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International comparison of selected European malaria recommendations for travellers

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ABSTRACT (English)

Background: Malaria ranks among the most frequently imported tropical diseases in Europe. It is potentially lethal. Many European countries therefore issue recommendations on malaria prevention to protect their travellers. However, the recommendations exhibit significant differences in both scope and content.
Objectives: This thesis intends to compare European malaria recommendations for travellers, analysing the differences. The aim is to lay the foundations for future efforts to harmonise a European guideline.

Methods: Internet research gathered malaria recommendations for European travellers by screening the web using the specific terms “recommendations”, “malaria”, and “travellers” in different European languages and reviewing national tropical medicine society websites. Selection criteria focused on detailed, accessible recommendations, considering historical links to malaria-endemic regions and high numbers of imported cases. Seven national recommendations from the UK, Germany, the Netherlands, Belgium, France, Spain, and Italy, published before 31 December 2020, were compared. The results were compiled in an Excel data sheet using Microsoft Office 2019 Professional Plus, version 2206.

Findings: Key findings included discrepancies in the definitions of malaria risk areas, with significant differences in the data used on the distribution of Plasmodium species in different countries and regions. In addition, there were differences in chemoprophylaxis recommendations and in advice on the procedure of emergency self-treatment. Furthermore, there were discrepancies in recommendations for pregnant and breastfeeding women and for children. Recommendations on mosquito repellents and clothing colour also differed.

Conclusions: European malaria recommendations for travellers vary due to a non-standardised and largely non-transparent methodology. In addition, the use of national data on imported malaria cases and incomplete epidemiological information from developing countries leads to varied interpretations among professional societies and regulatory bodies. Differences in the national approvals of medicines and repellents also lead to inconsistent recommendations. This underlines the need for improved communication within Europe to enable comprehensive data exchange for harmonisation. Enhanced education, particularly for the most significant risk group of travellers “visiting friends and relatives” in their country of origin (VFRs), is essential as most imported malaria cases result from traveller non-compliance rather than ineffective medication.

Two issues could contribute to knowledge transfer: differences in repellents regarding age limits for children and use during pregnancy appear to depend more on the specific product as a

whole and its co-formulants, which affect absorption, than on the concentration of the active substance itself. Furthermore, wearing light-coloured clothing in tropical areas to protect against various mosquitoes, including nocturnal species, appears to be a sensible recommendation.

ABSTRACT (German)

Hintergrund: Malaria zählt zu den häufigsten importierten Tropenkrankheiten in Europa. Sie ist potenziell tödlich. Viele europäische Länder geben daher zum Schutz ihrer Reisenden Empfehlungen zur Malariaprävention heraus. Die Empfehlungen weisen jedoch erhebliche Unterschiede in Umfang und Inhalt auf.
Zielsetzung: In dieser Arbeit sollen die europäischen Malariaempfehlungen für Reisende verglichen und Unterschiede analysiert werden. Ziel ist es, die Grundlagen für künftige Bestrebungen um die Harmonisierung einer europäischen Leitlinie zu schaffen.
Methoden: Im Rahmen einer Internetrecherche wurden Malariaempfehlungen für europäische Reisende gesammelt, indem nach den Begriffen "Empfehlungen", "Malaria" und "Reisende" in verschiedenen europäischen Sprachen gesucht und die Websites der nationalen Gesellschaften für Tropenmedizin überprüft wurden. Die Auswahlkriterien konzentrierten sich auf detaillierte, zugängliche Empfehlungen unter Berücksichtigung historischer Verbindungen zu Malaria-Endemiegebieten und hoher Zahlen importierter Fälle. Sieben nationale Empfehlungen aus dem Vereinigten Königreich, Deutschland, den Niederlanden, Belgien, Frankreich, Spanien und Italien, die vor dem 31. Dezember 2020 veröffentlicht wurden, wurden verglichen. Die Ergebnisse wurden in einem Excel-Datenblatt mit Microsoft Office 2019 Professional Plus, Version 2206, zusammengestellt.
Ergebnisse: Zu den wichtigsten Ergebnissen gehörten Diskrepanzen bei den Definitionen von Malariarisikogebieten, wobei signifikante Unterschiede bei den verwendeten Daten über die Verbreitung von Plasmodium-Arten in verschiedenen Ländern und Regionen bestanden. Darüber hinaus gab es Unterschiede bei den Empfehlungen zur Chemoprophylaxe und zum Vorgehen bei notfallmäßiger Selbstbehandlung. Außerdem gab es Diskrepanzen bei den Empfehlungen für schwangere und stillende Frauen und Kinder. Auch die Empfehlungen zu Mückenschutzmitteln und zur Farbe der Kleidung waren unterschiedlich.
Schlussfolgerungen: Die europäischen Malariaempfehlungen für Reisende variieren aufgrund einer nicht standardisierten und weitgehend intransparenten Methodik. Zusätzlich führen die Verwendung nationaler Daten über importierte Malariafälle und unvollständige epidemiologische Informationen aus Entwicklungsländern zu unterschiedlichen Auslegungen durch Fachgesellschaften und Aufsichtsbehörden. Unterschiede bei den nationalen Zulassungen von Arzneimitteln und Repellents führen ebenfalls zu uneinheitlichen Empfehlungen. Dies unterstreicht die Notwendigkeit einer verbesserten Kommunikation innerhalb Europas, um einen umfassenden Datenaustausch zur Harmonisierung zu ermöglichen. Eine verstärkte Aufklärung, insbesondere für die wichtigste Risikogruppe der Reisenden, die Freunde und Verwandte in ihrem Herkunftsland besuchen, die „Visiting Friends and Relatives (VFRs)“, ist unerlässlich, da die meisten importierten Malariafälle eher auf eine

Nichteinhaltung der Empfehlungen durch die Reisenden als auf unwirksame Medikamente zurückzuführen sind.
Zwei Fakten könnten zum Wissenstransfer beitragen: Die Unterschiede bei den Mückenschutzmitteln hinsichtlich der Altersgrenzen für Kinder und der Verwendung während der Schwangerschaft scheinen eher vom spezifischen Produkt als Ganzes und seinen Beistoffen abzuhängen, die die Absorption beeinflussen, als von der Konzentration des Wirkstoffs selbst. Außerdem scheint das Tragen von heller Kleidung in tropischen Gebieten zum Schutz vor verschiedenen Mückenarten, einschließlich nachtaktiver Spezies, eine sinnvolle Empfehlung zu sein.

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LIST OF ABBREVIATIONS

ACPR= adequate clinical and parasitological response on day 28

ACT= artemisinin-based combination therapy (including treatment with AL, AP and DP)

AFI= Annual *P. falciparum* Index (= *Pf*API)

AL= artemether/lumefantrine

AP= atovaquone/proguanil

API = Annual Parasite Index

ART= antiretroviral therapy

AVI= Annual *P. vivax* Index

B= Belgium

BfArM= Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)

BP= bite protection, exposure prophylaxis

BPR= Biocidal Products Regulation

C= chloroquine

CHP= chemoprophylaxis

C+P = chloroquine and proguanil

CYP= cytochrome P 450

D= doxycycline

DEET= N, N-diethyl-m-toluamide

DOAC= direct oral anticoagulant

DP= dihydroartemisinin/piperaquine

E= Spain

EC Oil (H/C) = eucalyptus citriodora oil, hydrated cyclised

ED= endocrine disruption, endocrine disruptor

ECHA= European Chemicals Agency

EMA= European Medicines Agency

ESM= emergency standby medication

EW= emulsion-in-water formulations

F= France

FDC=fixed-dose combination

G= Germany

G6PD-deficiency= Glucose 6-phospate dehydrogenase deficiency

HHRA=human health risk assessments

IPT(p) = intermittent preventive treatment (during pregnancy)

INR= International Normalized Ratio

IT= Italy

IR3533= 3-ethylaminoproprionate

M= mefloquine

NL= Netherlands

P= proguanil

Pf= Plasmodium falciparum

Pf API= *Plasmodium falciparum* Annual Parasite Incidence (= AFI)

PfHRP2= *Plasmodium falciparum* histidine-rich protein 2

PMD= para-menthane 3,8 diol (now called Eucalyptus citriodora oil, hydrated, cyclised)

PMDRBO= para-menthane 3,8 diol Rich Botanic Oil (previous name for PMD used in the EU)

Po= Plasmodium ovale

Pv= Plasmodium vivax

RDT= rapid diagnostic test

SPF= sun protection factor

SVHC= Substance of Very High Concern

UK= United Kingdom

v= yes/is available

VFR= visiting friends and relatives

WMR= World Malaria Report

x= no/is not available

A. INTRODUCTION

A.1 Epidemiology of malaria

Malaria is one of the most common parasitic infectious diseases in the world. In 2021, around 247 million cases of malaria were reported worldwide. Approximately 619,000 people died from malaria, with children under 5 years of age accounting for 76% of the deaths [1].

While efforts to eliminate malaria in endemic areas are progressing, the Global Technical Strategy for Malaria 2016-2030 of the World Health Organization (WHO) aims to continue reducing the incidence and mortality rates of malaria by at least 90% by 2030 [2]. However, data on imported cases from the USA, UK, and the GeoSentinel analysis demonstrate that malaria continues to threaten the health of travellers and plays an important role in the field of travel medicine [3]. Furthermore, the setback on malaria control caused by the COVID-19 pandemic is considerable, highlighted by rising figures in malaria cases and deaths reported by WHO for 2021 [4].

In Germany, the number of imported reported malaria cases has stabilised at around 900-1,000 per year since 2014. In 2019, the last year before the Corona outbreak, 993 imported malaria cases were reported. Of these, 46% had Germany as their country of origin [5].
Among these cases, the reasons for travel were as follows: visit friends or relatives (38%), tourism (30%), humanitarian aid, development service or missionary service (14%), business trips or other trips for professional or educational purposes (11%), military missions (6%), and the reason for travel was not provided (1%). In cases where the country of origin differed from Germany, the reasons for travel were as follows: visit friends or relatives (85%), tourism (5%), business trips (4%), and the reason for travel was not provided (6%) [5].

Malaria is a potentially lethal infection. Imported malaria cases come from travellers with diverse travel motivations and needs, involving a variety of risk factors. In response, many European countries issue recommendations on malaria prophylaxis, considering different travel styles and individual risk factors in order to protect their travellers from malaria.

A.2 The malaria parasite

Malaria is a parasitic infectious disease caused by protozoa of the genus *Plasmodium*, transmitted by an infective female mosquito of the genus *Anopheles*. Humans are most commonly infected by five species of *Plasmodium (P.)*: *P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi*. Infections with other primarily zoonotic pathogens, e.g. *P. cynomolgi*

and *P. simium* have been reported [6]. Malaria spreads through human-to-human transmission via blood transfusion, organ transplants, needle sharing, or congenitally from mother to child [7].

A.2.1 Epidemiology of the parasite

P. falciparum causes over 95% of all malaria infections worldwide [4, 8]. Infections with *P. vivax* come second, accounting 2-3% of all cases worldwide in recent years [4, 8]. Infections with *P. ovale* and *P. malariae* are much rarer, and the zoonotic *P. knowlesi*, which originates from macaque monkeys, occurs in Southeast Asia [9-11].

P. falciparum occurs in sub-Saharan Africa with high transmission and case numbers. In West, Central, East and Southern Africa, where transmission is high, it causes nearly 100% of all cases. In countries with low transmission, the figure is around 90% [4].

In most endemic areas of Asia, case numbers are generally lower, and the proportions of *P. falciparum* and *P. vivax* are similar high. In the Americas, the proportion of *P. vivax* exceeds that of *P. falciparum* by a factor of more than two [4, 8, 12, 13].

A.2.2 Life cycle

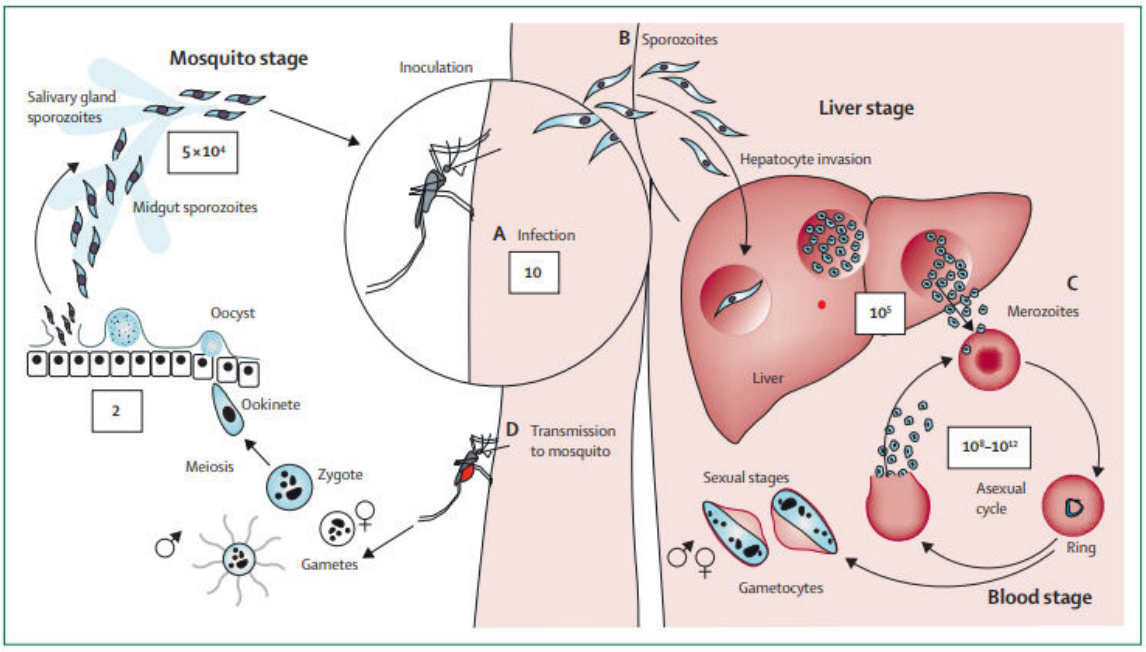

Figure I:

Parasite lifecycle of *Plasmodium* in the human body and the mosquito of the genus *Anopheles* [14]

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Following the bite of an infected female Anopheline mosquito the inoculated sporozoites of *Plasmodium spp.* reach the liver via the bloodstream, where they invade the hepatocytes (Figure I). Inside the liver cells, the parasites develop into hepatic schizonts carrying multiple merozoites (intrahepatocyte schizogonic cycle or liver stage).

After a period of 7 days to weeks, the merozoites are released within membrane-bound structures (merosomes), which then burst and liberate the merozoites into the blood steam, where they invade red blood cells.

They mature as so-called trophozoites within infected erythrocytes and multiply to finally destroy the red blood cells. The merozoites released infect further red blood cells (blood schizogonic cycle or blood stage) [14].

The asexual cycle in the blood stage takes about 48 hours for *P. falciparum, P. vivax*, and *P. ovale*, 72 hours for *P. malariae*, and 24 hours for *P. knowlesi* [14]. Clinically, this can be seen in tertian malaria *(P. vivax, P. ovale)* as periodic fever every 48 hours, and in quartan malaria *(P. malariae)* as periodic fever every 72 hours [11].

Some parasites transform into sexual stages of male and female gametocytes, which can be taken up by a new mosquito during a blood meal. They reproduce sexually in the mosquito gut, eventually restarting the cycle again [12].

In *P. vivax* and *P. ovale* malaria, some sporozoites, after infecting liver cells, develop into so-called hypnozoites with low metabolic activity. These hypnozoites can reactivate after several months, resulting in hepatic and subsequent erythrocytic schizogonic cycles. Clinically, this manifests as repeated relapses [12].

A.3 Clinical malaria

Malaria is a potentially serious febrile illness with a minimum incubation period of 7 days. Therefore, symptoms may appear as early as 7 days after the first exposure or as late as months to years thereafter [7, 10]. The range of clinical symptoms extends from asymptomatic parasitaemia to uncomplicated malaria, to severe malaria, and to death [9, 11]. The degree of immunity of the host, the parasite species and the duration of untreated infection are the primary determinants of malaria.

With regard to laboratory parameters, malaria is commonly associated with thrombocytopenia. The leukocyte count in malaria is often normal or low. Laboratory signs indicative of haemolysis and anaemia may develop. The inflammatory parameters C-reactive protein (CRP) and procalcitonin (PCT) can be significantly elevated [9, 11]. (Table I shows the characteristics of

the different forms of malaria; sometimes an absolute minimum incubation period of 6 days for falciparum malaria is given in the literature, as here [11]).

Table I:

Different forms of malaria, their pathogens and distinguishing characteristics [11] *(Permission has been granted by the publisher)*

Disease	Species	Incubation period	Parasitaemia	Special features
Falciparum malaria	*Plasmodium falciparum*	6-30 days, occasionally longer	unlimited	frequently severe courses, high lethality if untreated
Tertian malaria	*Plasmodium vivax, Plasmodium ovale*	12 days up to > 1 year	maximum 2-3%	relapse prophylaxis* usually necessary, severe courses rare
Quartan malaria	*Plasmodium malariae*	12-30 days, in individual cases long incubation period possible	maximum 1-2%	multiplication cycle of 72 hours, persistent infection with recurrences after years later possible
Knowlesi malaria	*Plasmodium knowlesi*	> 1 week	Up to >10% possible	Occurs only in Southeast Asia, severe courses possible

**Relapse: reactivation of tertian malaria by parasite stages that can persist inapparently in the liver for weeks and months (hypnozoites). These must be treated with specific drugs [11].*

Generally, the clinical appearance is divided into two main disease categories: uncomplicated and severe malaria.

A.3.1 Uncomplicated Malaria

The clinical symptoms of malaria are nonspecific. Fever is the leading symptom often accompanied by myalgias, arthralgias and headache, also sweating and chills, sometimes abdominal pain, vomiting and diarrhoea.

A.3.2 Severe Malaria

Infections by *P. falciparum* and P. *knowlesi*, and rarely by *P. vivax*, may, if left untreated, evolve into severe malaria. Severe Malaria is defined by clinical or laboratory evidence of vital organ dysfunction or hyperparasitaemia [11].

For endemic countries, the WHO defines severe malaria by one or more of the following criteria listed in Table II. National definitions in non-endemic regions vary. In Germany, for example, the threshold for “hyperparasitaemia” is set at 5%, hence lower than the 10% set by WHO [11, 15].

Table II:

Diagnostic criteria for severe malaria [15] *(Permission has been granted by the WHO)*

Severe falciparum malaria: For epidemiological purposes, severe falciparum malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia. • Impaired consciousness: A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children • Prostration: Generalized weakness so that the person is unable to sit, stand or walk without assistance • Multiple convulsions: More than two relapses within 24 h • Acidosis: A base deficit of > 8 mmol/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing). • Hypoglycaemia: Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL) • Severe malarial anaemia: Haemoglobin concentration ≤ 5 g/ dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10,000/ µL • Renal impairment: Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L • Jaundice: Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/ µL • Pulmonary oedema: Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/ min, often with chest indrawing and crepitations on auscultation • Significant bleeding: Including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena • Shock: Compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill). • Hyperparasitaemia: *P. falciparum* parasitaemia > 10%
Severe *vivax* and *knowlesi* malaria: defined as for *falciparum* malaria but with no parasite density thresholds.
Severe *knowlesi* malaria is defined as for *falciparum* malaria but with two differences: • *P. knowlesi* hyperparasitaemia: parasite density > 100,000/ µL • Jaundice and parasite density > 20,000/ µL

A.4 Diagnostic tests for malaria

Travellers with fever returning from malaria-endemic areas should be considered to have malaria until ruled out [9].

