: 100/nl, creatinine: 1.2 mg/dl	35	8 18.6%	21	6 22.2%	14	2 12.5%
'Asymptomatic VFR #1': Migrant from sub-Saharan Africa, living in Europe since 5 years, was VFRs, no prophylaxis, good general condition, fully conscious, parasitaemia: 2%, Hb 9 g/dl, thrombocytes: 100/nl, creatinine: 1.2 mg/dl	25	18 41.8%	14	13 48.1%	11	5 31.2%
'Asymptomatic VFR #2': Migrant from sub-Saharan Africa, living in Europe since 5 years, was VFRs, no prophylaxis, good general condition, parasitaemia: 1%, Hb 13 g/dl, thrombocytes: 200/nl, creatinine: 0.8 mg/dl	3	40 93%	3	24 88.9%	0	16 100%
'Sick Tourist #1': 55-year-old tourist, history of hypertension, high fever, good general condition, fully conscious, parasitaemia 4%, Hb 8.5 g/dl and thrombocytes 160/nl.	42*	0 0%	27	0 0%	15*	0 0%
'Sick Tourist #2': 28-year-old tourist, no medical history, fever, good general condition, fully conscious, parasitaemia 5%, Hb 9 and thrombocytes 120/nl.	42	2 4.6%	25	2 7.4%	16	0 0%
'Asymptomatic Tourist #1': 65-year-old tourist, history of hypertension, low-grade fever, fully conscious, good general condition, parasitaemia 1%, Hb 10 g/dl and thrombocytes 120/nl.	29	14 32.6%	18	9 33.3%	11	5 31.2%
'Asymptomatic Tourist #2': 25-year-old tourist, no medical history, low-grade fever, good general condition, fully conscious, parasitaemia 2%, Hb 10 g/dl and thrombocytes 160/nl.	22	21 48.8%	14	13 48.1%	8	8 50%

*One centre without answer.

followed up patients. Centres were asked for their routine follow-up schedule including the applied examinations.

Seventeen centres scheduled a visit on day 2 (day 1 being the day of diagnosis and begin of treatment); a full blood count and creatinine were performed practically by every centre. Of these centres, four scheduled a visit on day 2 only and 13 centres scheduled visits on days 2 and 3. Seven centres planned visits on day 3 only. Again, almost all centres performed a parasite and a full blood count on day 3. Two centres scheduled their first follow-up visit on day 6 or 7. Regarding the issue of post-artemisinin delayed hemolysis,[15] no OPC scheduled visits on day 10 or 14 or performed LDH measurement.

Centres were requested to provide estimates of patients' adherence to follow-up visits. These ranged from 30 to 100% with a median of 80% (IQR 70–95%). Full compliance regarding the medication instructions was estimated from 50 to 100% with a median of 95% (IQR 83.75–100%). Unscheduled visits during the follow-up were reported to be 1–50% of outpatients (median 10%, IQR 2–20%). The main reasons are shown in Figure 1.

Hospital admission during follow-up was reported by 16 of the 27 OPCs (59.2%). Approximated percentages of patients admitted during follow-up ranged from 0 to 20% with a median of 0.5% (IQR 0–4.25%). Reasons for admission were repeated vomiting, adverse drug reactions, other travel-related infections or parasitological failure.

Finally, centres were asked for an estimated number of known life-threatening complications in patients treated as outpatients from causes related to malarial infection or antimalarial treatment during the last 10 years in absolute numbers. In total, 33 complications were reported by 9 of the 27 centres with outpatient therapy. The other centres did not report complications. Three deaths were reported by one centre during the last 10 years among patients treated as outpatients; further information on these deaths was not retrievable.

