

Variability in Malaria Prophylaxis Prescribing Across Europe: A Delphi Method Analysis

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Background. The indications for prescribing malaria chemoprophylaxis lack a solid evidence base that results in subjectivity and wide variation of practice across countries and among professionals.

Methods. European experts in travel medicine, who are members of TropNetEurop, participated in a survey conducted using the Delphi method. This technique aims at evaluating and developing a consensus through iterations of questionnaires, controlled feedback, and statistical group responses.

Results. A first questionnaire, including questions about controversial issues in prescribing malaria prophylaxis, required responses on a visual scale between 1 and 10. The questionnaire included issues on problematic prescribing, characteristics of drugs, relevance of geography, and importance of insect bite prevention. The repeat questionnaire with the group response from the first round revealed an increasing consensus on most issues. A second survey considered 14 practical scenarios (including two internal standards) and investigated preferred choice of prophylaxis. A significant consensus was noted in 8 of 14 scenarios, which did not increase after a second round. The analysis revealed a wide variation in prescribing choices with preferences grouped by region of practice, and a greater willingness to prescribe in northern and southern Europe than in central Europe. The second round showed a 9.5% change of opinion.

Conclusions. The study shows that improving the evidence base on efficacy and tolerability and risk of malaria for prescribing chemoprophylaxis is needed as is further discussion across Europe to achieve harmonization of prescribing practice.

Malaria is widespread through tropical and subtropical areas, and virtually, all travelers from temperate countries to endemic destinations are at

risk of exposure to the infection. Consequently, chemoprophylaxis for those travelers is often recommended, regardless of duration of stay, conditions of travel, precise destination, and season. The risk of drug toxicity is not negligible,^{1,2} and a careful risk–benefit balance of chemoprophylaxis must be undertaken in each case. Moreover, some changing social aspects of travelers, in particular the increasing number of elderly people, children, migrants, and short-term business travelers, have made prescribing more difficult.

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Few evidence-based studies on the risk of infection in travelers and variation of prescribing are available in literature,³⁻⁷ and guidelines tend to be generic, when advising chemoprophylaxis indications for endemic regions.⁸⁻¹¹ A case-by-case decision tends to overrule guidelines, and as a general consequence, a high degree of subjectivity is present in prescribing, which leads to large variation in practice.

The Delphi approach is a consensus development technique, which was introduced in 1952, and may be used for situations where there is no unanimity of opinion due to absence of scientific evidence.¹²⁻¹⁴ Experts' views are explored to enable decisions to be made on best current opinions. Iteration of questionnaires, controlled feedback, and statistical group response are essential requisites of the method.¹⁵

The aims of this study were to investigate the opinions of major European experts and to identify whether a consensus exists in complex prescribing situations. Where consensus was not achieved, the study attempted to create agreement or common practice. A secondary aim was to investigate the value of the Delphi technique in indications for malaria chemoprophylaxis.

Methods

This study was undertaken among participating members of TropNetEurop, a European network of travel and tropical medicine centers, created to report cases of imported infections and exchange and improve practice among professionals (www.tropnet.net).¹⁶ A steering committee of six experts in travel medicine, chosen among TropNetEurop members and recognized as leaders in this field, prepared and discussed the questionnaires. These were subsequently sent for completion to managers of all member sites of the network (46 sites before September 2005 and then 47 sites).

In the first phase, the questionnaire included primarily open questions about problems encountered in prescribing malaria prophylaxis (Appendix 1). Each question included a number of choices, and responses were reflected on a visual scale from 1 to 10. The responses were analyzed as distribution of scores, median, and first to third quartile difference. Respondents were anonymously shown the results of this first round as cumulative statistics to reflect the opinion of the group. Thereafter, the same questionnaire was administered once again to investigate if consensus could be improved (questionnaire no. 2).