Malaria requires rapid and species-specific diagnosis, since the prognosis depends essentially on adequate therapy at an early stage. Diagnostic tests should only be performed by medical staff that has been appropriately trained and has sufficient experience in malaria diagnostics. [11].

A.4.1 Light microscopy

The gold standard for diagnostics is light microscopy using thick and thin blood films. The thick film demonstrates approximately 10-20 times more sensitivity than the thin film [16]. Its detection limit is at approximately 10-50 parasites per microlitre of blood, corresponding to a <0.001% parasitaemia. Thin films allow easy assessment of parasitaemia and provide species determination and prognostic assessment via parasite staging (Figure II) [9, 11, 12, 14, 17].

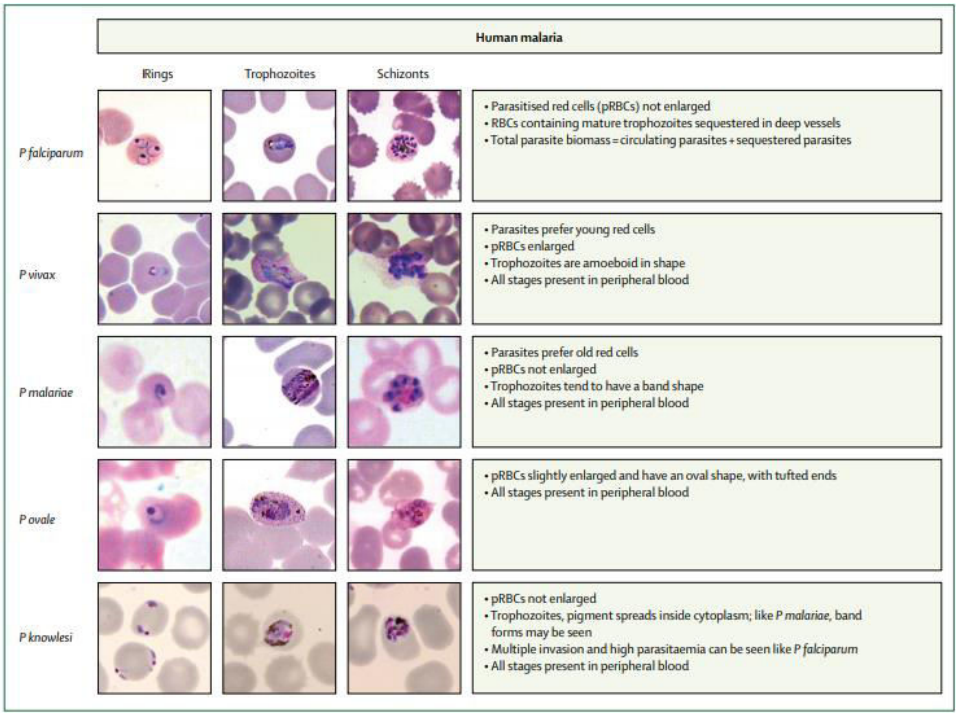

Figure II:

Blood films showing different forms of malaria [12] *(Permission has been granted by the publisher)*

A.4.2 Rapid diagnostic test (RDT)

In malaria-endemic regions and while travelling through remote areas, microscopy as the gold standard of malaria diagnostics is often not available. There may be a lack of laboratory facilities as well as a lack of trained staff.

Rapid diagnostic tests (RDTs) can be helpful for initial orientation, especially if microscopy is not available in adequate time and quality [11].

In RDTs, parasite-specific antigens are detected by lateral flow immunochromatography [17]. They detect species-specific antigens (e.g. *Plasmodium falciparum* histidine-rich protein 2, PfHRP2) or pan-malaria antigens (e.g. lactate dehydrogenase or aldolase). New-generation tests vary in sensitivity between 2-200 parasites per microlitre of blood. RDTs are simple and fast but also expensive and cannot quantify parasitaemia [9, 12].

Sensitivity for detection of *P. falciparum* is high, however, detection of *non-falciparum species,* sensitivity is still suboptimal [18].

In recent years, mutations of in the gene encoding for PfHRP2 have been reported which may lead to a false negative RDT result [19]. This is an alarming trend since large parts of Africa meanwhile rely on RDTs a primary diagnostic tool. It may also affect the health of travellers [20].

With a positive test result of the RDT, treatment can usually be started immediately; however, microscopy (with determination of the species and parasite density) should be arranged at the same time. With a negative RDT result microscopic clarification must be carried out immediately to rule out the possibility of an undetected infection [11].

A.4.3 Polymerase chain reaction (PCR)

In resource-rich settings polymerase chain reaction (PCR) is used for diagnostic and research purposes. This method is very sensitive (<1 parasite per microlitre of blood) and specific. Although it is more sensitive than microscopy, it is not as quick in determining the result. In addition, PCR does not allow to reliably quantify parasitaemia and is not everywhere available; furthermore it is relatively expensive [7, 11, 17].

A.5 Malaria prevention and treatment for travellers

Since travellers from non-endemic countries have a higher risk for severe manifestations, prevention and early treatment are key tools in the field of travel medicine in Europe and other industrialised regions.

Prevention of malaria is based upon assessment and awareness of risk factors, exposure prophylaxis (in particular protection from mosquito bites through habitat avoidance as well as physical and chemical protection), and chemoprophylaxis in high-risk malaria areas.

In case of possible malaria infection, early diagnosis and antimalarial treatment are crucial. If travellers suffer a febrile infection in remote areas without fast and easy access to medical care, self-administered emergency standby treatment is an option to avoid complications [7, 10, 11].

A.5.1 Risk factors

To protect travellers from malaria, individual assessment during pre-travel consultation is important. This assessment should include the destinations, purpose and mode of travel, duration of stay, season, and other relevant factors. Travellers need to be informed about the importance of malaria as a potentially fatal disease, the mode of transmission, the symptoms of malaria and individual risk factors [7, 10, 21].

Environment risk factors such as altitudes below approximately 1,500 metres [22], high air humidity during seasonal rain periods, temperatures in the range of approximately 20° to 30° C [23], and more rural than urban areas [7, 24, 25] increase mosquito breeding and hence biting activity, which peaks between dusk and dawn [26].

Further risk factors for transmission related to the style of travel are: simple type of accommodation without air-conditioning or mosquito nets [7], long or frequent stays in malaria-endemic areas with frequent change of the place of stay [21]. Individual risk factors of travellers for more severe malaria manifestations are: chronic disease, immunosuppressive therapy, old age, pregnancy, and young age [10, 21].

Travellers born in endemic countries but residing outside malaria areas who want to visit friends and relatives (VFR), mostly in sub-Saharan Africa, have a special high risk of malaria. They often fail to seek pre-travel advice, frequently spend extended periods in rural areas, and are often unaware that their semi-immunity to malaria waned over time and protection is reduced [3, 7, 10, 13, 27]. Severe malaria is, however, rarely seen in this group.

A.5.2 Exposure prophylaxis

Protection from mosquito bites using chemical and physical barriers, or a combination of both, is key to avoiding malaria infection [28]. The most effective chemical repellents applied to the skin include DEET (N, N-diethyl-m-toluamide), icaridin, and the hydrated and cyclised active form of eucalyptus citriodora oil (EC Oil (H/C)), which serves as an alternative to DEET. Long clothing

and insecticide-treated mosquito nets [26, 29], as physical barriers, are well-supported by data and studies used for recommendations to travellers to endemic areas [10, 28, 30].

A.5.3 Chemoprophylaxis

Chemoprophylaxis is the preventive use of antimalarial drugs before, during and shortly after a stay in high-risk areas for malaria [7, 31]. This treatment acts on the malaria parasite during the entire period of exposure and for a certain time afterwards in order to eliminate the parasite after infection but before the onset of symptoms [32].

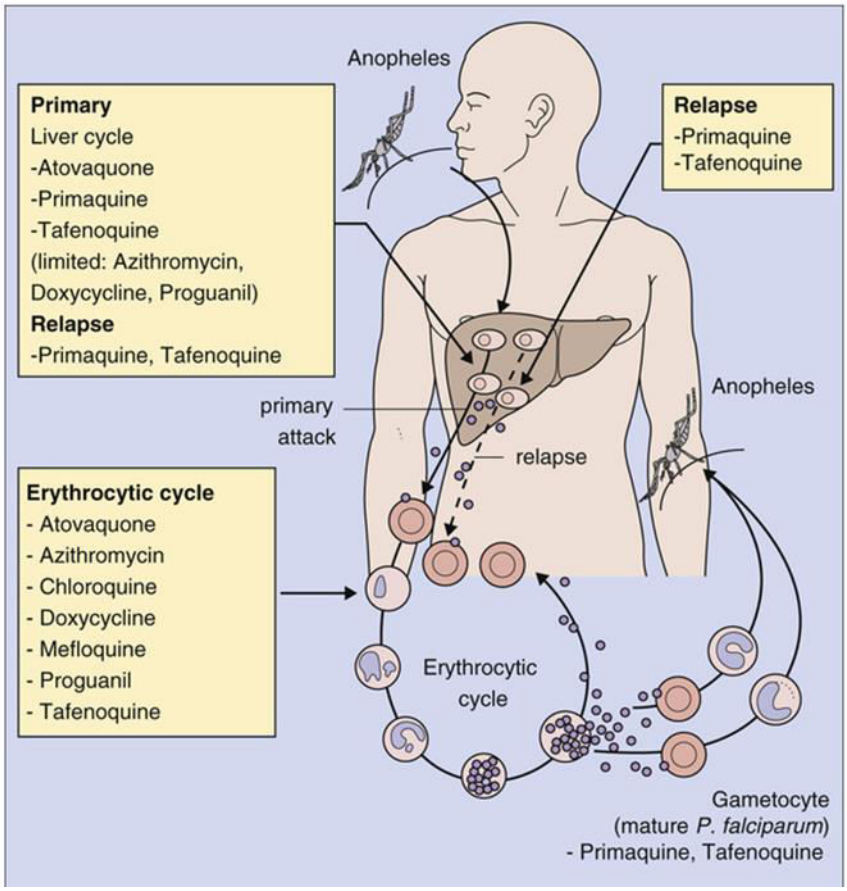

Figure III:

***Plasmodium* lifecycle and sites of action of antimalarial drugs [10]** *(Permission has been granted by the publisher)*

To choose the most appropriate chemoprophylaxis for an individual traveller, many factors need to be considered in addition to the travel destination to a “high-risk” malaria area [31] and the presence of antimalarial drug resistance. Other factors include the length of stay, travel style, seasonal travel, and individual risk factors of the travellers (mentioned above) [7, 10].

The drugs currently used and licensed for chemoprophylaxis in Europe prevent *P. falciparum* infections and act only on the first episode of *P. vivax and P. ovale* infections [32]. However, they are inactive on the dormant liver stages (the hypnozoites) and therefore ineffective at preventing *P. vivax* and *P. ovale* relapses [32-36].

For eradication of presumptive hypnozoites ("terminal prophylaxis"), in addition to chemoprophylaxis, another medication must be used at the end of the exposure to prevent delayed onset of malaria or relapses caused by hypnozoites of *P. vivax* or *P. ovale* [7, 11, 33]. However, this practise is very uncommon in Europe.

The active substance primaquine acts against hypnozoites, but is also active against the liver schizonts of all species of malaria [37]. In Europe it is only used for antirelapse therapy [11] in patients with *P. vivax* or *P. ovale* malaria, whereas in other regions (e.g. USA and Australia) it is also used for (primary) chemoprophylaxis in areas with predominant *P. vivax* [7, 33, 35]. Tafenoquine, closely related to primaquine and with a longer plasma half-life, is neither licensed nor recommended in Europe. It is licensed in the US and Australia for primary and terminal chemoprophylaxis [7, 11, 33, 35]. Both primaquine and tafenoquine can cause haemolysis in patients with G6PD-deficiency. Therefore, G6PD deficiency must be ruled out in any patient for whom primaquine or tafenoquine is considered [7, 11, 33, 34].

Table III:

Use and dosage of antimalarial drugs for chemoprophylaxis [32] *(Permission has been granted by the publisher)*

Drug	**Dose (adult)**	**Dose regimen**	**Beginning of prophylaxis (before exposure)**	**End of prophylaxis (after exposure)**
Atovaquone-proguanil (AP)	250 mg/ 100 mg	Daily	1 day	7 days
Mefloquine (M)	250 mg	Once a week	1-3 weeks	4 weeks
Doxycycline (D)	100 mg	Daily	1-2 days	4 weeks
Chloroquine (C)	300 mg (base) =500 mg salt	Once a week	1 week	4 weeks
Primaquine* **** G6PD testing is mandatory before its use***	30 mg (base) [usually =2 tabs]	Daily	1 day	3-7 days

The drugs licensed in Europe for chemoprophylaxis inhibit either the liver stage development (causal prophylaxis) or the asexual blood stages (suppressive prophylaxis) (Figure III) [15, 36].

Causal prophylaxis with atovaquone/proguanil (and primaquine) can be terminated 7 days after leaving the malaria area. In contrast, suppressive prophylaxis with the substances mefloquine, doxycycline, chloroquine, and proguanil (as a single substance) must be taken for 4 weeks after leaving the malaria-endemic area to eliminate asexual parasites of the blood cycle [15, 32] (see Table III).

A.5.3.1 Atovaquone/proguanil (AP)

Atovaquone/proguanil (AP) is a fixed-dose combination (FDC) used for chemoprophylaxis and emergency standby treatment of malaria. AP synergistically acts against the liver- and blood stages of *Plasmodium spp.* It is not active against relapses of tertian malaria as it does not act on the hypnozoites [10, 32, 36].

The chemoprophylactic regimen for AP is shown in Table III.

AP can also be used as emergency standby medication (ESM) or for treatment of uncomplicated malaria. AP treatment follows a once-daily schedule for 3 consecutive days [7, 10, 38].

Adverse reactions/ side effects mainly include headache, abdominal complaints such as abdominal pain, nausea, or vomiting, neuropsychiatric side-effects such as sleep disturbances, unusual dreams or rarely depression, and dermatological complaints such as rashes and pruritus [10, 32, 38].

AP is not licensed for children weighing below 5kg (in some recommendations below 11kg), not recommended in pregnancy due to insufficient information about the safety in pregnancy and contraindicated in severe renal impairment (creatinine clearance < 30mL/ min) [7, 10, 38].

Generally, AP prophylaxis is well tolerated and side effects are rare, but it is relatively expensive compared to other antimalarial drugs [32, 39].

A.5.3.2 Mefloquine (M)

Mefloquine (M) only acts against the blood stages of all *Plasmodium* species. It is not active against hypnozoites and therefore cannot prevent relapses of tertian malaria [10, 32, 36].

Adverse reactions/ side effects include headache, dizziness, nightmares, confusion, paraesthesia, tremors, ataxia, gastrointestinal disturbances, liver dysfunction, cardiac toxicity, and arrythmias. Rare but serious adverse reactions are neuropsychiatric complaints such as psychosis or seizures, which might lead to persistent neurological manifestations [7, 10, 32, 36, 40].

M is contraindicated in travellers with epilepsy, active psychiatric disorders such as depression, anxiety, and psychosis. It is also not recommended for travellers with cardiac conduction abnormalities or a history of blackwater fever, a complication of falciparum malaria with massive intravascular haemolysis causing haemoglobinuria [7, 10, 32, 40].

Despite its potentially severe side effects M has several aspects that make it an appealing drug for those who tolerate it. It has to be taken only once a week, which makes it an attractive choice for children [10, 41] or people unable to take tablets on a daily basis. Furthermore, it is the only antimalarial chemoprophylaxis that can be taken during all trimesters of pregnancy. It is also considerably cheaper than AP [10, 32].

A.5.3.3 Doxycycline (D)

Doxycycline (D) is a tetracycline antibiotic, which is active against blood stages of all malaria parasites. It is among the WHO-recommended drugs for malaria prophylaxis. In many countries it is used “off-label” for this indication. It is not active against hypnozoites of *P. vivax* and *P. ovale* [10, 32, 36].

Adverse reactions/ side effects are gastrointestinal complaints such as abdominal pain, nausea, vomiting, and diarrhoea. Dermatological side-effects include rashes and increased photosensitivity, which may cause problems in travellers exposed to the sun in tropical countries. In addition, long-term use renders female travellers susceptible to vaginal candidiasis. A severe complication is oesophageal ulceration. It is therefore recommended to take D with ample fluids in an upright position. D should be taken with food as it may cause nausea if taken on an empty stomach [7, 10, 32, 42].

It is contraindicated in patients with allergy against tetracyclines, for children below 8 years (in some recommendations below 12 years), and during pregnancy and breastfeeding [7, 10, 32, 42].

A benefit of using D for malaria might be the (presumed) additional protection against certain bacterial infection such as leptospirosis and rickettsia infections, as well as traveller’s diarrhoea. It is the cheapest option between the commonly used antimalarials. The disadvantage is its daily and comparatively long intake until 4 weeks after leaving the malaria area [32].

A.5.3.4 Chloroquine (C)

Chloroquine (C) may be used for chemoprophylaxis in few areas, where chloroquine resistance is not yet present. These are areas of Central America, the Caribbean, and Middle Eastern

countries. C acts against the blood stages of all *Plasmodium* species and does not act against hypnozoites [10, 32, 36].

Adverse reactions/ side effects include gastrointestinal disturbances, headache, dizziness, blurred vision, insomnia, and pruritus. In high doses retinopathy may occur [7, 10, 36].

It is contraindicated in patients hypersensitive to 4-aminoquinoline compounds or with G6PD-deficiency, pre-existing retinopathy, CNS disorders, myasthenia gravis, epilepsy, or psychosis [7, 10, 43].

There are controversial discussions about the use of C during pregnancy and whether C is contraindicated for patients with G6PD- deficiency [44, 45]. In addition, it is the widespread resistance of most *P. falciparum* to C, which considerably restricts the use [10, 43].

A.5.3.5 Proguanil (P)

Apart from its combination with atovaquone in AP, proguanil (P) may be used in combination with chloroquine in areas without high-grade chloroquine resistance. It acts against the liver and blood stages of all malaria parasites. It is not active against hypnozoites [10].

P prophylaxis should be taken daily, starting 1 week before entering the malaria area, continuing through the time, and for 4 weeks after leaving. As mentioned above it, should only be taken in combination with chloroquine [7, 10].

Mild adverse reactions/ side effects such as anorexia, nausea, and diarrhoea may occur. It may also cause oral ulcerations [36].

There is no known absolute contraindication [10].

A.5.4 Emergency standby treatment

When fever appears during or after a stay in a malaria area, the traveller may start presumptive self-treatment as first-aid measure if the following facts are taken into account: the presence of fever and possibly other symptoms, the incubation period of at least 7 days, and/or lack of timely access to medical care. Presumptive emergency self-treatment of a possible malaria infection should only be understood as initial treatment course. The traveller should always be advised to continue seeking medical help as soon as possible [10, 36, 46].

Emergency standby treatment is based on the recommendations for treatment of uncomplicated malaria (in the respective country). Artemether/lumefantrine, atovaquone/proguanil, or dihydroartemisinin/piperaquine are well-tolerated fixed-dose combinations (FDCs) licensed in

Europe for treatment of uncomplicated malaria and suggested by several international recommendations as emergency standby medication as a first-aid measure for travellers [10, 47].