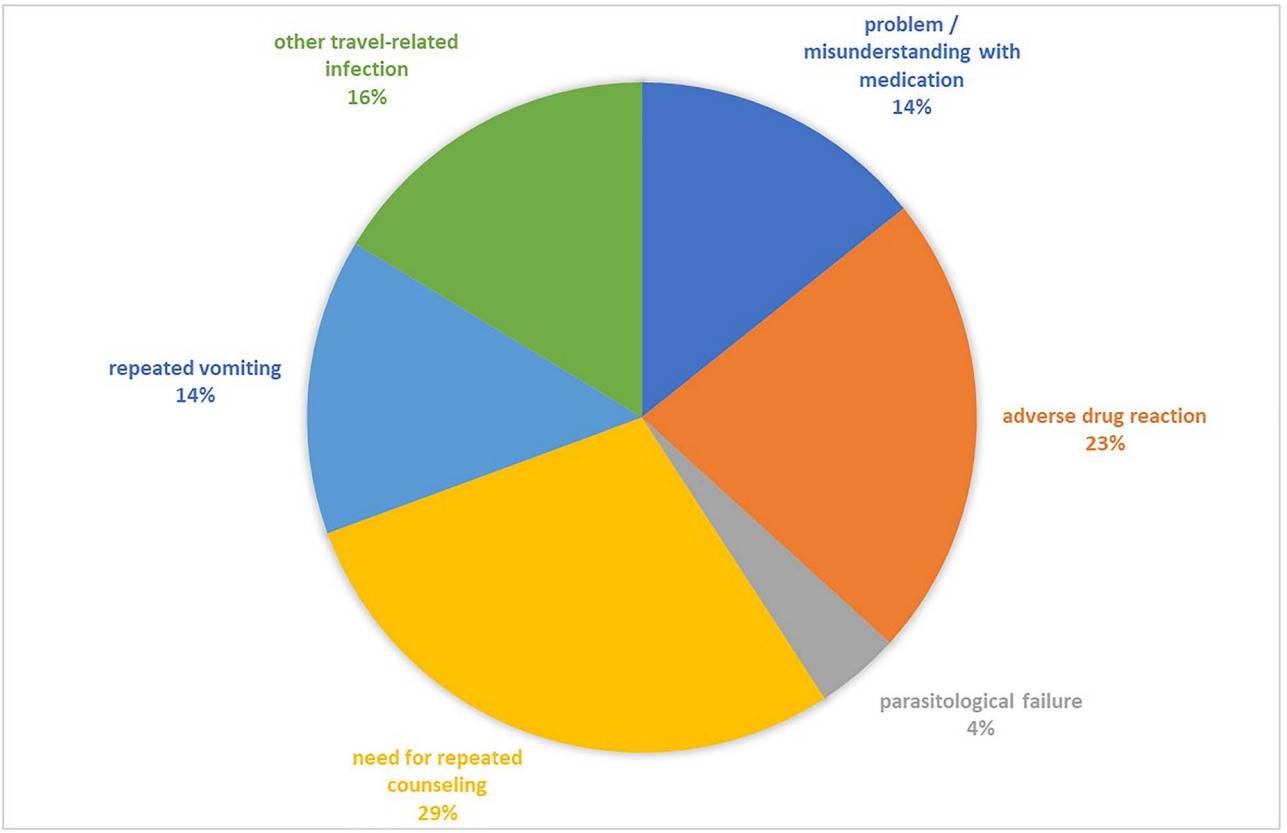

Figure 1. Reasons for unscheduled presentation. Unscheduled visits during follow-up were reported in a median of 10% of outpatients; the different reasons are given in percentages

Discussion

This study gives insight into the heterogeneous management of *P.f.* malaria patients outside endemic regions among clinical tropical medicine referral centres. Although there is no consensus on this topic among experts, the majority of centres includes the outpatient treatment of *P.f.* malaria patients in their clinical routine. This approach is supported by the availability of well-tolerated and rapidly acting ACTs; no clinical evidence is, however, available evaluating this approach so far in the artemisinin era. Harmonized international or European recommendations for the outpatient management of uncomplicated *P.f.* malaria patients outside endemic areas do not exist. National guidelines do not provide consensus guidance on this topic, as even centres in the same country apply different management approaches. In the example of Germany, half of the centres deviated from their national guideline by providing outpatient treatment to their patients, which is explicitly discouraged in the national guideline.

In terms of patient selection, this study found that no factor stands out on its own as a criterion for outpatient treatment. However, three groups of factors can be identified: first, clinical criteria including laboratory parameters, clinical condition and no repeated vomiting, hence, the ability to swallow the oral drugs. Second, 'soft' factors or logistics such as patient compliance, reachability by phone, support at home, distance to the hospital, etc. Third, patient origin and place of residence as surrogates for the concept of semi-immunity was of importance. The only recent and prospective study on outpatient treatment with atovaquone-proguanil conducted in the UK was relatively small and showed a readmission rate of 5.3% and no deaths in 106 patients treated on an outpatient basis—criteria of the second type were not included as selection criteria.[13]

Regarding the role of laboratory tests, the most important parameter was parasitaemia, ranging from 0.1 to 5%; OPCs tended to accept a higher median parasitaemia than IPCs (2 vs 1%, $P = 0.56$). However, patients in previous studies by Bottieau *et al*. and Sharma *et al*. using atovaquone-proguanil, mefloquine or quinine had a low median parasitaemia of <0.22 and <0.1%, respectively.[13,14] Thus, there are still no prospectively collected data on outpatients with higher parasitaemia or with the use of ACTs.

Overall, patients originating from an endemic country are managed differently than non-immune travellers as our model cases illustrate. Answers regarding the definition of semi-immunity varied significantly and underlined that there is no consensus standard definition. However, the origin of the patient and the amount of time residing in a malaria endemic country were factors in the decision to treat on an outpatient basis. Related to this, semi-immunity was also mentioned in half of the answers regarding the 'ideal malaria outpatient for outpatient treatment.' Previously, a large UK registry study demonstrated that VFR-travel as a proxy for semi-immunity is associated with a lower chance of death when compared with short-term tourist travellers (adjusted odds ratio of death of 8.2 associated with tourist travellers compared with VFRs).[16] On the other hand,

semi-immunity of African patients must be further studied, as many local residents and people originating from endemic areas live or lived in larger cities where malaria endemicity is often very low. Such persons might better be considered to have the same malaria risk as visiting tourists.