A second-phase questionnaire was generated on the basis of phase 1 responses and investigated prescribing preferences using 14 travel scenarios where participants selected their preferred chemoprophylaxis and gave reasons for their choice (questionnaire no. 3, Table 1). This questionnaire was repeated with group's opinions available as summarized data (questionnaire no. 4).

Agreement was evaluated by the use of a homogeneity index for categorical variables, scoring 1 for complete consensus and 0 for no consensus (equal distribution throughout the three response choices: yes, no, and uncertain).¹⁷

All results were collected using Microsoft Excel, and data were statistically analyzed by SPSS software. The study was undertaken between May and November 2005.

Results

Phase 1 questionnaire was sent to 46 experts, with a 65% (30) response rate. Responses to questions were given using a score from 1 (minimum relevance) to 10 (maximum relevance). The results of the first round are reported in Figure 1. The second round was sent with minor modifications to the 30 experts who had responded to round 1 and was returned by 22 (74.3%).

The median score changed by at least one unit, between questionnaires 1 and 2, in 8 of 48 questions (only those experts who responded to both were included). The degree of consensus improved (as the difference between the first and the third quartile decreased at least one unit) in 36 of 48. A significant change in the group's opinion was seen only in the importance of potential compliance (question 3, item 4), where the median score decreased from a relative importance of 8.0 to 6.0 and the interquartile difference decreased from 4.5 to 2.0.

Phase 2 questionnaires containing travel scenarios were sent to 47 experts (one center was added to TropNetEurop at that time). Thirty-five questionnaires (74.4%) in the first round were returned and were evaluable (Table 1). The inclination of the panel of experts to prescribe prophylaxis ranged from a minimum of 4 to a maximum of 13 affirmative responses (from 0 to 3 answers "uncertain"). Prescribing varied by country of practice: the mean affirmative responses among participants from northern Europe (Scandinavia and British Isles, $n = 12$) were 10.6 (SD ± 1.6), from central Europe (Germany, Switzerland, Belgium, Czech Republic, and Poland, $n = 11$) were 6.9 (SD ± 1.2), and from

Table 1 Questionnaire 3 and responses about giving prophylaxis or not in proposed scenarios (more than one answer about the type of drug used was possible)

	Yes	No	Uncertain	Type	Changed opinion (second round)
1. Female, 40, visiting relatives in India for 2 mo (Karnataka and Kerala and 2 wk in Goa).	16	17	2	CP = 9, M = 6, AP = 3, D = 3	8
2. Male, 50, healthy, traveling to Cameroon for 1 wk/mo (rural and urban) for years.	17	15	3	AP = 16, M = 5, D = 1	3
3. Female, 20, traveling in Rajasthan, Uttar Pradesh, and Bihar (India) for 4 wk, mostly in rural area.	21	13	1	CP = 7, M = 7, C = 5, AP = 4, D = 3	7
4. Female, 45, traveling in Thailand (Bangkok, Pattaya, and Phuket) for 2 wk.	0	35	0		0
5. Male, 35, healthy, staying in R. Dominicana, Punta Cana, for 2 wk for tourism.	13	19	3	C = 12, AP = 2, M = 2	6
6. Female, 45, traveling to Namibia in August, including 2 d in Kavango river area.	18	13	4	AP = 17, M = 4, D = 1	5
7. Male, 30, going to Congo for 12 mo, business with nongovernmental organization, previous intolerance to mefloquine.	28	6	1	D = 19, AP = 7, M = 7, CP = 4, C = 1	4
8. Male, 25, traveling for 2 mo in Mexico, Guatemala, Costa Rica, and Panama (backpacker).	16	14	5	C = 17, CP = 3, AP = 1, M = 1	3
9. Female, 30, traveling to Thailand, Cambodia, and Vietnam for 2 mo (5 d in multiresistance areas).	27	7	1	D = 21, AP = 18, M = 2	3
10. Male, 25, working in an agriculture project in south Ivory Coast for 1 mo.	35	0	0	M = 28, AP = 20, D = 12	0
11. Male, 30, human immunodeficiency virus infection, traveling throughout Peru and Bolivia for 3 wk (including Amazon basin).	29	2	4	AP = 21, M = 16, D = 10, CP = 2, C = 1	3
12. Female, 35, migrant from Burkina Faso to Europe, traveling for vacation to her native country for 6 wk, with her 3-year-old son, born in Italy.	34	0	1	M023, AP = 12, CP = 2	1
13. Male, 50, hepatitis C virus cirrhosis (compensated) traveling to Mozambique for 1 mo for business.	32	1	2	AP = 23, D = 11, M = 11, C = 1	1
14. Female, 50, traveling to Kenya, 1-wk safari in central Kenya, 1 wk in Malindi in holiday's village, in January.	35	0	0	AP = 29, M = 21, D = 6	0