A.5.4.1 Artemether/lumefantrine (AL)

Artemether/lumefantrine (AL) is a FDC, which can be used for emergency standby treatment. It acts against the blood stages of all *Plasmodium spp* [7, 10, 48].

AL emergency standby treatment consists of a 3-day schedule given with an initial dose, followed by five further doses given at 8, 24, 36, 48, and 60 hours, respectively. AL should be taken with food or a milky drink [7, 10, 49].

AL is generally very well tolerated. Rare adverse reactions are nausea, abdominal pain, dizziness, headache, sleep disturbance, and cough. AL can occasionally lead to QTc prolongations in the ECG [49]. It is therefore contraindicated in patients with conditions resulting in QTc prolongation, a family history of congenital long QT syndrome, or sudden death, as well as in patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia) that may affect cardiac conductivity [49]. It is also not recommended in children below 5kg of weight and during breastfeeding [7, 49].

Since November 2022, the WHO has recommended AL as the preferred treatment option for the treatment of uncomplicated malaria during the entire pregnancy, including the first trimester [15, 50].

A.5.4.2 Atovaquone/proguanil (AP)

(See chapter 1.5.3.1)

A.5.4.3 Dihydroartemisinin/piperaquine (DP)

Dihydroartemisinin/piperaquine (DP) is a FDC, which is only recommended by some countries for emergency standby treatment. It acts against the blood stages of *Plasmodium spp*. [10, 48].
DP emergency standby treatment follows a 3-day schedule, with a daily dose given on 3 consecutive days [10, 51]. Unlike AL, DP should be taken on an empty stomach. The drug is usually well tolerated.
Adverse reactions/ side effects include headache, anaemia, nausea, diarrhoea, and vomiting. It can occasionally lead to tachycardia or QTc prolongations [51].
It is therefore contraindicated in patients with conditions resulting in QTc prolongation, a family history of congenital long QT syndrome, a history of symptomatic arrhythmias, or clinically

relevant bradycardia, as well as in persons with electrolyte disturbances (hypokalaemia, hypocalcaemia and hypomagnesaemia) that may affect cardiac conductivity.
It is also not recommended in children below 5 kg of weight and during breastfeeding [51].
For the treatment of uncomplicated malaria during pregnancy (including the first trimester, which has been updated by WHO in 2022), DP may be considered if first-line AL is not recommended or not available [15, 50].

A.6 Drug resistance of antimalarials

Resistance to chloroquine by *P. falciparum* began to appear in 1960 [10, 52] and is now present in almost all malaria areas except from Central America, the Caribbean, and some of the Middle Eastern countries [10, 32]. Resistance to mefloquine has developed in some areas in Southeast Asia, mainly in the Greater Mekong Region, including border areas of Thailand with Cambodia and Myanmar [10], and to a lesser extent in Africa and Amazon Basin [53].
Chloroquine resistant *P. vivax* has developed in Papua New Guinea and at some sites in Oceania, India, Asia, and parts of South America [10, 52].

Resistance to atovaquone/proguanil has been reported very rarely. Most documented cases have been reported from Africa [10].

Recently, resistance to the artemisinin and non-artemisinin components of artemisinin-based combination therapy has emerged in parts of Southeast Asia [52], again in the Greater Mekong Region from where chloroquine resistance arose. Evidence is accumulating that artemisinin-resistance is also emerging Africa, so far without relevant clinical consequences [54].

A.7 Aims

Malaria is one of the most common tropical diseases imported into Europe. It is potentially lethal. Therefore, many European countries provide recommendations on malaria prophylaxis to protect their travellers from malaria [3, 5]. The recommendations vary considerably in scope and content [55].

The overall objective of this thesis was to describe and compare differences in different malaria recommendations for travellers from different European countries with a relevant number of imported malaria infections and available guidelines. These differences were analysed and weighted up through literature review, a conducted study, and communication with experts in order to lay the foundations for future efforts to harmonise a European guideline.

B. MATERIALS AND METHODS

Malaria recommendations for travellers were retrieved through internet research. The worldwide web was screened via Google Search using the following terms in the specific national languages of the individual European countries: “recommendations”, “malaria”, and “travellers”. In addition, the websites of the national tropical medicine societies of the individual European countries were reviewed.

It was evaluated which European countries provided detailed and accessible recommendations on malaria prevention for travellers.

Only guidelines published before 31 December 2020 were included. Recommendations with an obvious commercial background were excluded. In addition, preference was given to recommendations from countries that, due to their history, have close relations with malaria-endemic regions and see a relevant number of imported cases.

Most recommendations were only written in one of the local languages and had to be translated. In addition to the author's foreign language skills, the translation engine "DeepL" and the online dictionary “Leo.org” were used as an aid (“www.deepl.com” and “www.leo.org”). These following seven national recommendations were finally selected and used for the comparison in the results section:

United Kingdom (UK): Chiodini P, Patel D, Whitty C. Guidelines for malaria prevention in travellers from the United Kingdom, 2019. London: Public Health England; 2019 [56] [56]

Germany (G): Rothe C, Rosenbusch D, Alberer M, Burchard G, Bühler S, Erkens K, et al. Empfehlungen zur Malariaprophylaxe. Recommendations for antimalarial prophylaxis; 2020 [57]

Netherlands (NL): Landelijk Coördinatiecentrum Reizigersadvisering. Malaria. Landelijk Coördinatiecentrum Reizigersadvisering; 2020 [58]

Belgium (B): Crough M, Maniewski-Kelner U. Malaria: Wanda. Travel in good health; 2020 Available from: https://www.wanda.be/en/a-z-index/malaria.[59]

France (F): Camus D, Chidiac C. Recommandations sanitaires pour les voyageurs, 2020 (à l’attention des professionnels de santé). Haut Conseil de la santé publique (HCSP); 2020 [60]

Spain (E): Morales R, Rodriguez N, Otero S, Cabanas L, Agüero F, Oliveira I. Recomendaciones Para La Prevención De La Malaria En Viajeros 2019. Barcelona: Esmon Publicidad, S.A.; 2019 [61]

Italy (IT): Calleri G, Gobbi FG, Napoletano G, Odolini S, Romi R, Rossanese A, et al. INDICAZIONI DELLA PROFILASSI ANTIMALARICA NEI VIAGGIATORI IN AREA ENDEMICA. Società Italiana di Medicina Tropicale e Salute Globale (SIMET); 2018 [62]

These seven national recommendations were compared with regard to parameters listed in the tables of the chapter "Appendices". The parameters were selected from the following areas: formal and general aspects, exposure prophylaxis, chemoprophylaxis, emergency standby self-treatment, persons at risk, and country recommendations.

Results for each parameter were entered into an Excel data sheet for comparison, using Microsoft Office 2019 Professional Plus, version 2206.

C. RESULTS

C.1 Comparison of formal aspects of the recommendations

Institutional background, Authors/ Editors, Year of publication/ last updates
All recommendations have a similar institutional background from national specialist societies. All authors are academic with a background in the field of tropical medicine and/or travel medicine. The year of publication varies between 2018 and 2020.

Format of publication
The format of publication differs between the recommendations. In the UK, E, and IT, a full downloadable internet brochure is published, similar to G, which publishes a journal article that may also be downloaded from the webpage of the Society for Tropical, Travel Medicine and Global Health (DTG). Furthermore, F publishes two chapters of a downloadable internet brochure about travel medicine. In the NL, the recommendation brochure is accessible only to registered members. However, there is also an open-access web page with general information. B exclusively publishes all malaria recommendations on an open-access web page.

Member list of the editing board
All recommendations include a member list on their editing board, B names the authors and the NL mention the existence of a malaria working group.

Declaration of conflict of interest
All recommendations but B and IT include a conflict-of-interest declaration.

Updates/ cycle of publication
The updates appear in 1–2-year intervals. IT publishes the recommendations in larger intervals.

Reference list/ literature list/ bibliography
A reference list is included in all recommendations except on the web pages of the malaria recommendations by B. E publishes their bibliography chapter wise.

Malaria maps of key countries and regions

Malaria maps of key countries or key regions are available in every recommendation except those of F and IT. IT publishes only one world map for overview.

Table of country recommendations

All recommendations have specific tables of recommendations by country. IT has a table of world regions with country recommendations as sub-items.

List of repellent products

A list or a link to a list of repellents products on the market is provided only by recommendations of G, F, and E.

(See Tables of Formal Aspects I and II in Appendix A)

C.2 Comparison of general aspects

C.2.1 Checklists on how to give advice

All recommendations include checklists on how to give general advice for journeys to malaria-endemic areas, except B.

The UK and IT name the ABCD-rules, which are short forms of “Awareness-Bite Prevention-Chemoprophylaxis-Diagnose promptly and treat without delay” and which constitute the basic rule of malaria consultation. In addition, they publish information on how to give advice for the appropriate chemoprophylaxis.

G, NL, and F provide a general checklist on how to give advice for the whole medical malaria consultation.

E shows a checklist for the malaria consultation of long-term travellers.

(See Table General Aspects I in Appendix B).

C.2.2 Risk exposure

For the comparison of the assessment of risk exposure regarding where and when mosquitos bite, the following parameters were assessed: altitude, rainy season**,** temperature**,** rural/ urban area, and the time period from dusk till dawn.

All seven recommendations provide information on one or more of these parameters.

The UK, G, and IT report that malaria is rarely found at an altitude of more than 2,000 meters. F and E differentiate between Africa, South America, and Asia: above 1,500 meters altitude in

Africa and above 2,500 meters in South America and Asia, malaria is rarely found. The NL and B do not discuss the topic of the altitude.

The UK, G, NL, F, E, and IT mention that the rainy season represents an increased risk of being bitten by mosquitoes and thus becoming infected with malaria.

The UK and IT state that high humidity and a temperature in the range of 20 to 30°C are further risk factors, and that malaria does not occur in regions with temperatures below 16°C.

All recommendations report a higher risk in rural than in urban areas. All recommendations indicate that being bitten by *Anopheles* mosquitoes is an increased risk factor during the period from dusk till dawn.

(See Table General Aspects II in Appendix B).

C.3 Comparison of recommended methods for mosquito protection (exposure prophylaxis)

C.3.1 DEET

All malaria recommendations for travellers agree that the active substance DEET (N, N- diethyl-m-toluamide) is the most effective mosquito repellent. However, there are different recommendations on the use of active substance concentrations in malaria areas. The UK and E recommend effective concentrations of the active substance DEET between 20 and 50%, while G, NL, B, and F recommend the use between 30 and 50%. IT recommends the use of concentrations of 5-30% and recommends concentrations of DEET above 30% in high-risk areas of malaria.

C.3.1.1 DEET and duration of protection

All recommendations agree that the concentration of DEET correlates with the duration of action and that there is no further benefit in duration of protection beyond a concentration of 50%.

The UK comments on the duration of protection in more detail: 1 to 3 hours for 20%, up to 6 hours for 30% and up to 12 hours for 50% of DEET concentration. B offers similar information, with a protection duration of about 8 hours at a concentration of 40-50%. The NL indicate how frequently per day DEET should be applied to the skin in different concentrations in malaria areas: 20% five times a day; 30% four times, 40% three times and 50% twice a day. E gives a protection time of 6 to 12 hours at a DEET concentration of 20-35%. F does not provide any information on this.

(See Table Bite Protection: DEET in Appendix C).

C.3.1.2 DEET and sunscreen

All recommendations indicate that if DEET and sunscreen are to be applied simultaneously, sunscreen should be applied first and DEET should only be applied 20-30 minutes later. Only IT does not provide any information on this. In addition, the UK and B recommend applying sunscreen with an SPF of 30 or higher to compensate for the DEET-related reduction in SPF. (See Table Bite Protection: DEET in Appendix C).

C.3.1.3 DEET and children

Recommendations for DEET concentration used in children vary widely: the highest recommended concentration is 50%, the lowest is 10%. The lower age limits for the use of DEET also differ from "≥ 2 months" to "≥ 2 years" (see Table IV).

Table IV:

Recommendations on limits of concentration of DEET and age limits on the use in children

DEET: children	UK	G	NL	B	F	E	IT
Concentrations of DEET	≤ 50%	≤ 50%	≤ 50%/ ≤ 30%	20- 30%	30-50%/ 10-20%	≤ 50%	10%
Age limits	≥ 2 months	≥ 2 years	≥ 2 years/ < 2 years	≥ 6 months	≥ 2 years/ < 2 years	≥ 2 months	≥ 2 years

(See Table Bite Protection: DEET in Appendix C).

C.3.1.4. DEET and pregnancy/ breastfeeding

The recommendations on the use of the active substance DEET to protect against mosquito bites during pregnancy and breastfeeding vary: in the UK, G, F, and E, DEET is approved in concentrations up to 50% for the entire time of pregnancy and during breastfeeding. The NL and B approve concentrations of up to 30% of DEET for pregnancy, IT recommends concentrations up to 10%. (Breastfeeding is not mentioned in each case).
(See Table Bite Protection: DEET in Appendix C).

C.3.2 Icaridin/ Picaridin

Nearly all recommendations state that the use of the active substance icaridin/ picaridin is recommended as an alternative to DEET in concentrations of 20% or more for skin protection against mosquitoes in malaria areas**.** The lower age limits for the use of icaridin/ picaridin differ extremely from "≥ 6 months" to "≥ 13 years" (see Table V).

Table V:

Recommendations of limits of concentration of icaridin and age limits on the use in children

Icaridin: children	UK	G	NL	B	F	E	IT
Concentrations of icaridin	≥ 20%	≥ 20%	15%	20-25%	≥ 20-25%	≥ 20%	≤ 40-45%
Age limits	---	≥ 6 months	≥ 13 years	≥ 2 years	≥ 2 years	---	≥ 2years

Table VI:

Recommendations of icaridin use during pregnancy

Icaridin: pregnancy	UK	G	NL	B	F	E	IT
Use during pregnancy	---	---	Not recommended	May be used	20% concentration approved	----	----

(See Table Bite Protection: other repellents in Appendix C).

C.3.3 IR3535

The recommendations of the UK, G, E, and IT mention that the active substance IR3535 for mosquito protection will most likely be less effective than DEET and should therefore only be used as second choice.

B and F generally recommend a concentration of 30% of IR3535 in malaria areas and indicate a concentration of 20% for use during pregnancy and for children from the age of 6 months. E does not discuss the topic of the concentration of IR3535, but approves the use of IR3535 for children from an age of 1 year. All other recommendations do not provide information on the concentration of IR3535, age limits, or use during pregnancy and breastfeeding.

(See Table Bite Protection: other repellents in Appendix C)

C.3.4 Eucalyptus citriodora oil, hydrated, cyclised (EC Oil (H/C))

The recommendations and information on the use of the hydrated and cyclised active form of eucalyptus citriodora oil (EC Oil (H/C); previous naming: para-menthane 3,8 diol; previous abbreviations: PMD or PMDRBO) as a mosquito repellent differ significantly.

The UK states that concentrations of 30% of EC Oil (H/C) are supported by studies. G publishes that repellent products of EC Oil (H/C) with concentrations ranging from 5-30% are available and could be used depending on the duration of targeted protection times according to the manufacturer's instructions for use. B, F, and E recommend concentrations of 20-25% of EC Oil (H/C).

The lower age limits for the use of EC Oil (H/C) differ from “≥ 6 months” to “≥ 3 years” (see Table VII).

Table VII:

Recommendations on limits of concentration of EC Oil (H/C) and age limits on the use in children

EC Oil (H/C): children	UK	G	NL	B	F	E	IT
Concentration of EC Oil (H/C)	30%	5-30%	---	20-25%	≤ 20%/ ≥25%	≥ 20%	≤ 40-45%
Age limits	---	≥ 3 years	---	≥ 6 months	≥ 6 months (for concentrations ≤20%) ≥ 2 years (for concentrations ≥25%)	≥ 3 years	---

Additionally, F informs that up to a 20% concentration of EC Oil (H/C) is approved during pregnancy. All other recommendations do not comment on the use during pregnancy.
(See Table Bite Protection: other repellents in Appendix C).

C.3.5 Oil of citronella

All recommendations agree that oil of citronella is unsuitable for use in malaria areas because of its highly volatile nature, thus featuring only short-term protection. Only the NL and IT do not provide information on repellent products based on the oil of citronella.
(See Table Bite Protection: other repellents in Appendix C).

C.3.6 Other topical repellents

Other repellents such as geraniol or petroleum jelly, which are not meant for use on human skin, were mentioned in recommendations of G and E. Their efficacy was mentioned in a few studies only, but ultimately not recommended for protection against Anopheline mosquitoes.

C.3.7 Comparison of recommendations regarding insufficient methods of mosquito protection

Regarding insufficient or inappropriate methods of mosquito protection all recommendations address all or at least some of the following issues: herbal products, homeopathy, buzzers, vitamins B1 and B12, garlic, yeast extract, tea tree oil, essential oil (e.g. oil of lemon eucalyptus (before being hydrated and cyclised), lotus flower, lavender).
The UK and E mention all of these issues, G, B, and F emphasise warnings about products made of the plant artemisia.
(See Table Bite Protection: insufficient methods in Appendix C).

C.3.8 Impregnated mosquito net/ air condition

All malaria recommendations for travellers unanimously mention the use of impregnated bed nets for overnight stays as a combined chemical and physical barrier for mosquito protection, and recommend the use of air conditioning for closed rooms, where available.
(See Table Bite Protection: mechanical barriers in Appendix C).

C.3.9 Clothing

All malaria recommendations advise the use of insecticide-impregnated long-sleeved clothing in malaria-endemic areas. G, E, and IT highlight the use of light-coloured clothing, while the UK recommendations state that there is no evidence that the colours of clothing are relevant to mosquitoes. The NL, B, and F do not discuss the topic of colours.

(See Table Bite Protection: mechanical barriers in Appendix C).

C.3.10 Insecticides for application on textiles: Permethrin/ Chrysanthemum cinerariaefolium

All recommendations indicate that the insecticide permethrin/ chrysanthemum cinerariaefolium (previous name: pyrethrum) should be used to impregnate clothes and mosquito nets for chemical protection. Furthermore, the UK recommends the use of permethrin for indoor residual spraying, while E and IT suggest the general use to impregnate surfaces in the environment.

(See Table Bite Protection: mechanical barriers in Appendix C)

C.4. Comparison of chemoprophylaxis (CHP)

C.4.1 Chemoprophylaxis for adults

As effective malaria chemoprophylaxis in high-risk areas for adults in general, all seven selected malaria recommendations for travellers mention the active substances atovaquone/proguanil (AP) as fixed drug combination, doxycycline (D), and mefloquine (M). G and B exclusively recommend only these three substances. Additionally, the UK, NL, and E recommend the combination of chloroquine (C) and proguanil (P) as (C+P) in chloroquine-sensitive areas in Central America (north of the Panama Canal), in Haiti, and the Dominican Republic. F and IT only mention C for chloroquine-sensitive areas, the use of P is not specified.

(See Table Chemoprophylaxis in Appendix D).

C.4.2 Chemoprophylaxis for children

As with the recommendations on chemoprophylaxis for adults, all seven selected malaria recommendations for travellers mention for children in general the active substances AP, D (for children from 8 years of age, in some recommendations from 12 years onwards), and M as effective chemoprophylaxis against malaria in high-risk areas. Additionally, the UK, NL, and E recommend C+P and F and IT only C for children in chloroquine-sensitive areas.

(See Table Chemoprophylaxis in Appendix D).