Thorough follow-up should be a major tool in outpatient management of *P.f.* malaria patients. Previous studies applied different follow-up strategies varying from presentation in the outpatient department during the first days of treatment to follow-up only by telephone.[12–14] Our data show that follow-up visits after treatment initiation are applied by most centres with outpatient management, however, with a varying degree regarding the frequency of visits. The median estimated rate of admission among outpatients in this study was very low; this was the case only in ≈1 out of 200 patients. Previously conducted prospective studies by Bottieau *et al*., Sharma *et al*. and D'Acremont *et al*., all report admission rates of around 5% during follow-up.[12–14] These studies were conducted prior to the use of ACTs, and adverse drug reactions (to quinine for example) led to several admissions.

Based on the estimated patient numbers in this study, ≈210–270 patients are treated as outpatients each year resulting in an estimated number of 2000–3000 patients over the last 10 years in the participating OPCs. Thirty-three cases of complications were recalled during the last 10 years, including three deaths, resulting in an estimated complication rate of 1.1–1.6% and a mortality rate of below 0.15%. In comparison, the observational study by Casalino *et al*. reports one death over 14 years among 6952 observed outpatients, which occurred in the years 2000–2003 prior to the use of ACTs resulting in a mortality rate of 0.01%.[11] On the other hand, the benefits of outpatient management were discussed in the recent prospective trials by Sharma *et al*. and Bottieau *et al*. Cost effectiveness of outpatient management was highlighted by both studies besides assumed higher patient satisfaction.[13,14] In addition, the observational study by Casalino *et al*. highlighted the overall lower hospitalization rate in general as important.[11] In summary, the option of outpatient treatment should only be offered to patients who are eligible for this form of management and who may have a personal benefit in terms of avoiding inpatient treatment and potential complications associated with it.

This study has limitations. The results presented are expert opinions only and are not directly based on clinical data. Our calculations are only an estimate as they are based on respondents' recollection and are not based on prospectively collected patient data. Most centres that participated were European centres and the results may not fully reflect experiences and views from non-European experts. We assume that participating centers are among those with highest experience in management of *P.f.* malaria, but their views may not be fully representative for medical practice in their respective countries.

Many referral centres for tropical medicine use the option of outpatient management of *P.f.* malaria patients in their clinical routine. Selection criteria are very heterogeneous, but in experienced hands, outpatient treatment seems to be a generally safe option as evidenced by the high numbers of malaria patients treated in our participating centres. A combined clinical assessment by ruling out severe malaria and organ complications as well as assessing social and logistical factors is usually applied to identify patients who can be managed as outpatients. Although ill-defined, the concept of semi-immunity or patient origin plays a major role in the clinical decision-making.

Table 4. Summary of criteria considered most relevant by experts for outpatient treatment

Absence of any severe *P.f.* malaria criteria (WHO or national criteria)
First dose of ACT in clinic or emergency room and observation for 4–6 h
No vomiting
Available via phone and sure compliance
Not living alone/support at home
Acceptance of daily follow-up
Semi immune (visitor from endemic area or VFR in non-endemic area for <5 years)
Laboratory criteria:
• Parasitaemia <1%
• Haemoglobin >10 g/dl
• Thrombocytes >100.000/µl
• Creatinine <1.5 mg/dl

The absence of criteria for severe malaria alone is obviously not sufficient for identifying patients suitable for outpatient care; for the group of uncomplicated malaria patients suitable for treatment as outpatients, new criteria including the use and frequency of follow-up visits need to be developed and validated in future studies. Most relevant potential parameters on the basis of answers of this survey for such a future definition according to expert opinions are summarized in Table 4. These parameters could be a first step for defining inclusion criteria in a prospective clinical *P.f.* malaria outpatient trial. Eventually, clinical practice should always be guided by the principle that all measures must be taken to avoid death as a consequence of outpatient treatment.

Supplementary data

Supplementary data are available at *JTM* online.

Author contributions

T.L. developed the study design, conducted and analysed the survey, interpreted the data and wrote the manuscript. T.Z. developed the study design, interpreted the data and contributed to/supervised writing of the manuscript. F.K. and M.S. were involved in the study design, data interpretation and review of the manuscript. J.C., G.C., C.R. and A.A. were involved in the development of the study design and the review of the manuscript. D.H., M.L., F.G., Z.B. and C.H. reviewed the manuscript.

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Conflict of interest

The authors have declared no conflicts of interest.

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