C = chloroquine; CP = chloroquine/proguanil; M = mefloquine; AP = atovaquone/proguanil; and D = doxycycline.

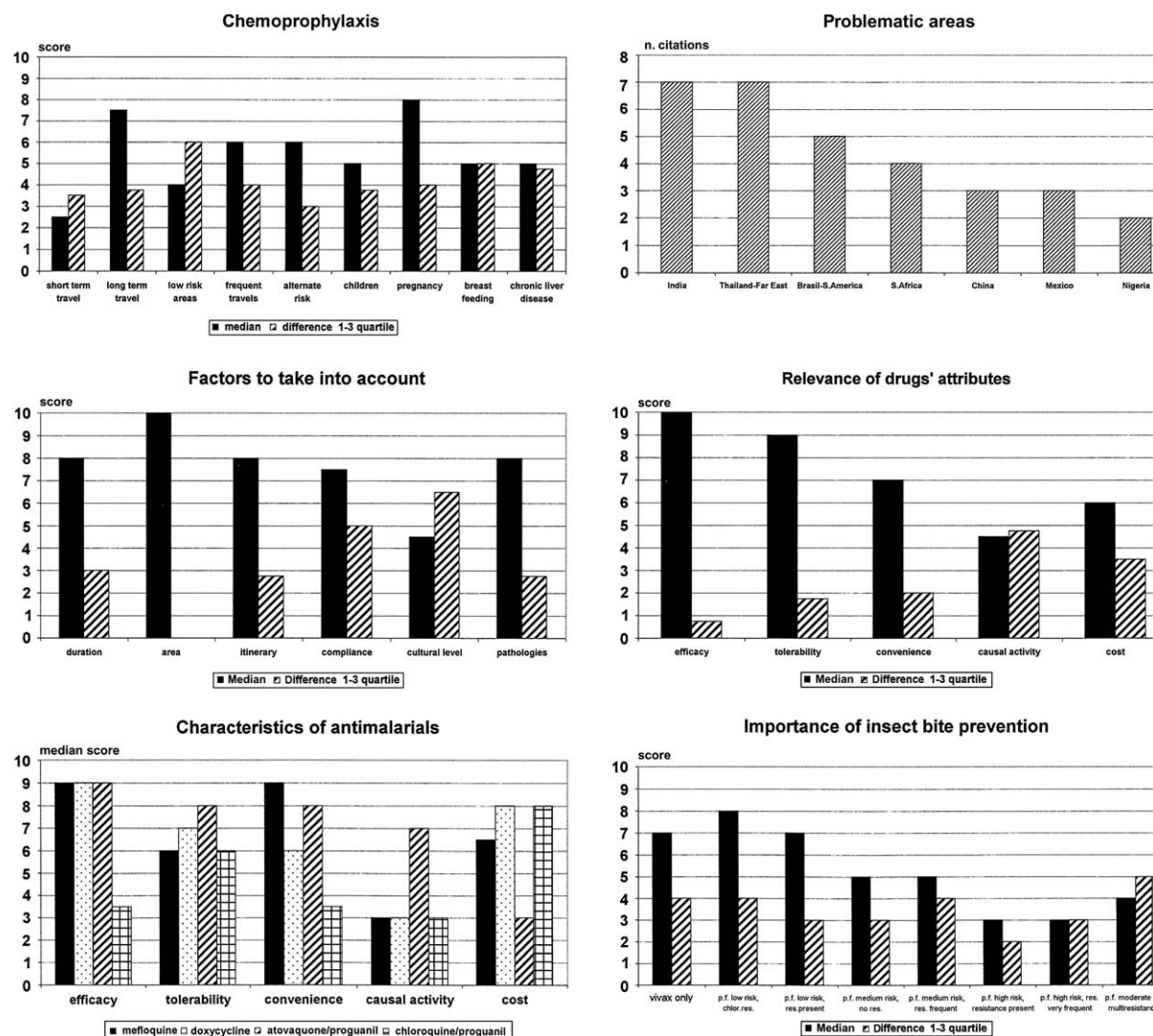


Figure 1 Responses given by experts to questionnaire no. 1 (see Appendix 1). Data are reported as median scores, expressing the opinion of the group, and first to third quartile differences, expressing the scores distribution, ie, the consensus. For problematic areas, *n* citations of every area.

southern Europe (Italy, Spain, Portugal, and France, $n = 12$) were 9.8 ($SD \pm 1.5$). The variance (*t*-test) was statistically significant between the first and the second group ($p < 0.0001$) and between the second and the third ($p = 0.0001$) but not between the first and the third. Figure 2 reports the different responses (yes/no/uncertain) in relationship to the area of practice.

The questionnaire was distributed again to those who had responded, including the summarized data of responses. Thirty-three of 35 questionnaires were returned (94.3%). Changes of opinion occurred in 