C.4.3 Dosage and recommendations for the individual active substances

C.4.3.1 Atovaquone/proguanil fixed drug combination (AP)

Most of the malaria recommendations advise usage and dosing for atovaquone/proguanil (AP) as listed. AP is available in an adult formulation (250 mg/100 mg) and a paediatric formulation (62.5 mg/25 mg).

Table VIII:

Common recommendations on usage and dosing for atovaquone/proguanil (AP) when used as chemoprophylaxis (CHP)

AP (CHP)	**Common recommendations**
Efficiency	*Pf, non-falciparum species* (not preventing relapses of *vivax* and *ovale* malaria); CHP, ESM; all malaria areas
Formulations of AP (in mg)	Adult 250/100 and paediatric 62.5/25
Prophylactic regimen	daily, starting 1-2 days before entering the malaria area, continuing through the time and for 7 days after leaving
Dosage (adults/children)	5-< 9 kg: 1/2 tablet (62.5/25); off-label-use 9-< 11 kg :3/4 tablet (62.5/25); off-label-use 11-< 21 kg: 1 tablet (62.5/25) 21-< 31 kg: 2 tablets (62.5/25) 31-< 40 kg: 3 tablets (62.5/25) ≥ 40kg: 1 tablet (250/100) adult formulation

Deviations:

All recommendations advise the (off-label) use of AP in children from 5 to 11 kg. IT only advises on-label-use for children from 11 kg. B also recommends use of AP from 5 kg, but does not discuss the topic if there is an off-label-use.

(See Table Chemoprophylaxis (AP and M: dosage and recommendations) in Appendix D).

C.4.3.2 Mefloquine (M)

All malaria recommendations agree, that the active substance mefloquine (M) should only be used after stringent risk assessment. They also inform that M is not licenced in G, NL, F, and E, but can be imported and used on-label for justified medical indication.

The majority of the malaria recommendations advise usage of M as listed:

Table IX:

Common recommendations on usage of mefloquine (M)

M (CHP)	Common recommendations
Efficiency	*Pf, non-falciparum species* (not preventing relapses of *vivax* and *ovale* malaria); CHP; all malaria areas except mefloquine-resistant areas in Asia
Formulation of M (in mg)	250
Prophylactic regimen	weekly, starting 1-3 weeks before entering the malaria area, continuing through the time and for 4 weeks after leaving

Deviations:

The dosage recommendations for M in children vary extremely as listed:

Table X:

Different dosage applications for mefloquine (M)

Dosage M (250 mg per tablet)	UK	G	NL	B	F	E	IT
1/8 tablet	---	5-< 9 kg	---	5-< 11 kg	5-< 15 kg	5-< 11 kg	5mg/ kg
1/4 tablet	6-< 16 kg	9-< 15 kg	5-< 21 kg	11-< 21 kg	15-19 kg	11-< 21 kg	---
1/4 + 1/8 tablet	---	15-< 19 kg	---	---	---	---	---
1/2 tablet	16-< 25 kg	19-< 31 kg	21-< 31 kg	21-< 31 kg	>19-30 kg	21-< 31 kg	---
3/4 tablet	25-< 45 kg	31-< 45 kg	31-< 45 kg	31-< 45 kg	> 30-45 kg	31-< 45 kg	---
1 tablet	≥ 45 kg	45-< 90 kg	≥ 45 kg	≥ 45 kg	> 45 kg	≥ 45 kg	---
1.5 tablets	---	90-< 120 kg	---	---	---	---	90-< 120 kg
2 tablets	---	≥ 120 kg	---	---	---	---	≥ 120 kg

In the NL and F, M is recommended as off-label-use for children from 5 to 15 kg.

(See Table Chemoprophylaxis (AP and M: dosage and recommendations) in Appendix D).

C.4.3.3 Doxycycline (D)

Doxycycline (D) is an antibiotic drug that is also used as an antimalarial. In G and IT, it is not registered for the use as antimalarial chemoprophylaxis, so the use is only off-label. In the UK, NL, B, F, and E, D is registered for this use (on-label).

Most recommendations advise usage of D as listed:

Table XI:

Common recommendations on usage of doxycycline (D)

D (CHP)	Common recommendations
Efficiency	*Pf,* non-falciparum species (not preventing relapses of *vivax* and *ovale* malaria); CHP; all malaria areas
Formulation of D (in mg)	100
Prophylactic regimen	daily, starting 1-2 days before entering the malaria area, continuing through the time and for 4 weeks after leaving

Deviations:

The recommendations advise the dosage of D as listed:

Table XII:

Different dosage applications for doxycycline (D) and age limits

Dosage D (100 mg per tablet)	UK	G	NL	B	F	E	IT
mg/kg body weight	---	---	2 mg/ kg	1,5 mg/ kg	---	1,5-2 mg/ kg	1,5mg/ kg
1/2 tablet	---	25-< 36 kg	---	---	< 40 kg	---	---
3/4 tablet	25-< 45 kg	36-< 50 kg	< 45 kg:	---	---	---	---
1 tablet	≥ 45 kg	≥ 50 kg	≥ 45 kg	adults	≥ 40 kg	adults	adults
2 tablets	if simultaneously co-medication carbamazepine, phenytoin	if simultaneously co-medication carbamazepine, diphenylhydantoin, barbiturates, rifampicin, or chronic alcohol abuse, enzyme induction may occur	---	---	---	---	if simultaneously co-medication carbamazepine, phenytoin, barbiturates
Age limits	≥ 12 years or ≥ 25 kg	≥ 8 years or ≥ 25 kg	≥ 12 years; children 8-11 years: off-label use	≥ 8 years	≥ 8 years	≥ 8 years	≥ 8 years or ≥ 25 kg

(See Table Chemoprophylaxis (D, C and P: dosage and recommendations) in Appendix D).

C.4.3.4 Chloroquine (C)

The use of chloroquine (C) for chemoprophylaxis of malaria is discussed inconstantly. G and B no longer list this drug. Most of the other malaria recommendations advise usage of C as listed:

Table XIII:

Common recommendations on the usage of chloroquine (C)

C (CHP)	Common recommendations
Efficiency	*Pf*, *non-falciparum species* (not preventing relapses of *vivax* and *ovale* malaria); CHP; chloroquine-sensitive areas: Central America (north of the Panama Canal) and Haiti & the Dom. Rep.
Formulations of C (in mg)	155 (UK), 100 (NL, F), 150 (E, IT)
Prophylactic regimen	weekly, starting 1 week before entering the malaria area, continuing through the time and for 4 weeks after leaving, only taken in combination therapy with proguanil

Deviations:

The usual amount per standard tablet of C differs between countries as listed (Table XIII). The recommendations from F differ in that a daily intake of a lower dosage is recommended instead of a weekly intake with a higher dosage (Table XIVa). The NL recommend the weekly intake, but instead of starting 1 week before entering the malaria area, only on the day of arrival in the malaria area, to be continued daily for 2 days and once a week thereafter (off-label-advice), continuing throughout the stay in the malaria area and for 4 weeks after leaving.

Table XIVa:

Dosage recommendations for chloroquine (C) and mode of application

Dosage C (in mg)	UK	G	NL	B	F	E	IT
Intake mode	weekly	---	weekly	---	daily	weekly	weekly
mg/kg body weight	---	---	5 mg/kg (< 50kg)	---	1,7mg/kg	5 mg/kg (< 36 kg)	5mg/kg
12,5mg	≤6 kg	---	---	---	<10 kg	---	---
25 mg	---	---	< 5 kg	---	≥10-16 kg	---	---
50 mg	---	---	5-< 11 kg	---	>16-33 kg	---	---
75 mg	6-< 10 kg	---	---	---	>33-45 kg	---	---
100 mg	---	---	11-< 21 kg	---	>45kg	---	---
112 mg	10-< 16 kg	---	---	---	---	---	---
150 mg	16-< 25 kg	---	21-< 30 kg	---	---	---	---
200 mg	25-< 45 kg	---	---	---	---	---	---
225 mg	---	---	---	---	---	36-< 46 kg	---
250 mg	---	---	31-< 45 kg	---	---	---	---
300 mg	≥ 45kg	---	≥ 45kg	---	---	46-< 61 kg	>45 kg
375 mg	---	---	---	---	---	61-75 kg	---
450 mg	---	---	---	---	---	> 75kg	---

Table XIVb:

Weight-dependent dosage of chloroquine (C)

Dosage per body weight	UK	G	NL	B	F daily intake	E	IT
10 kg	75 mg	---	50 mg	---	25 mg	50 mg	50 mg
20 kg	150 mg	---	100 mg	---	50 mg	100 mg	100 mg
30 kg	200 mg	---	150 mg	---	50 mg	150 mg	150 mg
40 kg	200 mg	---	250 mg	---	75 mg	225 mg	200 mg
50 kg	300 mg	---	300 mg	---	100 mg	300 mg	300 mg
60 kg	300 mg	---	300 mg	---	100 mg	300 mg	300 mg
70 kg	300 mg	---	300 mg	---	100 mg	375 mg	300 mg
80 kg	300 mg	---	300 mg	---	100 mg	450 mg	300 mg

(See Table Chemoprophylaxis (D, C and P: dosage and recommendations) in Appendix D).

C.4.3.5 Proguanil (P)

The active substance proguanil (P) as a single drug treatment is only listed in the recommendations of the UK, NL, and E, however, not for use on its own but only in combination with C. All other recommendations do not list P as individual substance anymore.

All recommendations generally advise against its use as a single substance, as the effect alone is too weak. P is not licensed in the NL and E, but can be imported and used on-label.

The UK, NL, and E recommendations advise usage of P as listed:

Table XV:

Common recommendations on usage of proguanil (P)

P (CHP)	Common recommendations
Efficiency	*Pf, non-falciparum species* (not preventing relapses of *vivax* and *ovale* malaria); CHP
Formulation of P (in mg)	100
Prophylactic regimen	daily, starting 1 week before entering the malaria area, continuing through the time and for 4 weeks after leaving, only taken in combination therapy with chloroquine

These are the different dosage applications for a tablet of P with a formulation per tablet of 100 mg:

Table XVI:

Different dosage applications for proguanil (P)

Dosage P (100 mg per tablet)	UK	G	NL	B	F	E	IT
1/4 tablet	≤6 kg	---	< 5 kg; 5-< 11 kg	---	---		---
1/2 tablet	6-< 10 kg	---	11-< 21 kg	---	---		---
3/4 Tablet	10-< 16 kg	---		---	---		---
1 tablet	16-< 25 kg	---	21-< 31 kg	---	---	< 55 kg	---
1 1/2 tablet	25-< 45 kg	---	31-< 45 kg	---	---		---
2 tablets	≥ 45 kg	---	≥ 45 kg	---	---	> 55 kg	---

(See Table Chemoprophylaxis (D, C and P: dosage and recommendations) in Appendix D).

C.4.4 Side effects, interactions, contraindications, and precautions of the individual active substances

The side effects, interactions, contraindications, and precautions were described in different styles and to varying extents.

B, which publishes all its recommendations on a webpage, does not discuss these topics at all.

All other recommendations have dedicated chapters on chemoprophylaxis discussing side effects, interactions, contraindications, and precautions of the recommended antimalarials. In addition, important information is sometimes given in separate chapters discussing travellers with special needs, such as children, pregnant and breastfeeding women, travellers on anticoagulation, or HIV-infected travellers.

Only IT found a more uniform and clear structure discussing side effects, contraindications, and precautions in the chapter of antimalarials and interactions in the chapters on travellers with special needs.

The information on side effects, interactions, contraindications, and precautions of all individual antimalarials for chemotherapy were summarised, then compared and listed on the tables “Side effects, CYP450, Interactions, Contraindications, Precautions" in Appendix D. None of the recommendations provide information on the frequency of side effects.

C.4.5 Chemoprophylaxis and handling of vomiting up antimalarials

There are different statements of the malaria recommendations for travellers regarding the management of vomiting after taking antimalarials as listed in Table XVII.

Table XVII:

Recommendations of dosage amounts for repeated intake of antimalarials according to time interval of vomiting after taking antimalarial drugs

Time interval of vomiting after intake of antimalarials	UK	G	NL	B	F	E	IT
< 30 min	full dose	full dose	full dose	---	---	AP: full dose	---
30-60 min	half dose	AP, AL: full dose M: half dose	full dose	---	---	AP: full dose	---
< 3 hours	---	---	---	AP: full dose	---	---	---

(See Table Chemoprophylaxis in Appendix D).

C.4.6 Recommendations for chemoprophylaxis for *non-falciparum* species

All recommendations except B distinctly discuss *non-falciparum species* and possibilities of chemoprophylaxis.

C.4.6.*1 Plasmodium vivax* and *ovale* and usage of primaquine

The recommendations from the UK, G, NL, F, E, and IT inform unanimously that *P. vivax* (*Pv*) and *P. ovale* (*Po*) create hypnozoites in the liver, which may trigger relapses. All inform that chemoprophylaxis with AP, M, D, and C+P does not protect from the creation of hypnozoites, and therefore does not prevent hypnozoite-induced relapses of *Pv* or *Po* malaria.

The recommendations mention that the active substance primaquine acts against hypnozoites.

All recommendations also agree that primaquine might potentially be used as (primary) chemoprophylaxis in *Pv* areas or as "terminal prophylaxis" to kill the hypnozoites at the end of a period of exposure.

All guidelines mention that primaquine is contraindicated in G6PD-deficiency because of the risk of inducing haemolysis.

B does not provide information on *Pv* and *Po* species nor on the active substance primaquine.

The NL, E, and IT additionally inform about a possible dosage of 30 mg base per day for adults and 0,5 mg/ kg in children.

(See Table Chemoprophylaxis (*non-falciparum species*) in Appendix D).

C.4.6.2 Information about *Plasmodium malariae*

There is not much information given in the recommendations about *Plasmodium malariae*. The UK and G inform that *P. malariae* and *P. knowlesi* look morphological similar, so that they can

be confused on a blood film. F and E report limited experience with quartan malaria and mention the usually rare and benign nature of the infection.
(See Table Chemoprophylaxis (*non-falciparum species*) in Appendix D).

C.4.6.3 Information about *Plasmodium knowlesi*

The recommendation of the UK, G, NL, F, E, and IT unanimously state that *Plasmodium knowlesi* causes a form of malaria endemic to Southeast Asia.
(See Table Chemoprophylaxis (*non-falciparum species*) in Appendix D).

C.5 Comparison of emergency standby treatment and the emergency standby medication (ESM)

C.5.1 Emergency standby treatment

As an alternative to chemoprophylaxis for destinations with lower transmission some guidelines for travellers recommend the use of emergency standby medication (ESM) when travelling to remote locations without access to health care.
All recommendations agree that ESM can only be seen as a first aid measure and can be used based on a presumption if the following facts are taken into account: the presence of malaria symptoms, the incubation period of at least 7 days and/or the absence of timely medical care. Travellers should always be advised to continue seeking medical help as soon as possible, regardless of the intake of ESM.

G, NL, B, E, and IT recommend the use of ESM for moderate-risk areas of malaria (in addition to exposure prophylaxis).
UK and F recommend ESM only for travellers already taking chemotherapy and visiting remote areas: They advise only to take ESM in case of prophylaxis failure. In addition, it is mentioned that the use should remain the exception and the active substances of ESM should be different from the drugs already used for chemoprophylaxis. (Normally the UK advises only chemoprophylaxis in high-risk areas, F even in moderate and high-risk areas).

As reference value at which emergency standby treatment should be initiated, the body temperature indicating "fever" is specified by the recommendations. In addition the "minimum time for access to medical care" is defined. This is used as a guidance to assess whether ESM needs to be prescribed. Another issue that the recommendations consider is the "duration of fever after which an ESM must be initiated". It is used to guide the traveller on when to take their medication after the fever has risen.
The individual differences of these conditions in the recommendations are listed in Table XVIII.

Table XVIII:

Recommendations for conditions when to use ESM

ESM and conditions	UK	G	NL	B	F	E	IT
Fever	38,0° C	38,0° C	38,5° C	38,0° C	38,0° C	38,0° C	37,5° C
Duration of fever after which to initiate ESM	24 h	24 h	24 h	24 h	12 h	24 h	24 h
Minimum time to access medical care	24 h	48 h	24 h	24 h	12 h	24 h	24 h

(See Table ESM: Emergency standby treatment in Appendix E).

C.5.2 Dosage and recommendations for emergency standby medication

C.5.2.1 Artemether/lumefantrine fixed drug combination (AL)

All recommendations agree that the fixed drug combination artemether/lumefantrine (AL) is only used as emergency standby medication (ESM) and not for chemoprophylaxis.

Most of the malaria recommendations advise the dosage and the intake requirements of AL as listed in Table XIX.

Table XIX:

Common recommendations and applications for emergency standby medication of artemether/lumefantrine (AL)

AL (ESM)	Common recommendations
Efficiency	*Pf*, *non-falciparum species* (not preventing relapses of *vivax* and *ovale* malaria); ESM; all malaria areas
Formulations of AL (in mg)	20/120
Prophylactic regimen	dose of tablets given initially, followed by 5 further doses each given at 8, 24, 36, 48, 60 hours
Dosage (adults/children)	5-< 15 kg: 1 tablet 15-< 25 kg: 2 tablets 25-< 35 kg: 3 tablets ≥ 35 kg: 4 tablets

Deviations:

AL is not licensed in E and IT and therefore not recommended in IT as ESM. E recommends it as ESM, which can be imported.

The UK, B, and F mention only the dosage scheme for adults, B adds in the recommendation to use it for adults and children ≥ 12 years and ≥ 35 kg.

The NL recommend for children below 5 years to use chemoprophylaxis instead of ESM in moderate-risk areas.
(See Table ESM (AL, AP and DP: dosage and recommendations) in Appendix E).

C.5.2.2 Atovaquone/proguanil fixed drug combination (AP)

All recommendations mention that the fixed drug combination atovaquone/proguanil (AP) can be used both as chemoprophylaxis and as ESM.
Most of the malaria recommendations advise for ESM the dosage and the intake requirements of AP as listed in Table XX.

Table XX:

Common recommendations and applications for emergency standby medication of atovaquone/proguanil (AP)

AP (ESM)	Common recommendations
Efficiency	*Pf, non-falciparum species* (not preventing relapses of *vivax* and *ovale* malaria); ESM, CHP; all malaria areas
Formulations of AP (in mg)	Adult 250/100 and paediatric 62.5/25
Prophylactic regimen	dose of tablets as a single dose on each of 3 consecutive days
Dosage (adults/children)	5-< 9 kg: 2 tablets (62.5/25) 9-< 11 kg :3 tablets (62.5/25) 11-< 21 kg: 1 tablet (250/100) 21-< 31 kg: 2 tablets (250/100) 31-40 kg: 3 tablets (250/100) > 40 kg: 4 tablets (250/100)

Deviations:
The UK, B, and F mention only the dosages scheme for adults, B adds in the recommendation to adjust the dose for children.
The NL recommend for children below 5 years to use chemoprophylaxis instead of ESM in moderate-risk areas.
(See Table ESM (AL, AP and DP: dosage and recommendations) in Appendix E).

C.5.2.3 Dihydroartemisinin/piperaquine fixed drug combination (DP)

The recommendations of dihydroartemisinin/piperaquine (DP) as fixed drug combination differ very much: DP is not licensed in the UK and therefore not recommended as ESM, also G does not recommend it. The NL do not list DP in the recommendations.
B, F, E, and IT advise the dosage and the intake requirements of DP for ESM as listed in Table XXI.