44 of 462 answers (9.5%). Overall, there were 17 changes of opinion toward an affirmative response (from no to uncertain or to yes) and 27 toward negative responses. The number of “uncer-

tain” decreased from 24 to 14. Many changes (13 toward no prophylaxis and 2 toward prophylaxis) concerned scenarios no. 1 and no. 3 regarding travel in the Indian subcontinent.

The consensus among participants to prescribe prophylaxis was measured through the use of homogeneity index (Figure 3).

Discussion

Findings from the first questionnaire are that long-term travel, frequent travel, travel where the risk varies by region, and pregnancy seem to be the most problematic situations, while responses on decision for prescribing in low-risk areas during breast feeding and chronic liver diseases are widely distributed across

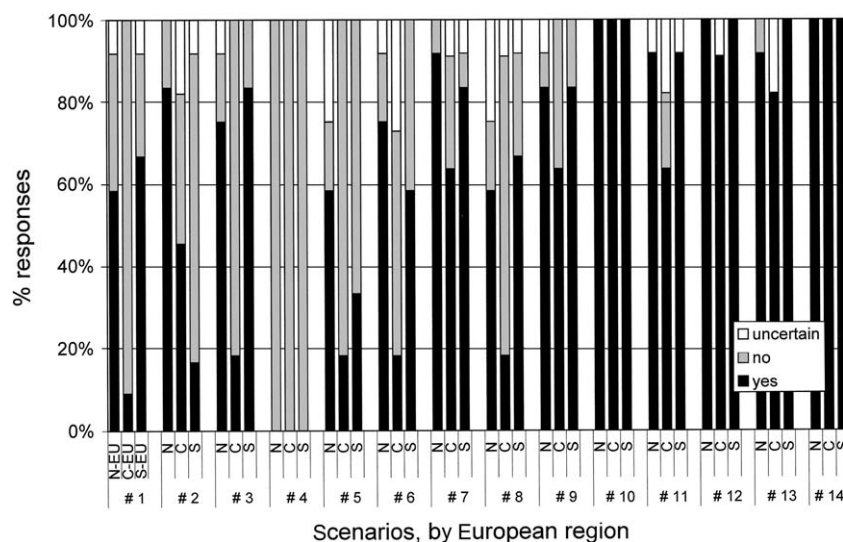


Figure 2 Proportionate responses to 14 case scenarios (see Table 1) in participants grouped by region of Europe (N = northern Europe, C = central Europe, and S = southern Europe).

the visual scale. As expected, the Indian subcontinent, the Far East, and South America are perceived as the areas causing greatest doubts because of the low malaria risk or multidrug resistance. When balancing risk and benefit of giving prophylaxis, participants recognized the importance of the travel itinerary and underlying medical pathology, but there was less agreement on the importance of compliance and reason for travel. Efficacy and, to a lesser extent, tolerability and convenience were considered important characteristics of drug regimens, while cost and causal activity (and thus a shorter duration of prophylaxis and *Plasmodium vivax* protection) were important

only for some experts. The evaluation of the different regimens atovaquone/proguanil, mefloquine, and doxycycline puts them equal, for different reasons; chloroquine/proguanil achieved a much lower score. The recommendation of bite prevention was considered very important, particularly in areas of low malaria risk or regions of *P. vivax* transmission, achieving a higher priority than the need for chemoprophylaxis, but its importance was not related to the risk of chemoprophylaxis failure due to drug resistance.

The second round shows that the group did not change its general opinion, except on the importance of potential compliance where both the

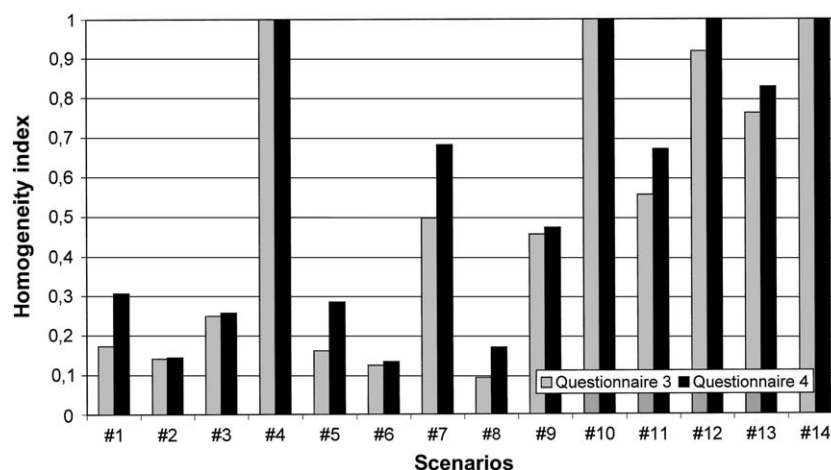


Figure 3 Homogeneity index in different scenarios (measured as 0 for no consensus and 1 for complete consensus). Questionnaire 3 was the first round of the second phase, and questionnaire 4 was the second round. The latter reflects change (or not) after seeing the prescribing preferences detailed from the first questionnaire; cases 4 and 10 were used as internal standards (prophylaxis never and always recommended by guidelines).

median score and the interquartile difference decreased, suggesting that this item was not that important when selecting a regimen. Individual scores moved closer to the median value in most questions, showing that respondents were influenced by the group's opinion, particularly on questions requiring a subjective answer: problematic aspects, factors to take into account, and role of insect bite prevention.

The questionnaire no. 3 highlights a large variation in responses in the group's willingness to prescribe prophylaxis in the scenarios presented. Respondents from northern Europe tended to prescribe prophylaxis more frequently compared to experts from central Europe, while the tendency of the respondents from Mediterranean countries to prescribe prophylaxis lies between the two groups. The variability within each group of countries was surprisingly low, which may reflect national guidelines, available drugs, type and expectations of travelers, or training. This diversity of practice might be harmonized through improved data on safety and tolerability and more detail on actual malaria risk and transmission to travelers. In particular, prescribing for travel to the Indian subcontinent and Central and South America requires a thorough revision. The continuous changes in drug resistance, new drugs, changing transmission, and the changing pattern of travel make malaria prophylaxis a moving target.