There is an adult formulation (320mg/40mg) and a paediatric formulation (160mg/20mg):

Table XXI:

Common recommendations and applications for emergency standby medication of dihydroartemisinin/piperaquine (DP)

DP (ESM)	Common recommendations
Efficiency	*Pf, non-falciparum species* (not preventing relapses of *vivax* and *ovale* malaria); ESM; all malaria areas
Formulations of DP (in mg)	Adult 320/40 and paediatric 160/20
Prophylactic regimen	dose of tablets as a single dose on each of 3 consecutive days
Dosage (adults/children)	5-< 7 kg: 1/2 tablet (160/20) 7-< 13 kg: 1 tablet (160/20) 13-< 25 kg: 1 tablet (320/40) 25-< 36 kg: 2 tablets (320/40) 36-< 75 kg: 3 tablets (320/40) 75-<100 kg: 4 tablets (320/40)

Deviations:

E and IT recommend to use DP as listed, but B and F only mention the dosages from 36 kg body weight for adults. They do not mention children's dosages.

(See Table ESM (AL, AP and DP: dosage and recommendations) in Appendix E).

C.5.2.4 Quinine plus doxycycline

Only the UK recommendations mention the combination of quinine and doxycycline for ESM for chloroquine- or multi-drug resistant *Pf*.

2 tablets of quinine 300 mg should be taken three times a day for 3 days, in combination with 1 tablet of doxycycline 100 mg twice daily for 7 days. No further information is mentioned.(See Table ESM (Quinine plus doxycycline, Quinine plus clindamycin: dosage and recommendations) in Appendix E).

C.5.2.5 Quinine plus clindamycin

The recommendations of the UK, NL, and IT mention the combination of quinine and clindamycin for ESM in pregnancy starting from the first trimester.

The UK recommends the mode of intake: 2 tablets of quinine 300 mg three times a day for 5 to 7 days in combination with 3 tablets of clindamycin 150 mg three times a day for 5 days.

(See Table ESM (Quinine plus doxycycline, Quinine plus clindamycin: dosage and recommendations) in Appendix E).

C.5.3 Side effects, interactions, contraindications, and precautions of the emergency standby medication

Not many of the recommendations comment on side effects, interactions, contraindications, and precautions with regard to ESM.

The information on side effects, interactions, contraindications, and precautions of all individual antimalarials for emergency standby therapy were summarised, then compared and listed on the tables “Side effects, CYP450, Interactions, Contraindications, Precautions" in Appendix D.

None of the recommendations provide information on the frequency of side effects.

(See Tables of Side effects, CYP450, Interactions, Contraindications, Precautions: AL, DP in Appendix E).

C.5.4 Restarting chemoprophylaxis after ESM

The UK, NL, F, E, and IT give recommendations on how to recommence chemoprophylaxis in high-risk areas after taking ESM.

The UK, E, and IT recommend completing ESM or treatment course and waiting 1 week after taking the first treatment dose to recommence chemoprophylaxis. The UK and E add that, if quinine is used as ESM, mefloquine prophylaxis should be resumed at least 12 hours after the last treatment dose.

The UK, NL, and F advise using a different ESM than the one used for chemoprophylaxis. G and B do not discuss the topic of restarting chemoprophylaxis after ESM.

(See Table ESM (CHP and RDT) in Appendix E).

C.5.5 Handling the rapid diagnostic test (RDT)

All recommendations agree that self-testing with using malaria rapid diagnostic tests (RDTs) is not generally recommended for travellers. RDTs should only be used in exceptional cases by trained, selected, high-risk groups of travellers or medical staff.

E does not discuss the topic of RDTs. F informs that according to French law the tests are only available for medical laboratories.

(See Table ESM (CHP and RDT) in Appendix E).

C.6 Comparison of recommendations for special groups

The comparison of recommendations for special groups of travellers, especially in relation to chemoprophylaxis and ESM, depends on the individual country's medication recommendations. In general, there are differences in regulations and licensing for the use of medications that vary from country to country, as mentioned in chapters C.4 and C.5.

The recommendations for the specific groups regarding the handling of mosquito protection and repellents, have already been discussed and compared in chapter C.3.

C.6.1 Pregnancy and breastfeeding

All recommendations mention that there is an increased risk for severe malaria during pregnancy. They agree that pregnant women should be advised to avoid travel to malaria areas. They all also agree that there is no certainty about the absolute safety of any of the antimalarials used during pregnancy and recommend that the risks and benefits of travelling to a malaria-endemic area should be strictly outweighed. For unavoidable travel all recommendations advise strictly following mosquito protection rules and using repellents.

C.6.1.1 Chemoprophylaxis in pregnancy

All recommendations advise to take M as first choice as chemoprophylaxis during pregnancy for all trimesters. The UK, NL, E, and IT also mention the use of C+P for chloroquine-sensitive areas and consider it safe for all trimesters of pregnancy.

Only the recommendations of F state that C is contraindicated during pregnancy. They therefore advise contraception for 8 months after use of C.

G and B do not mention the use of C and P in their recommendations for chemoprophylaxis.

Table XXII:

Recommendations on chemoprophylaxis (CHP) during pregnancy

Country recommendations	CHP in 1st trimester of pregnancy	CHP in 2nd and 3rd trimester of pregnancy
UK	M, C+P, D (may be used: 1st trim.)	M, C+P, AP (may be used: 2nd, 3rd trim.)
G	M, D (may be used: 1st trim.)	M
NL	M, C+P	M, C+P
B	M, D (may be used: 1st trim.)	M
F	M, D (may be used: 1st trim)	M, AP (may be used: 2nd, 3rd trim.)
E	M, C+P, D (may be used: 1st trim)	M, C+P, AP may be used: 2nd, 3rd trim.)
IT	M (mainly for 2nd and 3rd trim), C (+P),	M, C+P

(See Table Special groups I in Appendix F).

C.6.1.2 ESM in pregnancy

The recommendations on the use of ESM during pregnancy vary extremely (see Table XXIII).

Table XXIII:

Recommendations on ESM during pregnancy

Country recommendations	Pregnancy and ESM
UK	quinine plus clindamycin in the 1st trimester, AL or AP in the 2nd and 3rd trimester of pregnancy
G	not recommended, CHP with M also in low-risk areas
NL	not recommended, CHP with M also in moderate-risk areas, BP in low-risk areas; (quinine with clindamycin possible, AL: use from 2nd trimester possible)
B	not mentioned
F	AL, DP not recommended during 1st trimester
E	not mentioned
IT	quinine; M (2nd and 3rd trim. if no other option), AP

(See Table Special groups I in Appendix F).

C.6.1.3 Chemoprophylaxis prior to conception

The recommendations with regards to the time intervals after completing a course of chemoprophylaxis before attempting to conceive are largely in agreement.

The UK, E, and IT advise waiting for 1 week after taking D, 2 weeks after AP and 3 months after the last dose of M, before attempting conception.

The NL agree on the interval of 1 week for D. For AP it is suggested to wait until the time after the next menstruation.

Additionally, E mentions no interval for C. This is in sharp contrast with the recommendations from F that recommend waiting for 8 months after prophylaxis with C before planning a pregnancy.

(See Table Special groups I in Appendix F).

C.6.1.4 Breastfeeding

The recommendations on breastfeeding and the use of antimalarials also differ markedly: The only concordant feature is that all recommendations see D as contraindicated during breastfeeding.

In the recommendations of the individual countries, the categorisation between contraindications and precautions varies greatly.

Table XXIV:

Recommendations on the use of antimalarials during breastfeeding

Country recommendations	M	C(+P)	AP	D	AL
UK	recommended	---	not recommended	contraindicated	---
G	recommended	---	not recommended	contraindicated	---
NL	recommended	recommended	possible as off-label-use (for mothers with babies ≥ 5 kg)	contraindicated	possible as off-label-use (for mothers with babies ≥ 5 kg)
B	recommended	---	recommended	contraindicated	---
F	not recommended	contraindicated	first line treatment	contraindicated	---
E	recommended	recommended	may be used for mothers with babies ≥ 5 kg	contraindicated	---
IT	recommended	recommended	not recommended	contraindicated	---

(See Table Special groups I in Appendix F).

Remarkably, the French recommendations advise that the use of C is contraindicated during breastfeeding. In contrast, the UK, NL, E, and IT specifically recommend the use of C during the whole pregnancy and while breastfeeding in chloroquine-sensitive malaria area (see Table XXIV).

C.6.2 Children

All recommendations emphasise that children of travellers, especially below 5 years of age, have a particular risk for severe malaria. Recommendations agree that parents should be advised to avoid non-essential travel with their children to high-risk malaria areas. All recommendations unanimously advise that, in the event of unavoidable travel, strict mosquito protection measures, including the use of repellents, should be followed, and appropriate chemoprophylaxis should be taken.

C.6.2.1 Chemoprophylaxis in children

The common recommendation for antimalarial chemoprophylaxis in children regarding minimal weight/ minimum age is listed as follows (for dosing instructions see chapter C.4):

- AP (5-<11 kg: off-label-use)
- M (≥ 5 kg)
- D (≥ 8 years)
- C (+P) for children of every weight

All the deviations see Table XXV.

Table XXV:

Recommendations on chemoprophylaxis (CHP) in children

Country recommendations	AP	M	D	C(+P)
UK	recommended, (5-< 11 kg: off-label-use)	recommended, (≥ 5 kg)	recommended, (≥ 12 years)	C+P: recommended for children of every weight
G	recommended, (5-< 11 kg: off-label-use)	recommended, (≥ 5 kg)	recommended, (≥ 8 years, off-label-use)	---
NL	recommended, (5-< 11 kg: off-label-use)	recommended, (5 kg-< 15kg: off-label-use)	recommended, (8 -< 12 years, off-label-use)	C+P: recommended (C:< 10kg: off-label-use)
B	recommended, (≥ 5kg)	recommended, (≥ 5 kg)	recommended, (≥ 8 years)	---
F	recommended, (5-< 11 kg: off-label-use)	recommended, (≥ 5 kg)	recommended, (≥ 8 years)	C: recommended for children of every weight
E	recommended, (5-< 11 kg: off-label-use)	recommended, (≥ 5 kg)	recommended, (≥ 8 years)	C+P: recommended for children of every weight
IT	recommended, (≥ 11 kg)	recommended, (≥ 5 kg)	recommended, (≥ 8 years, ≥ 25kg)	C: recommended for children of every weight

(See Table Special groups I in Appendix F).

C.6.2.2 ESM in children

The common recommendations for ESM in children are listed as follows (for dosing instructions see chapter C.5). AL, AP, DP are all approved for children from 5 kg body weight.

For deviations see Table XXVI.

Table XXVI:

Recommendations on ESM in children

Country recommendations	AL	AP	DP
UK	---	---	---
G	recommended	recommended	---
NL	recommended, (≥ 15 kg)	recommended, (≥ 11 kg)	---
B	recommended, (≥ 12 years)	recommended	recommended, (≥ 36 kg, no further weight adjustment for children mentioned)
F	recommended	recommended	recommended, (it should only be an exception when used for children)
E	recommended	recommended	recommended
IT	not recommended	recommended	recommended

Additionally, G recommends not to travel with children to a malaria area where the nearest hospital is > 48 hours away.
The NL mention using chemoprophylaxis instead of ESM in moderate-risk areas for children below 5 years. Children below 5 kg should use chemoprophylaxis C+P, while those above 5 kg should change to M or AP.
(See Table Special groups I in Appendix F).

C.6.3 Long-term travellers

All recommendations have sections on long-term travellers which include general recommendations on the long-term use of antimalarial chemoprophylaxis on the minimum duration of chemoprophylaxis. There are no major differences in the recommendations (see Table XXVII).

Table XXVII:

Recommendations on the long-term use of antimalarials for chemoprophylaxis (CHP)

Medication Long-term use	UK	G	NL	B	F	E	IT
AP	≤ 1 year	6 months or longer	≤ 6 months	---	≥ 3 months	≤ 1 year	≤ 1 year
M	≤ 3 years	Up to years	≤ 2,5 years	---	---	≤ 3 years	≤ 3 years
D	≤ 2 years	Up to years	≤ 2 years	---	---	≤ 2 years	≤ 2 years
C(+P)	safe	---	---	---	---	safe	safe

There are also recommendations on the minimum duration of malaria chemoprophylaxis during the first long-term stay in a high-risk malaria area. G and NL advise a time period of at least 3 months, B and F mention a period of 3 to 6 months, IT recommends at least 6 months. Additionally, the NL, F, and IT advise taking chemoprophylaxis during the rainy season and the weeks thereafter. E recommends chemoprophylaxis at all times for high-risk areas; in moderate-risk areas, seasonal chemoprophylaxis is recommended during the rainy season, with the use ESM otherwise.

All recommendations agree that long-term travellers need tailored malaria advice depending on the purpose of stay and the medical care on site. In addition, all long-term travellers should follow the exposure prophylaxis mentioned in chapter C.3 and receive appropriate medication for chemoprophylaxis or emergency standby treatment.

(See Table Special groups II in Appendix F).

C.6.3.1 Visiting friends and relatives (VFR)

All recommendations mention the special group of migrants originating from malaria-endemic areas, who travel to their home countries for the purpose of “visiting friends and relatives “(VFR). VFR travellers tend to stay longer than tourist or business travellers and are more likely to visit higher risk rural areas with limited access to medical care.
All agree that the group of VFR-travellers requires appropriate travel medical advice as they account for a large proportion of imported malaria cases.
(See Table Special groups II in Appendix F).

C.6.3.2 Expatriates

All recommendations mention the special group of expatriates, who work abroad and live with their families for a longer period of time in particular malaria regions.
All recommendations agree that expatriates require appropriate travel medical advice including individual risk assessment.
(See Table Special groups II in Appendix F).

C.6.3.3 Backpackers

The information of backpackers as special group of long-term travellers is mentioned by the UK, G, NL, F, and E.
B and IT do not discuss the topic of backpackers.
The UK, G, NL, and F report that backpackers are long-term travellers, who often stay in changing locations with a potentially high risk of exposure.

Additionally, the UK, F, and E mention that this group is often young and less careful of their personal safety.
G adds that this group often do not have access to information about the local malaria situation and medical treatment options.
(See Table Special groups II in Appendix F).

C.6.4 Elderly travellers

Not all recommendations mention elderly travellers as a special group, for which special recommendations are needed.
The UK recommendations mention that elderly travellers need especially thorough protection against malaria. They emphasise the need to check interactions of antimalarials with co-medication, which elderly travellers commonly take. The NL, B, F, and IT only mention that elderly people (> 65 years) belong to a group with higher risk and need special attention depending on comorbidities. G and E do not discuss the topic of elderly travellers.
(See Table Special groups II in Appendix F).

C.6.5 Cruise ships

Only the UK and G mention passengers of cruise ships as a special group of travellers. The UK advises on good mosquito protection and states that in case of an overnight stay in a malaria area, chemoprophylaxis may be required. G informs that passengers must bring their own malaria medication on board. All the other recommendations do not provide information on cruises.
(See Table Special groups II in Appendix F).

C.6.6 Oil rigs

Only the UK and F discuss staff deployed on oil rigs. The UK recommends chemoprophylaxis for staff on oil rigs based in river estuaries. F states that staff on oil rigs belong to a group with short but frequent stays in malaria areas and advises using AP for chemoprophylaxis. All the other recommendations do not provide information on oil rigs.
(See Table Special groups II in Appendix F).

C.6.7 Flight crews and ship's crews

G and F advises AP for chemoprophylaxis for civil aviation and civil seafaring, as the staff belongs to a group of people with short and frequent stays in malaria areas. G additionally mentions the use of D for military staff. The NL state that the recommendation for malaria chemoprophylaxis come from the occupational health service. E recommends only ESM for short and frequent stays.

The UK, B, and IT do not provide information on aviation and seafaring.
(See Table Special groups II in Appendix F).

C.6.8 Last minute travellers and short-stay trips

The information given in the recommendations about last minute travellers and/or short-stay trips is highly heterogenous. The UK and G recommend the use of AP as first choice for last minute travellers, the UK also mentions D, because both antimalarials have to be started only 2 days before the journey.
Regarding short-stay travellers the NL consider prescribing ESM for travels, especially when they last less than 7 days. F considers a prescription of chemoprophylaxis in high-risk areas not absolutely necessary if the travel lasts less than 7 days and the BP-rules are conducted .
IT just mentions to prescribe chemoprophylaxis or ESM as usual.
B and E do not provide an information on last minute travellers and/or short-stay trips.
(See Table Special groups II in Appendix F).

C.7 Comparison of recommendations for special medical conditions

As already mentioned in the introduction of chapter C.6, the comparison of recommendations for special medical conditions, especially in relation to chemoprophylaxis and ESM, depends on the individual country's medication regulations mentioned in chapters C.4 and C.5.

C.7.1 Immunocompromised travellers

All recommendations unanimously agree that immunocompromised travellers belong to a group at high risk for severe malaria and therefore need reliable protection with exposure prophylaxis and chemoprophylaxis.

C.7.1.1 Splenectomised travellers

All recommendations state that asplenic individuals have a particular risk for severe malaria and therefore should be advised to avoid non-essential travel to malaria areas. If travel is unavoidable, strict exposure prophylaxis and if indicated chemoprophylaxis should be followed.
The UK and NL advise chemoprophylaxis even for low and moderate-risk areas, where normally BP or ESM is recommended.
(See Table Special medical condition I in Appendix G).

C.7.1.2 HIV

All recommendations agree that, when prescribing malaria prophylaxis to HIV-positive travellers on antiretroviral therapy (ART) possible interactions should always be assessed.

The recommendations from the UK, G, E, and IT mention that D has the smallest potential of interactions with HIV medication.
G, NL, and IT indicate that there are possible interactions between ART and AP, M, C, and P. However, there is no need to adjust the dose of the antimalarials. The NL additionally recommend to use chemoprophylaxis instead of ESM in moderate-risk areas.
F and B do not discuss this topic.
(See Table Special medical condition I in Appendix G).

C.7.1.3 Transplant patients

The UK, G, E, and IT recommend to check interactions of antimalarials with immunosuppressive substances of transplant patients. The UK and IT mention that ciclosporin toxicity increases with the intake of C, while G states that ciclosporin and tacrolimus toxicity increase with the intake of D or M.
E states that chemoprophylactic antimalarial drugs may increase concentrations of calcineurin inhibitors and mTOR inhibitors, predisposing to the development of heart rhythm disturbances, and recommend D and AP as safest options.
The NL, B, and F do not provide any information on transplant patients.
(See Table Special medical condition I in Appendix G).

C.7.2 Renal impairment

Most of the recommendations mention the contraindication for AP in patients with advanced renal impairment and a creatinine clearance of less than 30 ml/ min. They agree that there is no dose reduction necessary for M in severe renal failure, except B and F, who do not discuss the topic of renal impairment.

The UK, G, and E also favour the use of D in severe renal failure.

The recommendations regarding the use of antimalarials in different stages of renal impairment vary extremely, details are listed in Table XXVIII.

Table XXVIII:

Recommendations on the use of antimalarials and the handling with renal impairment

Country Recommendations	AP	P	M	D	C	AL
UK	contraindicated at a creatine clearance < 30ml/min	dose reduced like in table on p. 65 mentioned in the guidelines	may be used in severe renal failure	may be used in severe renal failure	---	---
G	contraindicated at a creatine clearance < 30ml/min	----	may be used in severe renal failure	may be used in severe renal failure	---	---
NL	contraindicated at a creatine clearance < 30ml/min	the dosage should be halved at a creatine clearance 30-60 ml/min; contraindicated at a creatine clearance < 30ml/min	recommended treatment in moderate-risk areas as CHP	---	---	contraindicated at a creatine clearance < 30ml/min; recommended treatment in moderate-risk areas as ESM
B	---	---	---	---	---	---
F	---	---	----	---	---	---
E	contraindicated at a creatine clearance < 30ml/min	contraindicated at a creatine clearance < 30ml/min	no dose adjustment	no dose adjustment	no dose adjustment if creatinine clearance is >10 ml/min	---
IT	contraindicated at a creatine clearance < 30ml/min	---	no dose adjustment	dose adjustment (reduction)	dose adjustment (reduction)	---

(See Table Special medical condition I in Appendix G).

C.7.3 Liver disease

The recommendations on the use of antimalarials in patient with different stages of liver impairment vary extremely, all the details are listed in Table XXIX.

Table XXIX:

Recommendations on the use of antimalarials and the handling with liver disease

Country Recommendations	AP	M	D	C	P	AL
UK	with severe impairment possible	with moderate impairment possible	with severe impairment possible	with mild impairment possible	with moderate impairment possible	---
G	with Child-Pugh-Stage A and B possible	contraindicated	with Child-Pugh-Stage A and B possible	contraindicated	contraindicated	with Child-Pugh-Stage A and B possible
NL	---	contraindicated for severe liver disease	contraindicated for severe liver disease	---	---	contraindicated for severe liver disease
B	---	---	---	---	---	---
F	---	---	---	---	---	---
E	no dose adjustment	contraindicated at severe stage	no dose adjustment	contraindicated at severe stage	no dose adjustment	---
IT	with severe impairment possible	with moderate impairment possible	with mild impairment possible	with mild impairment possible	---	---

(See Table Special medical condition I in Appendix G).

C.7.4 Cardiac disease

The recommendations of G and NL list that cardiac arrhythmias, long QT syndrome, familial sudden cardiac death, and co-medication with metoprolol, imipramine, and amitriptyline as contraindications for AL.

G, E, and IT do not recommend M in travellers with cardiac pathology or alterations.

Additionally, G does not recommend the use of M with the co-medication of class 1 A antiarrhythmics.

F mentions a risk of cardiotoxicity for C.

The UK and B do not discuss this topic.

(See Table Special medical condition I in Appendix G).

C.7.5 Anticoagulation and direct oral anticoagulation

All recommendations agree that patients on anticoagulation affecting on the International Normalized Ratio (INR) should ensure that their INR is stable before taking antimalarials, except B, who does not provide any information on anticoagulation. Additionally, all but B state that the

effect of coumarins (including warfarin) is possibly enhanced by AP, P, D, and M. C may also enhance the effect, which only E mentions.
The UK, G, NL, and IT also mention the limited experience with direct oral anticoagulants (DOACs). They state that DOACs are possibly enhanced by M.
The NL and IT also mention the possible enhanced effect of DOACs by P, D, and AP.
(See Table Special medical condition II in Appendix G).

C.7.6 Epilepsy

All recommendations agree that epilepsy is a contraindication for M, except B, which does not provide any information on epilepsy. The UK, NL, E, and IT add that epilepsy is a contraindication for C.
The UK, G, and IT advise the possible use of AP and D as chemoprophylaxis for patients with epilepsy, but also recommend dose adjustment for D (200 mg instead of 100 mg with co-medication of carbamazepine, phenytoin, barbiturate.)
(See Table Special medical condition II in Appendix G).

C.7.7 Glucose 6-phospate dehydrogenase deficiency (G6PD-deficiency)

All recommendations unanimously mention that G6PD-deficiency is a contraindication for primaquine as it can lead to significant haemolysis, except B, which does not provide any information on G6PD-deficiency. F and IT additionally inform that G6PD-deficiency is no contraindication for any of the chemoprophylactic active substances licensed in F and IT.
E also mentions that during pregnancy it is not possible to determine this enzyme deficiency in the fetus.
(See Table Special medical condition II in Appendix G)

C.7.8 Sickle cell disease and thalassaemia

The recommendations of the UK and IT state that patients with sickle cell disease and thalassaemia need rigorous antimalarial protection because of the risk of haemolysis in the homozygous form.
All other recommendations do not provide any information on sickle cell disease and thalassaemia and the use of antimalarials.
(See Table Special medical condition II in Appendix G).

C.7.9 Acute porphyria

The UK recommendations mention that D is unsafe for antimalarial chemoprophylaxis in patients with acute porphyria. The NL mention C to be used only with caution in patients with porphyria.

All other recommendations do not discuss the topic of porphyria.
(See Table Special medical condition II in Appendix G).

C.7.10 Psoriasis

The recommendations of the UK, NL, and E mention the risk of exacerbation of psoriasis if taking C.
All other recommendations do not provide an information on psoriasis and the use of antimalarials.
(See Table Special medical condition II in Appendix G).

C.7.11 Smoking cessation

The recommendations of the UK mention not to use C or M for patients taking bupropion for smoking cessation as the risk of seizures may be increased.

All other recommendations do not discuss the topic of smoking cessation.

(See Table Special medical condition II in Appendix G).

C.8 Comparison of country recommendations

C.8.1 Methodology and definitions of malaria risk areas

The information on methodology and definitions/ grades of malaria risk areas given by the selected recommendations under review differs.
G, B, and IT use the Annual Parasite Index (API), defined by the WHO as the “number of confirmed new cases from malaria registered in a specific year, expressed per 1,000 individuals under surveillance, for a given country, territory, or geographic area” [63].
In addition, G and IT combine the API with the number of documented malaria cases among 100,000 travellers per year.
The NL do not discuss the topic of the methodology applied to assess the risk areas.
The UK and F only name the sources, which are based on the country risk assessment and data from imported cases for their country.
E mainly uses the WHO *Plasmodium falciparum* Annual Parasite Incidence (*Pf*API), also named Annual *Falciparum* Index (AFI). The AFI, as opposed to the API, only includes falciparum malaria, whereas the API includes malaria cases of all species [64]. For detailed sources and definitions see Table XXX as listed:

Table XXX:

Methodology and definitions of malaria risk areas

Country	Methodology of risk areas
UK (Edited 2019)	The methodology, how risk areas are defined, is based on country risk assessment (see below) and data on malaria in the UK. The level of endemicity and malaria species are assessed from different sources: - The World Malaria Report and WHO Global Malaria Program - Estimates of the *P. falciparum* parasite rate and entomological inoculation rate published by from the Oxford University Malaria Atlas Project (http://www.map.ox.ac.uk/) - Number of cases and deaths in-country from published and unpublished sources - Information for Central and South America from the CDC - Returned traveller data reported to the PHE Malaria Reference Laboratory, London (MRL) database (See www.gov.uk/government/publications/malaria-report-form) [56; p.98-100] 1. low risk: BP 2. moderate risk: BP 3. high risk: BP+CHP(+ESM) [56, p.42- 50]
G (Edited 2020)	1. API ≤ 1 and ≤ 1 (case)/ 100,000 (travellers): low risk: BP 2. API > 1-10 and > 1-10/ 100,000: moderate risk: BP+ESM 3. API > 10 and > 10/ 100,000: high risk: BP+CHP Methodology: Bundesamt für Gesundheit (BAG) and Expertenkomitee für Reisemedizin (EKRM). Malariaschutz für Kurzzeitaufenthalter (Reisen bis zu 3 Monaten) Jan 2016. [57; p. 174]
NL (Edited 2019/ 2020)	1. low risk: BP 2. moderate risk: BP+ESM 3. high risk: BP+CHP [58; p. 1-2] (The definition of low- /moderate- and high-risk areas was not further specified and stated in the recommendations of NL).
B (Edited 2020)	In B the maps are mainly based on WHO malaria report with following definitions: 1. API <1, low risk: BP 2. API = 1-10, moderate risk: BP+CHP or ESM for travellers with risk factors 3. API > 10, high risk: BP+CHP These are the cut-offs used in case of mainly *P. falciparum.* If it is mainly *P. vivax*, the risk level is shifted down. (information from the author Dr. Ula Maniewski-Kelner of https://www.wanda.be/en/a-z-index/malaria based on WHO report [59])
F (Edited 2020)	1. minimal (low) risk: BP 2. moderate and high risk: BP+CHP(+ESM) (p.28, pink tablet) [60; p. 6] F only mentions that the classification of areas with high or low transmission in a country or to the travellers are based on reports from - the WHO (World Malaria report 2019), - the CDC (Yellow book 2020) and - Public Health England (Guidelines for malaria prevention in travellers from the UK 2019) [60; p. 35]

E (Edited 2019/ updates 2020)	The expert group from E considers data from: - *Plasmodium falciparum* Annual Parasite Incidence (*Pf*API) of the WHO - data about imported malaria cases to Spain from “Red Nacional de Vigilancia Epidemiológica (RENAVE) " (i.e., the national network of epidemiological surveillance) - expert opinion and classifies the risk areas as follows: 1. Risk-free areas (no indigenous transmission of malaria): no prophylaxis measures recommended 2. Areas with a malaria-free WHO- country certificate (malaria-free in recent years): no prophylaxis measures recommended 3. Areas in the process of elimination (no indigenous transmission for at least 3 years): BP 4. Very low-risk areas (decline in indigenous transmission): BP 5. *Pf*API <1: low-risk area: BP 6. *Pf*API = 1-10: moderate-risk area: BP+ assess need of ESM 7. *Pf*API ≥ 10: high-risk area: BP+CHP The individual country recommendations discuss the topic of the percentage of circulating Plasmodium species according to the latest data published by WHO in 2018 The number of cases always refers to indigenous cases as described in the WHO World Malaria Report 2018. According to this report for some countries the percentage of circulating Plasmodium species described does not reach 100% or is not described at all. Additional information from CDC has been added for these countries. [61; p. 18-20]
IT (Edited 2018)	IT refers to the following literature references: 1. Rombo l. Who needs drug prophylaxis against malaria? My personal view 2005 2. Petersen E. Malaria CHP: when should we use it and what are the options? 2004 3. Behrens Rh. The incidence of malaria in travellers to South-East Asia: is local malaria transmission a useful risk indicator? 2010 and considers the API and annual malaria cases/ 100,000 travellers 1. <1 (case)/ 100,000 (travellers) and /or API <1, low risk: BP and diagnosis 2. > 1-10/ 100,000, and /or API=1-10, moderate risk: BP+ ESM and diagnosis 3. > 10/ 100,000 and /or API > 10, high risk: BP+CHP and diagnosis [62; p. 6-7]

C.8.2 Tables and maps of country recommendations

The comparison of the malaria maps and tables of Ethiopia, Kenya, Cambodia, India, Brazil, and Colombia differs regarding the consideration of different parasite indices and sources mentioned in the chapter C.8.1.

F and IT do not use malaria maps at all, they only use tables to inform about high-, moderate-, and low-risk areas for the individual regions, cities, and states of the of the individual countries.

In some recommendations only maps of the world regions are used, while sometimes more detailed maps of the individual countries and additional tables are used.

A compilation of the maps and the different data of the distribution of *Plasmodium species* are mentioned in the tables below for comparison.

For a comprehensive comparison of the common recommendations for the individual regions, cities, and states of the countries of Ethiopia, Kenya, Cambodia, India, Brazil, and Colombia, as well as an analysis of the differences between these recommendations and the information about drug resistances, please refer to the tables in Appendix H.

An analysis of the differences and discrepancies of the methodology is shown in the discussion in chapter D.2.7.

C.8.2.1 Ethiopia

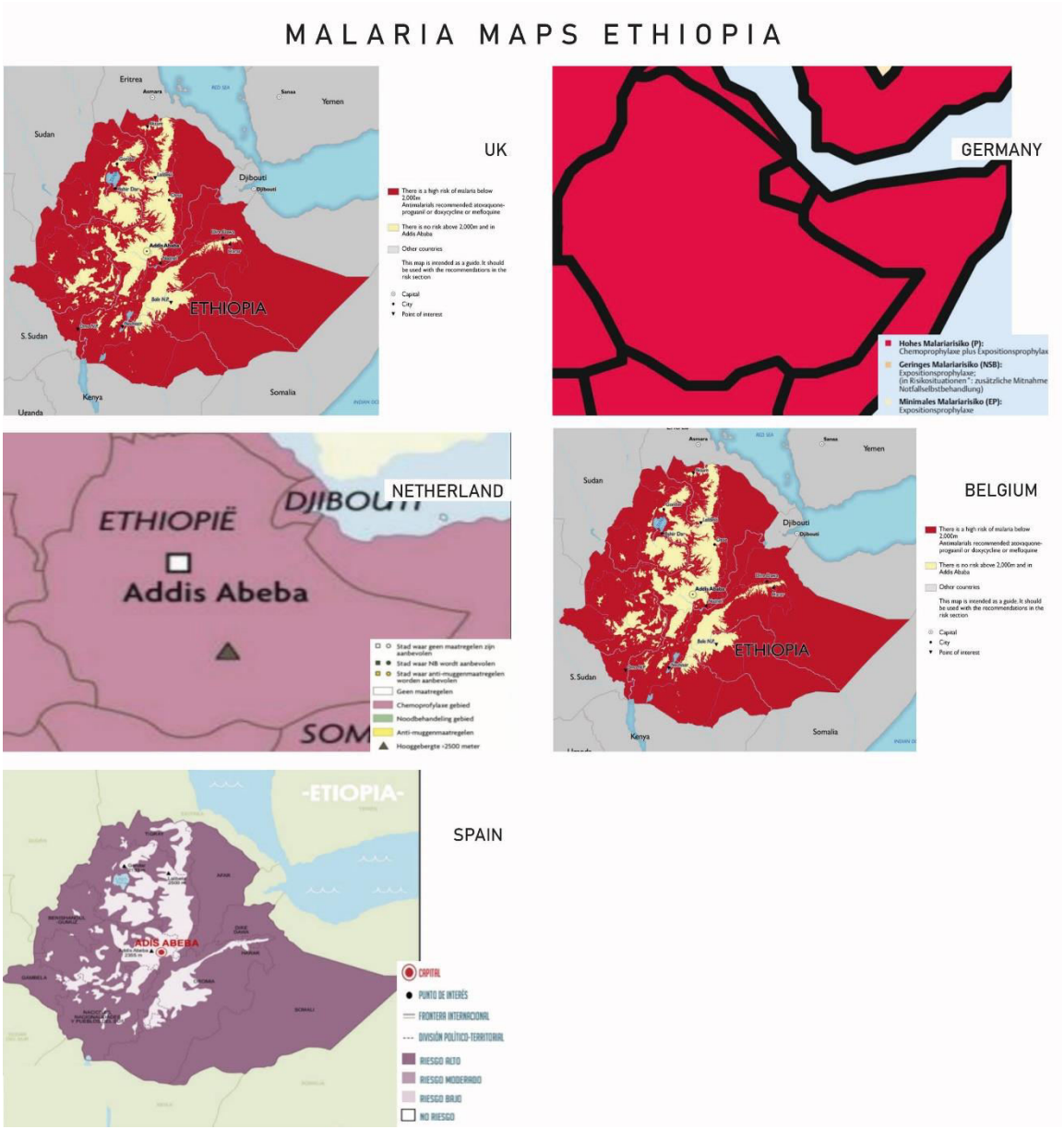

Figure IV:
Comparison of malaria maps of Ethiopia

Table XXXI:

Comparison of data on the distribution of the *P. falciparum* and *P. vivax* in Ethiopia

Countries	*Pf*	*Pv*
G	89%	11%
NL, B, F, E	60-70%	30-40%
UK, IT	---	---

(See Table Ethiopia in Appendix H).

C.8.2.2 Kenya

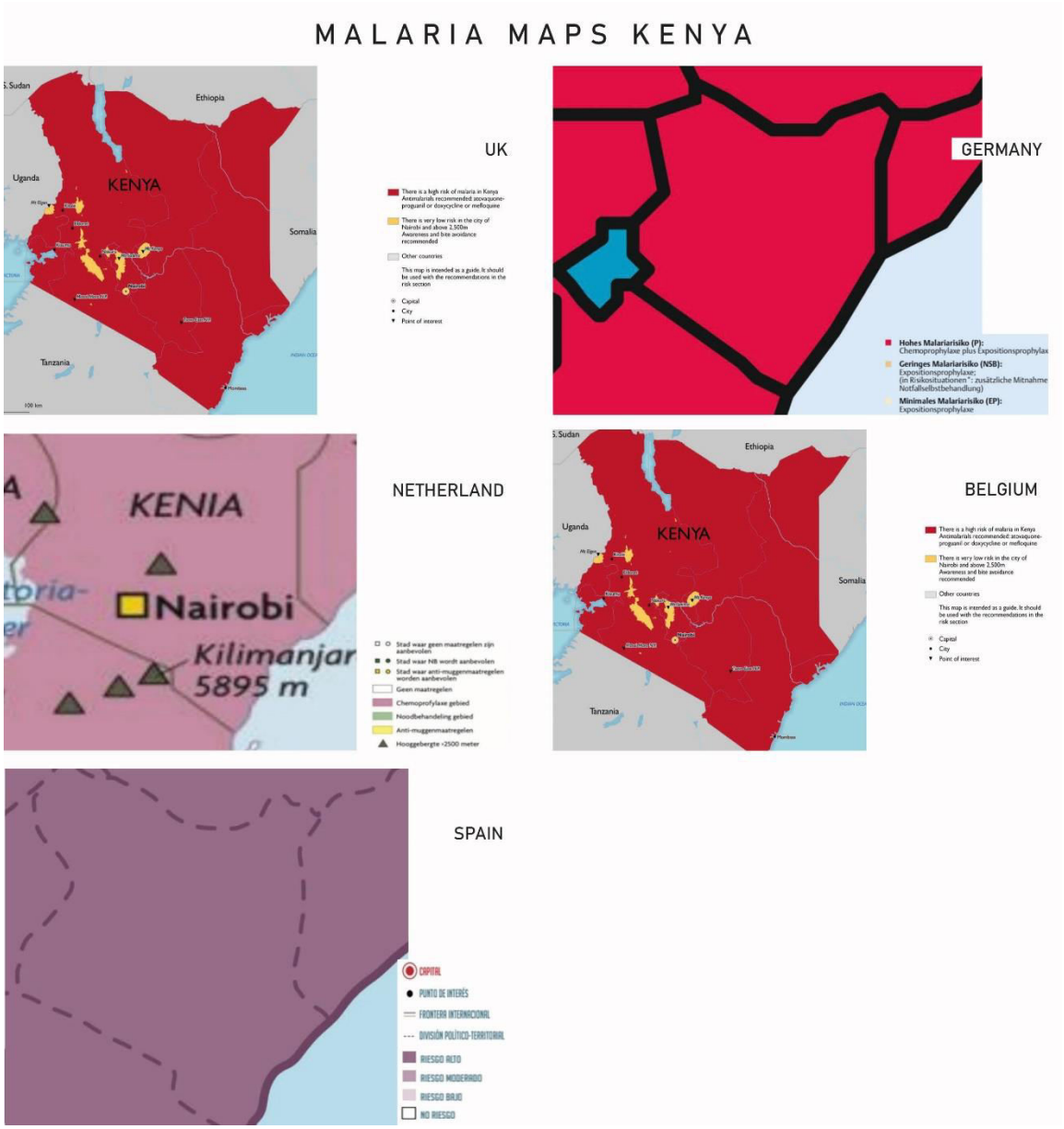

Figure V:
Comparison of malaria maps of Kenya

Table XXXII:

Comparison of data on the distribution of the *P. falciparum* and *P. vivax* in Kenya

Countries	*Pf*
G, NL, F, E	> 99%
UK, B, IT	----

(See Table Kenya in Appendix H).