A number of respondents, despite knowledge and experience, expressed "uncertainty" about prescribing: possibly, the detail in the scenario was inadequate to reach a decision.

The responses to individual scenarios (Figure 3) revealed a low consensus, as examined by a homogeneity index, in 6 of 14 cases. Complete consensus was achieved only in three cases, but two of these (no. 4 and no. 10) were internal standards, used as positive and negative controls and reflecting international guidelines.⁸ Scenarios related to traveling to India or Central/South America, were controversial, and were responsible for the discrepancy in responses of northern European and central European experts and associated to the maximum number of "uncertain" responses. This may be partly due to objective factors (eg, cost of drugs and a different cultural appreciation of the relative importance of cost in different settings) that account for the relative homogeneity within each main group of countries in Europe. But a more likely explanation is clearly related to the lack of evidence for prescribing prophylaxis, leading to decision making largely based on personal opinions and also on referral centers' level. The role of standby treatment was not

investigated in this case, but in the opinion of many experts, it should be considered in all cases when malaria is present and chemoprophylaxis is not used.

In responding to the second round (questionnaire no. 4), the opinion changed in 9.5% of cases, mostly from "yes" or "uncertain" to "no," and many changes were related to scenarios in the Indian subcontinent; current prescribing pattern for this area was widely debated by the group and by the scientific community in that period.¹⁸ However, the consensus did not increase as was noted during phase 1 and remained low in the same scenarios.

Conclusions

The Delphi questionnaires administered to a group of European experts in travel medicine showed a considerable variation in opinion in prescribing prophylaxis from the theoretical point of view (phase 1) and in prescribing intentions assessed through scenarios (phase 2). The lack of agreement may be partly due to insufficient details in single questions or scenarios and/or to the heterogeneity of national guidelines across Europe. The Delphi analysis was able to increase consensus in theoretical questions, but not in prescribing practice, showing that a substantial effort is still needed to generate the evidence base for the use of malaria prophylaxis.

In highlighting the lack of consensus, this study led to research and collection of evidence to correct this deficit. A recent TropNetEurop analysis has resulted in evidence-based recommendations for malaria prophylaxis for travelers to the Indian subcontinent,¹⁸ while research and discussion are ongoing on malaria risk in Central and South America. A cost-benefit approach would also assist with rational prescribing.

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Declaration of Interests

The authors state that they have no conflicts of interest.

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Appendix 1 Questionnaire 1: Responses to Each Item Were Given on a Visual Scale 1 to 10

What are in your opinion the most problematic aspects in prescribing malaria prophylaxis?

- Short-term travel
- Long-term travel
- Low-risk areas
- Frequent travels
- Alternate risk travel
- Children
- Pregnancy
- Breast feeding
- Chronic liver disease

Which areas are most controversial in your practice, with regard to advices of malaria prophylaxis?

Which factors do you take into account in prescribing malaria chemoprophylaxis?

- Duration of stay
- Area
- Itinerary
- Likely compliance
- Cultural level of the patient
- Underlying pathologies

How do you evaluate the different available drugs for malaria chemoprophylaxis, in drug-resistant area, according to different attributes?

	Efficacy	Tolerability	Convenience	Causal activity	Cost	Overall (mean score)
Relevance of drugs' characteristics						
Evaluation of drugs						
Mefloquine						
Doxycycline						
Atovaquone/proguanil						
Chloroquine/proguanil						

How do you evaluate the importance of insect bite prevention measures compared to chemoprophylaxis in different geographic areas?

- *Plasmodium vivax* only
- *Plasmodium falciparum*, low risk, no chloroquine resistance
- *P falciparum*, low risk, chloroquine resistance present
- *P falciparum*, medium risk, no chloroquine resistance
- *P falciparum*, medium risk, frequent chloroquine resistance
- *P falciparum*, high risk, chloroquine resistance present
- *P falciparum*, high risk, chloroquine resistance very frequent
- *P falciparum*, moderate risk, multidrug resistance