C.8.2.3 Cambodia

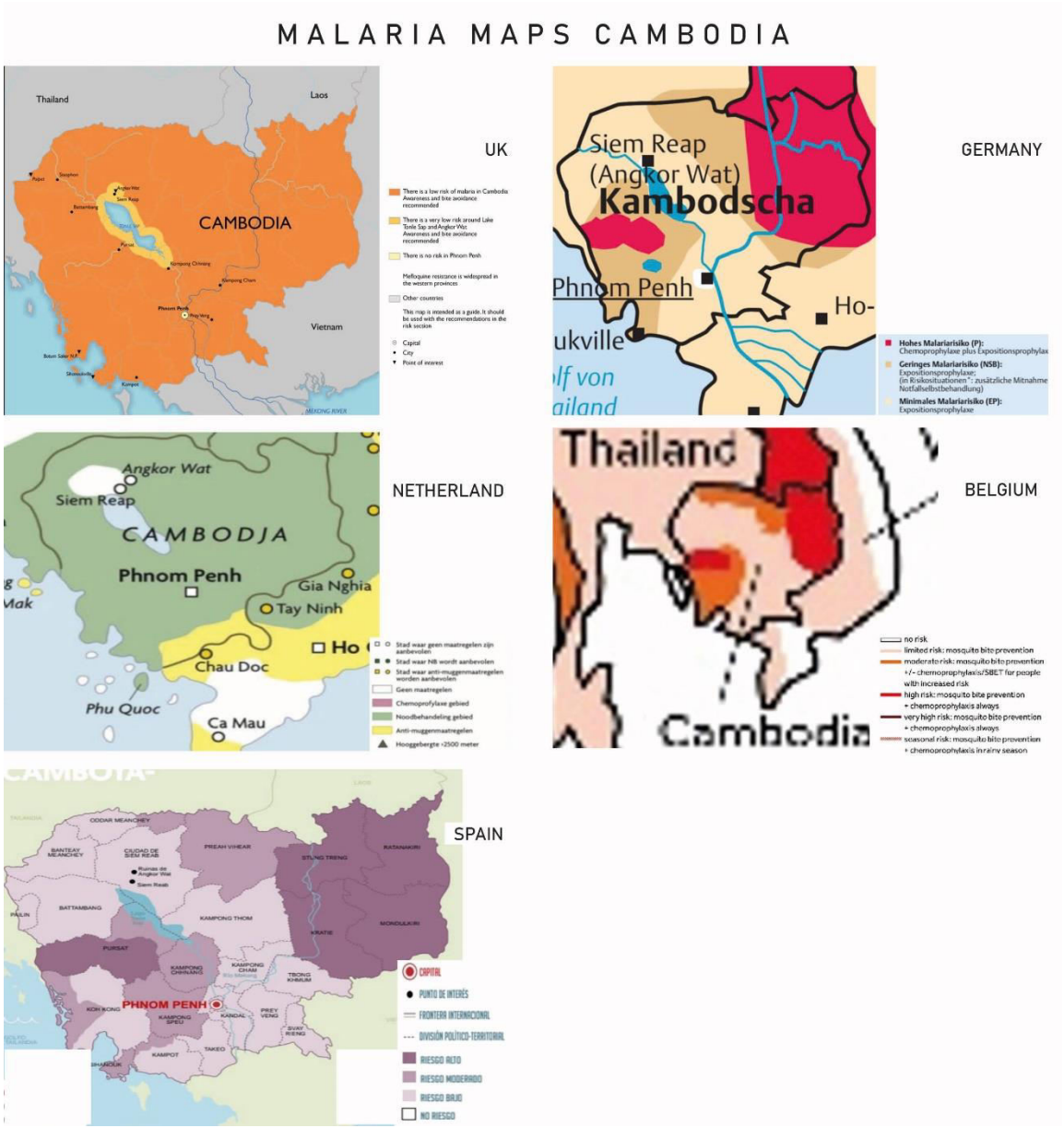

Figure VI:

Comparison of malaria maps of Cambodia

Table XXXIII:

Comparison of data on the distribution of the *P. falciparum* and *P. vivax* in Cambodia

Countries	*Pf*	*Pv*	*P. knowlesi*
G	25%	74%	rarely
NL	64-86%	12-36%	rarely
E	58%	41%	---
UK, B, F, IT	---	---	---

(See Table Cambodia in Appendix H)

C.8.2.4 India

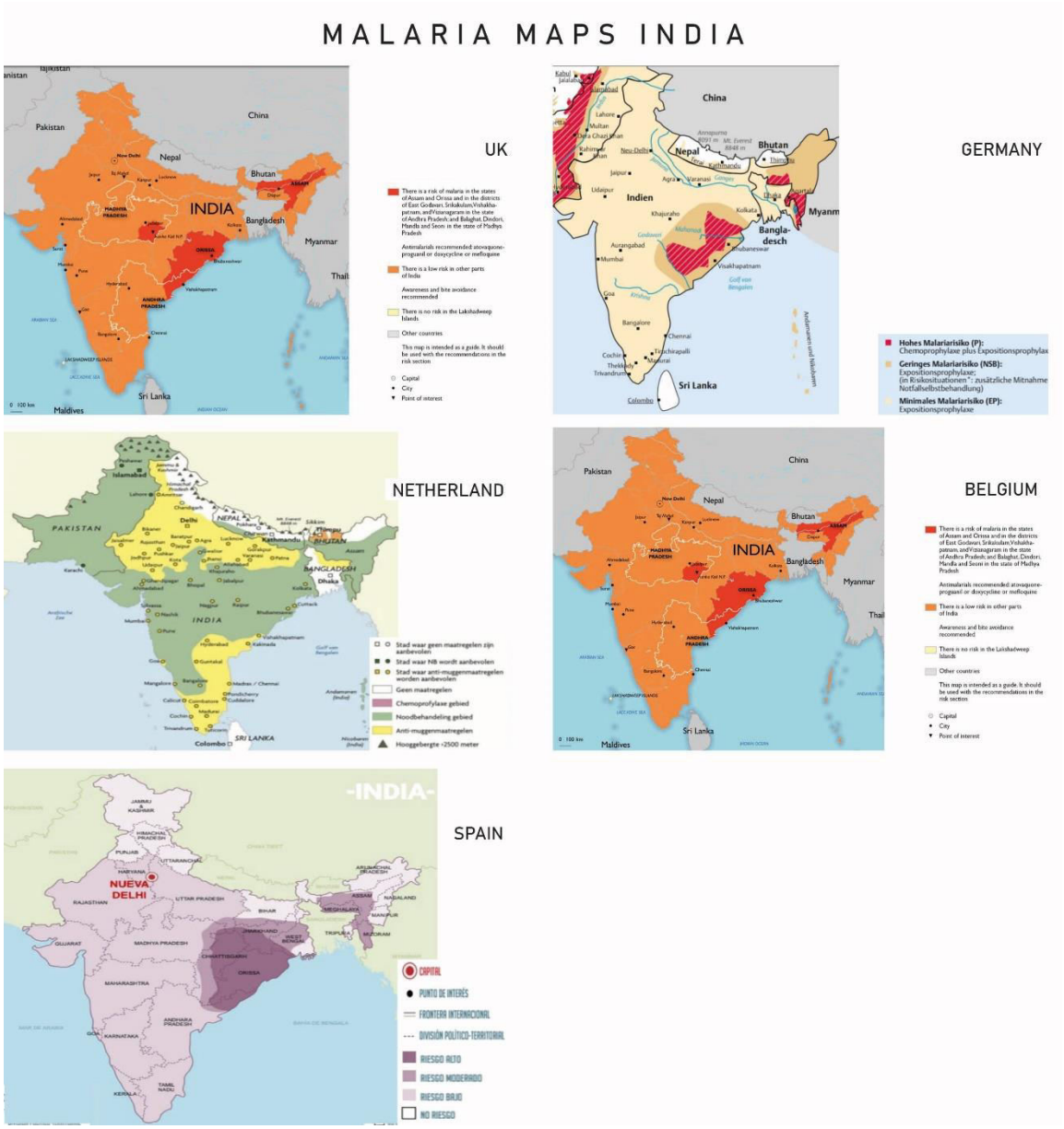

Figure VII:
Comparison of malaria maps of India

Table XXXIV:

Comparison of data on the distribution of the *P. falciparum* and *P. vivax* in India

Countries	*Pf*	*Pv*
G	48%	52%
NL, B	7-66%	34-93%
F	40-50%	50-60%
E	62%	37%
UK, IT	---	---

(See Table India in Appendix H).

C.8.2.5 Brazil

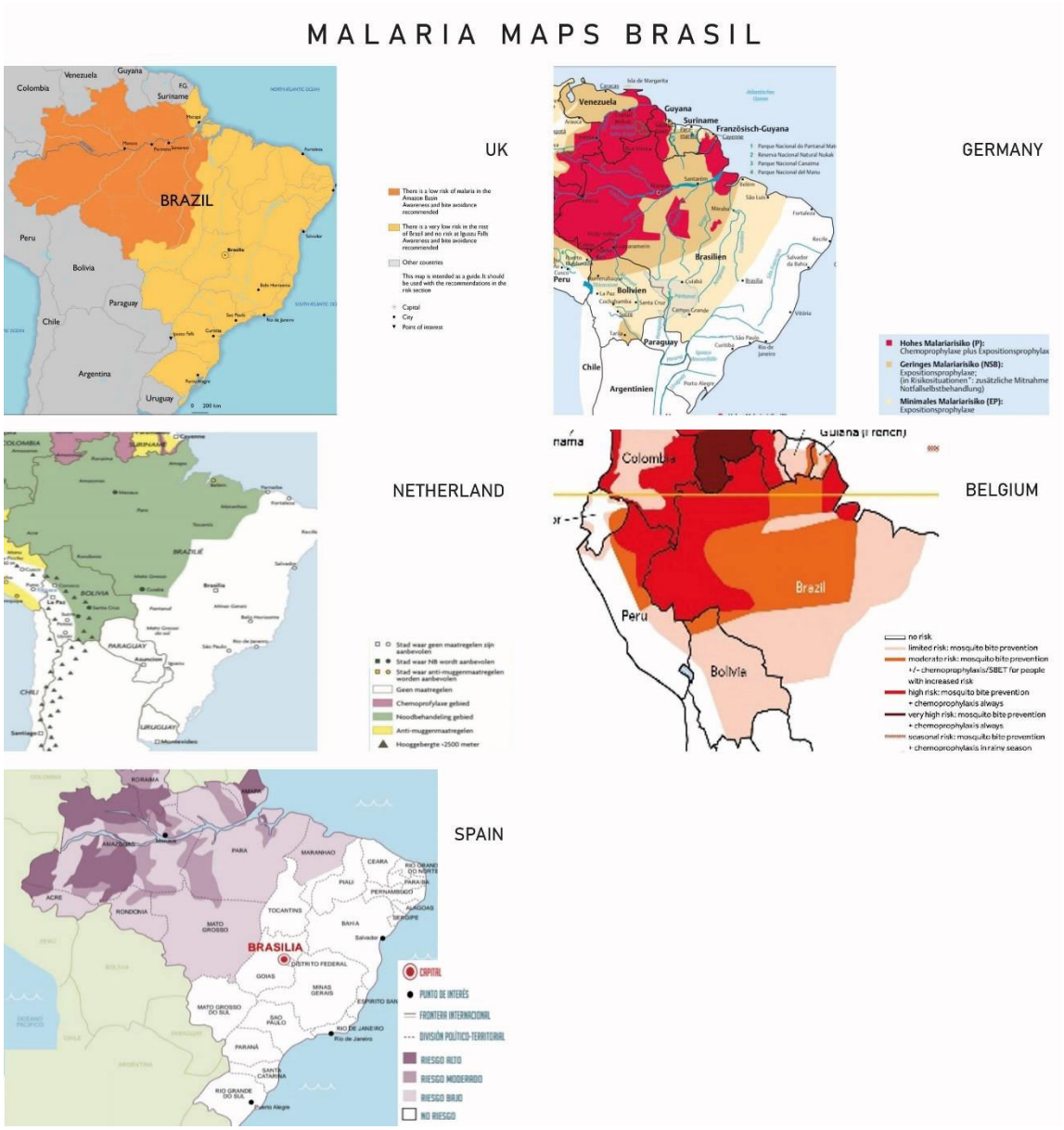

Figure VIII:
Comparison of malaria maps of Brazil

Table XXXV:

Comparison of data on the distribution of the *P. falciparum* and *P. vivax* in Brazil

Countries	*Pf*	*Pv*
G, B, E	10%	90%
NL	15-16%	84-85%
UK, F, IT	---	---

(See Table Brazil in Appendix H).

C.8.2.6 Colombia

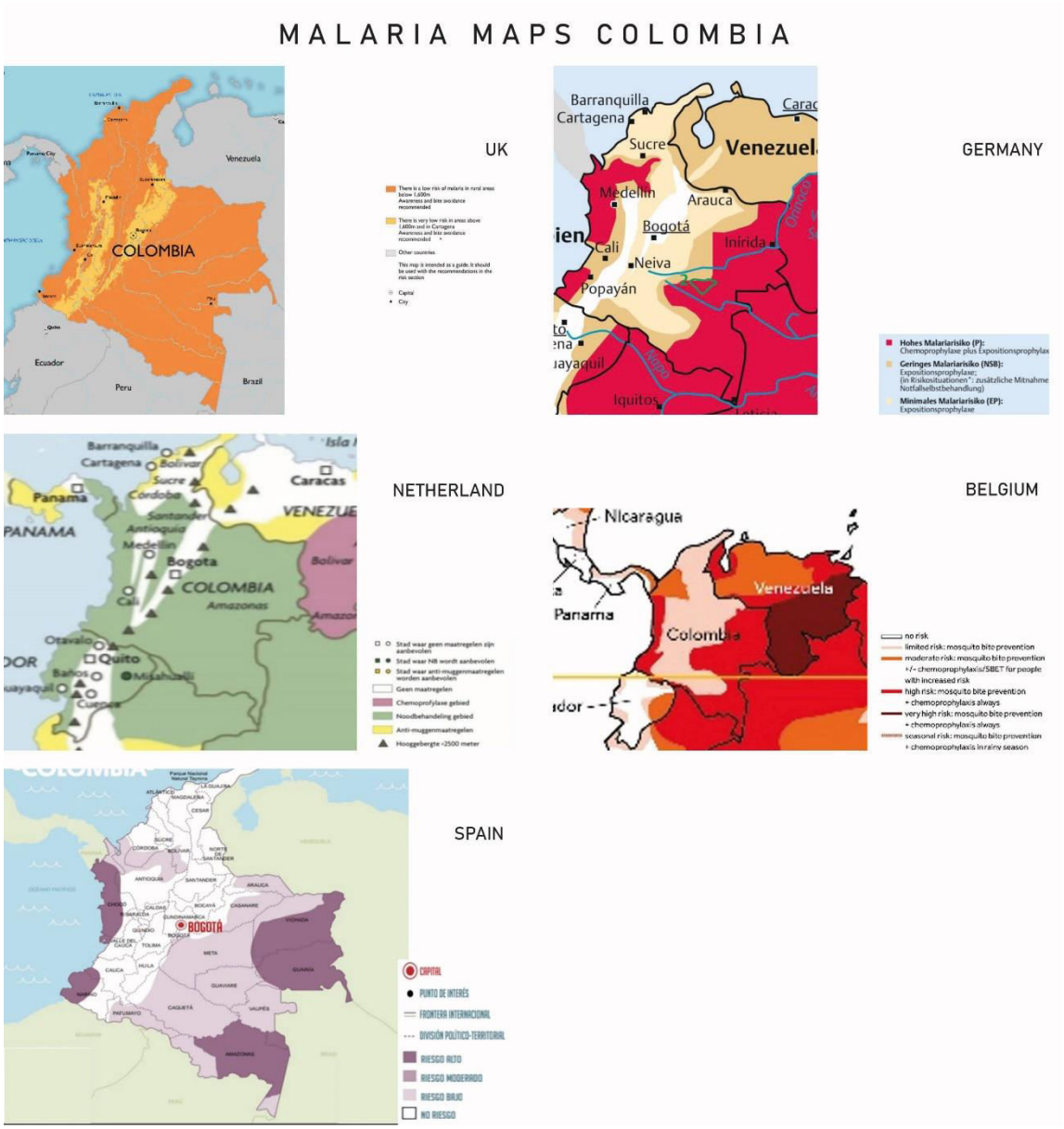

Figure IX:
Comparison of malaria maps of Colombia

Table XXXVI:
Comparison of data on the distribution of the *P. falciparum* and *P. vivax* in Colombia

Countries	*Pf*	*Pv*
G	50%	50%
NL	34-50%	---
B	60%	---
F	34%	66%
E	58%	42%
UK, IT	---	---

(See Table Colombia in Appendix H).

D. DISCUSSION

D.1 Summary of the main differences

The overall aim of this thesis was to compare the malaria recommendations for travellers from the United Kingdom (UK), Germany (G), the Netherlands (NL), Belgium (B), France (F), Spain (E), and Italy (IT) and to detect and analyse possible discrepancies.

In summary, the major findings and differences were:

1. The format of publication of the recommendations varies between a subscriber's brochure, a downloadable journal article, an internet brochure, and open-access web page. (This may result in information being processed or presented differently or even omitted).

2. There are different recommendations for the use of mosquito repellents. The information given on the repellents DEET, icaridin, and EC Oil (H/C) differs widely regarding concentration and age limits for children, as well as the use during pregnancy and breastfeeding.

3. All recommendations advise wearing long clothing. However, they differ on the importance of the colour of the clothing. Some recommend light-coloured clothing, while one emphasises that there is no evidence that the colour of clothing is relevant to mosquitoes.

4. Regarding effective chemoprophylaxis for malaria in high-risk areas all selected recommendations mention atovaquone/proguanil (AP), doxycycline (D), and mefloquine (M). The majority still suggest chloroquine (C) and proguanil (P) as combination therapy (C+P) in chloroquine-sensitive areas in Central America and the Caribbean.

5. Instructions and application mode for the individual active substances of chemoprophylaxis are inconsistent.

- The dosage recommendations for M, D, C, and P vary considerably.
- In some countries D is not registered for the use as antimalarial chemoprophylaxis, so the use is only off-label.
- The age limit information for D varies between ≥ 8 years and ≥ 12 years.
- Some countries recommend dosage adjustments of D during therapy with carbamazepine and phenytoin.
- For C, dosage recommendations and mode of intake vary significantly.

- The recommendations for the use of C during pregnancy and breastfeeding and before conception are completely contrary.

6. All recommendations agree with the basic use of primaquine for the treatment of infections with *Plasmodium vivax*/*ovale*. However, the information on the exact use of the antirelapse treatment is incomplete and it is not recommended for chemoprophylaxis throughout Europe.

7. The recommendations for the use of emergency standby medication (ESM) vary. Some advise the use of ESM in moderate-risk areas, while others regard the use of ESM only as an exception, alongside chemoprophylaxis, in high-risk areas and/or moderate-risk areas where prophylaxis has failed.

8. The recommendations regarding the "minimum time for access to medical care", which should be used as a point of reference for the ESM prescriber to assess whether ESM needs to be prescribed or not, differ between 12 and 48 hours.

9. The recommendations for the use of ESM differ.
- Artemether/lumefantrine (AL) and AP for adults are suggested in all but one recommendations.
- Dihydroartemisinin/piperaquine (DP) is recommended by most of the recommendations.
- The recommendations for ESM for the use in children vary.

10. During pregnancy, M is advised by all recommendations as first choice for chemoprophylaxis.
For ESM in pregnancy, the recommendations vary. Some suggest the use of quinine plus clindamycin in the first trimester and AL or AP from the second trimester. Others do not recommend the use of ESM at all and instead recommend chemoprophylaxis already in low-risk malaria areas.

11. During breastfeeding, M is recommended for chemoprophylaxis by all but one recommendation, while D is unanimously deemed contraindicated. The use of AP or C during breastfeeding is very controversially discussed.

12. The recommendations for chemoprophylaxis in children in high-risk malaria areas are largely in agreement. For ESM in children, AL and AP are recommended by the majority of the recommendations. Furthermore the use of DP is generally recommended by more than the half.

13. The methodology and, therefore, the definitions of malaria risk areas differ.
Some recommendations use the WHO Annual Parasite Index (API) of malaria and additionally consider the incidence of malaria in travellers. One country uses the *Plasmodium falciparum* Annual Parasite Index (PfAPI) instead.
Other countries are less precise and name only the literature sources, which are based on the individual country risk assessment and data from imported cases of their country.

14. The data on the distribution of *Plasmodium* species in the six countries studied- Ethiopia, Kenya, Cambodia, India, Brazil, and Colombia- vary. The difference is greatest for Cambodia, where the data on the ratio of the distribution *Plasmodium falciparum* to *Plasmodium vivax*, 25%:74% and 86%:12%, are almost contradictory.

D.2 Discussion of the major differences

D.2.1 Mosquito repellents: use in children and during pregnancy

All recommendations agree that DEET is the most effective repellent to protect the skin from mosquitoes. The concentration correlates with the duration of action, formulations containing 50% and slightly below are considered just as effective as those with higher concentrations. This also demonstrates a mathematical calculation on dosage versus hours of 95% protection level for DEET against *Aedes aegypti.* The formula Y = 3.63177 + 1.91966 log X can be used to approximate the duration of protection (Y) for a given dosage (X) [65].

Recommendations for the use of DEET, icaridin, and EC OIL (H/C) regarding concentration limits and age limits for children, as well as use during pregnancy and breastfeeding, vary widely.

There are several reasons for these differences, which concern different areas.
One concern is the specific feature of the different formulations as well as the co-formulants used in the repellents. For each of these co-formulants, the EU meanwhile requires endocrine disruptor (ED) statements from the supplying industry, which must be conducted and submitted to the authorities [66]. EDs are natural and/or anthropogenic chemical compounds that interfere with the normal function of the endocrine system of humans and cause adverse health effects by disrupting the endogenous hormone system [67, 68].
Repellent formulations often contain ethanol as the main solvent. Ethanol itself is teratogenic, causing a range of physical abnormalities in foetuses when they are exposed to it during prenatal development [69]. This substance is still suspected of being an ED candidate and a Substance of Very High Concern (SVHC), with its assessment currently pending by the

competent authority in Greece [66, 70, 71]. SVHCs are defined as primarily substances that are carcinogenic, mutagenic or toxic to reproduction, as well as substances with persistent and bio-accumulative characteristics or endocrine-disrupting chemicals [72].
Ethanol in skin formulations is particularly unsuitable for pregnant women, as it may have a teratogenic effect if applied in larger quantities and/or over extended periods [66, 70]. The precise amount of repellent applied to the skin is difficult to control, as factors such as evaporation and absorption vary with environmental conditions [66, 73, 74].
As an alternative to ethanol, propan-2-ol can be used as a solvent. It is assessed as more favourable in toxicological terms [66, 75], but it is more expensive and therefore less commonly used [66]. Another alternative includes emulsion-in-water formulations (EW), so-called (micro)emulsions. These formulations are typically ethanol-free and instead include water and emulsifiers. Although theses formulations are more complex and therefore more expensive, they are comparably effective for longer periods of time [66].

Another reason for the different age limits for children, as well as for use during pregnancy and breastfeeding, is the variability in regulatory assessments by the authorities.
The risk assessment procedure of EU Biocidal Products Regulation BPR 528/2012 is a two-stage process. Initially, active substances used in biocidal products are assessed in an EU-wide procedure and subsequently included in a positive Union list of approved active substances. Subsequently, applications for authorisation can be submitted for whole products containing these already evaluated and approved active substances [76].
Biocidal products, including repellents, are approved at the national level and can be transferred to other EU Member States via the mutual recognition procedure. For products with similar use conditions across the EU, Union-wide authorisation is possible [66, 76]. However, EU Member States often differ considerably in their view and implementation of guidelines and directives [66]. For instance, EU Member States should follow the Human Health Risk Assessments (HHRA) for repellents, which must consider all relevant health parameters [66, 77], but they may also set their own, often more stringent thresholds [66]. This can result in variations of age limits for children and suitability during pregnancy and breastfeeding.
Although the BPR 528/2012, provides a uniform authorisation framework [78], significant delays occur in processing approvals for active substances in product type PT19 (repellents and attractants) [66, 79]. These delays result from insufficient resources, delays in the provision of supplementary data by applicants, several complex technical issues concerning specific dossiers, amendments to guidance documents and the adoption of new scientific criteria for endocrine disruptors [79, 80]. The entire active substance review programme of the EU, as mandated by the BPR 528/2012, is expected to last until 2025 [80]. There may also be extensions [79].

Prolonged delays increase the time for new biocidal products to be classified as safe and effective for market access. Consequently, this also often necessitates adjusted, stricter rules for license renewals, resulting in new assessments of age limits for children and updated recommendations for pregnancy [66].

Another potential reason for the inconsistency in age limits for children, as well as in use during pregnancy and breastfeeding, could be inaccuracies in the efficacy tests. According to information from the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung) [81, 82], there have been past issues with exposure assessment in efficacy tests of mosquito repellents applied on human skin. This discrepancy was due to the application quantity by the WHO guidelines [74], being too high compared to the actual application quantity intended for use [81]. Consequently, the European Chemicals Agency (ECHA) has issued recommendations for harmonising the assessment of human exposure to repellent [73]. There are further discussions and recent developments on this topic that have not yet been completed and published [81].

In conclusion, the differences in repellents regarding age limits for children, as well as use during pregnancy and breastfeeding, can be attributed to the varying compound repellent products and the differing regulatory assessments across EU Member States. The differing application restrictions depend more on the entire product formulation, including co-formulants, which affects the absorption of the active substance in the body, than on the concentration of the biocidal active substance itself. Future research should concentrate on the development of safer, more cost-effective alternatives to ethanol and improvements to regulatory assessments. It would be beneficial for the recommendations to provide lists of the repellents approved in the country and, if possible, sort them according to age limits in children and use during pregnancy. Rather than providing information on the active substance concentrations alone, this could be a more appropriate approach.

D.2.2 Mosquitoes and clothing colour preference

The recommendations for travellers regarding the colour of clothing to achieve protection against Anopheline mosquitoes differ. Some recommendations advise the use of light-coloured clothes, whereas others do not comment on clothing colours. One recommendation states that there is no evidence that the clothing colour is relevant to mosquitoes.
Light-coloured clothing is very likely to be relevant for protection against diurnal mosquitoes [83-86], such as the mosquito species *Aedes*, transmitting arboviral infections such as yellow fever, dengue, zika and chikungunya [87]. However, it is unclear whether this also applies to nocturnal

mosquitoes such as Anophelines. After a thorough search of the literature on this topic, no relevant study was found.
Mosquitoes in general seem to be guided differently by colours depending on their physiological status. Different results have been obtained regarding colour preferences in different behavioural situations, such as resting [88, 89], sugar-feeding [90, 91], oviposition [92], and host-seeking, although no study in this regard has been found on the species *Anopheles*:
Early studies conducted in the 1920s and 1930s found that Anopheline mosquitoes resting on coloured cloths preferred light colours [88]. Another study investigated the resting preference of *Anopheles gambiae* on various colours of fabrics and bare walls inside rural houses and found again a preference for light colours [89]. In terms of sugar feeding, *Anopheles gambiae* appear to prefer to feed on the nectar of light-coloured flowers [90, 91]. In contrast, a study on the ovipositional behaviour of *Anopheles sinensis* discovered that the number of eggs laid on a black substrate was significantly higher than on a white substrate. Furthermore, the hatching rate on the black substrate was significantly higher than on the white substrate [92].

Based on the current knowledge, while host-seeking for blood meals, nocturnal female mosquitoes are attracted by the carbon dioxide emitted by the host from distances of up to 50 m [93-95]. Within several metres, they track human sweat odours (mainly fatty, lactic and uric acids and ammoniac) [93, 96, 97] and subsequently visually locate their host [98]. Even closer, convective heat and moisture from human skin guide them to the potential host [94, 99].
Anophelines seem to recognise colours by perceiving the spectrum of light they reflect or absorb. Electroretinography revealed sensitivity to UV light (350-420 nm) and cyan-green light (500-520 nm) [86]. Although mosquitoes can distinguish between specific wavelengths, colour doesn't seem to notably impact their behaviours. They are more influenced by brightness, vertical patterns, and motion [100, 101]

These conflicting and overall scarce data prompted us together with a research team of the University of Sciences Techniques and Technology of Bamako, Mali, to conduct a field study in Mali to better advise travellers. To the best of our knowledge, our study is the first to simulate visually contrasting colour stimuli (black, white, and black/white contrasting striped) in host search by continuously observing the three most common vector mosquitoes - *Anopheles, Culex,* and *Aedes* - outdoors under different light conditions during the day, and on bright or dark nights. The observation period extended continuously over 24 hours on 10 consecutive days around full or new moon [102].
Since we aimed to provide practical advice for travellers and our primary focus was on studying the clothing colour preference of nocturnal mosquitoes, it is important to note that colours appear as shades of grey in the dark. Therefore, we only investigated contrast vision.

Figure X:

Experimental setup: Mosquito Magnet traps [103], which combust propane and release CO_2 to simulate the human breath as attractant, were covered with black, striped, and white fabric and set apart at an 8 m interval. Mosquitoes passed the textile covers from below and the holes on the sides, getting sucked into the trap [102]. *(Permission has been granted by the publisher)*

Under field conditions, both nocturnal and diurnal female mosquitoes were attracted from a distance by carbon dioxide. Closer up, the colour of the traps could then be visually distinguished during the day and on bright nights. Black and striped targets attracted significantly more of all three vector mosquito species tested than white targets. However, on dark nights, no significant preferences for the different coloured targets could be observed [102].

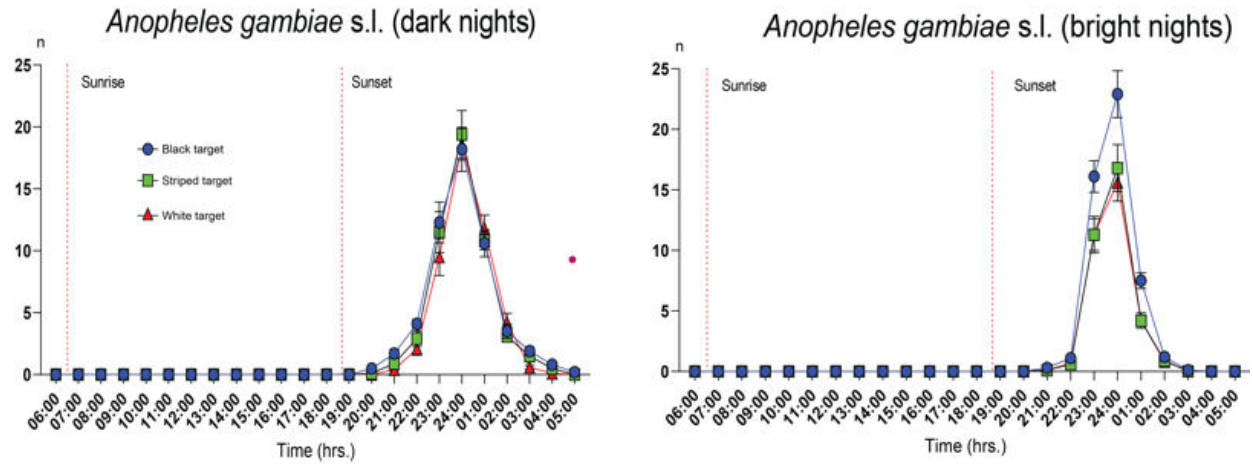

Figure XI:

Average female mosquito catches of Anophelines per hour with Mosquito magnet traps using three differently coloured targets during the daytime, and on dark or bright nights [102]. *(Permission has been granted by the publisher)*

Regarding Anophelines, on bright nights, white targets were approached up to 34% (164/ 492) less than black (Fig. XI) [102].

The results suggest that light-coloured clothing may significantly reduce mosquito biting rates during the day and on bright night. This effect may also be observed on dark nights if outdoor activities occur in illuminated areas. Therefore, wearing light-coloured clothing as a protective measure against *Anopheles*, *Aedes*, and *Culex* mosquitoes in tropical regions is a sensible recommendation [102].

D.2.3 Use of chloroquine as chemoprophylaxis in travellers

All recommendations suggest the use of atovaquone/proguanil (AP), doxycycline (D, and mefloquine (M) for chemoprophylaxis in travellers to high-risk malaria areas.
The majority, additionally, still recommend chloroquine (C) and proguanil (P) as combination therapy (C+P) in chloroquine-sensitive areas. Only G and B do not recommend C for travellers anymore.

The malaria recommendations of G do not advise C as chemoprophylaxis anymore for simplification and to avoid errors [104]:
Chloroquine resistance has spread to nearly all areas of the world where *falciparum* malaria is transmitted [10, 11, 32, 52]. There are very few areas where C is still sensitive, e.g. parts of central America and the Caribbean. Travel Medicine in G is not limited to specialist units with qualified practitioners but largely practiced by General Practitioners with variable recent knowledge of this specialist matter. The German board responsible for the national recommendation fear that - recommending C for use in these areas, may unnecessarily complicate the recommendations and may erroneously lead to prescription of C for areas with chloroquine-resistance [104].
Regarding *vivax* malaria, more and more chloroquine resistance has been described [11, 105]. Additionally, for prophylaxis (or treatment) with C it must be ensured that there is no mixed infection involving chloroquine-resistant *P. falciparum* [11]. During travel, the rate of misdiagnosis is more frequent and often mixed infections are overlooked [104].

In the case of the recommendations from B, in addition to the arguments mentioned by G, the format of publication may also play a role. The fact that B only publishes its recommendations on an open-access web page, the target readership is not only trained staff in the field of travel medicine, but also every ordinary citizen. Therefore presumably, special attention was paid to convey simple and clear messages, avoiding misinterpretation as to the use of C in resistant areas.

A study from Zimbabwe reported a sharp decline in chloroquine-resistant *P. falciparum* within 10 years after termination of chloroquine monotherapy as the national treatment strategy. Consequently, resistant *P. falciparum* reverted to wild type [106]. A study from Malawi showed similar results [107].
Perhaps in a few years we may reconsider the wider use of chloroquine in travel medicine.

D.2.4 Differences in instructions of application mode for the individual drugs of chemoprophylaxis and emergency standby medication

There were major differences when comparing the instructions for taking antimalarials, the dosage per body weight, the information on the age limit, the advice on dose adjustment due to possible interactions in treatment with other medicines, and use during pregnancy and breastfeeding.

The EMA together with the individual national authorities of the EU member countries (like the BfArM for Germany) are responsible for the authorisation of drugs, including drugs for prevention and treatment of malaria.
Most antimalarial drugs are already very old and approved purely on a national basis in the different EU member states. This applies to all antimalarials mentioned in this work except Eurartesim, the fixed drug combination of dihydroartemisinin/piperaquine (DP) [108-110].
Only such new antimalarials are centrally authorised throughout the EU and thus also have harmonised product information [108, 109, 111].
Not all drugs are approved in every single EU country. In addition, dosage recommendations vary between EU countries. This may also be reflected in the individual national recommendations [108].
Sometimes there are differences in the pediatric dosages of individual active substances due to ongoing or recently completed examination procedures based on new data. The topicality of the various national guidelines lags behind. There is no overview of the European decisions on the active substances mentioned in this thesis [108].

The following examples may help to understand why recommendations and instructions regarding application modes differ between countries.
According to the information of the compared recommendations themselves:

- M is not licensed (anymore) in G, NL, F, and E, but is recommended for chemoprophylaxis and can be imported [57, 58, 60, 61].
- D is not registered in G and IT for use as antimalarial, but is recommended off-label [57, 62]. In G this is most probably rather a monetary issue, since D is an old and cheap drug and the license processing for a new indication, like in this case for malaria

chemoprophylaxis, would be presumably lengthy and not cost-effective for pharmaceutical companies.

- AL is not licensed in Italy and therefore not recommended in the national recommendations [62].

The use of DP as an ESM is viewed very differently by the professional societies. It is not licensed in the UK [56], and not recommended in G and NL for the use in travel medicine as ESM. [57, 58].
Concerns have been raised regarding the cardiac toxicity of dihydroartemisinin/piperaquine. DP has been associated with a prolonged QT interval, which may be linked to an increased risk of ventricular fibrillation and sudden cardiac arrest. Since 2011, when DP was licensed, the EMA has recommended performing an ECG before drug administration [111, 112]. This recommendation naturally limits its use as an ESM in the field of travel medicine.
In the meantime, the drug has been investigated in many studies, including a meta-analysis of 94 studies with around 200,000 patients, in which the risk of unexplained cardiac death after DP intake was compared with the baseline rate of sudden cardiac death in Mozambique. The authors did not find an increased risk of sudden cardiac death in individuals on DP [113].

Above-mentioned examples might help to explain why, despite the centralised EU-wide authorisation and thus also harmonised product information of DP, the national professional societies of the EU member states may have different opinions and interpretations of its use in the field of travel medicine.

D.2.5 Emergency standby medication (ESM): Different conditions for using ESM and minimum time for access to medical care

The conditions under which emergency standby medication (ESM) should be recommended for travellers vary between countries.
Emergency standby treatment is based on the recommendations for treatment of uncomplicated malaria of the respective country. It should be regarded as a first aid measure [47]. Emergency self-treatment of presumptive malaria should be started if malaria symptoms occur after an incubation period of at least 7 days and when medical care cannot be accessed in time. Even if ESM has been taken, travellers should seek medical care as soon as possible [10, 46, 47].

Most of the recommendations advise the prescription of ESM for areas with moderate malaria risk, while the UK and F see ESM only as an additional tool alongside chemoprophylaxis in case of presumed prophylaxis failure. The UK advises its use only for people already taking

chemoprophylaxis in high-risk areas [56], and F advises its use under the same conditions but in high and/or moderate-risk areas [60].

A meta-analysis of the use of ESM for malaria in travellers revealed that the majority of individuals prescribed with ESM failed to utilise it, and compliance with pre-travel recommendations for ESM use was inadequate [114].
Another recent systematic review and meta-analysis with the same result of suboptimal use of ESM by travellers came to an additional conclusion: if the emergency standby treatment use is to continue, general changes to the strategy should be considered, e.g. better selection of travellers at high risk for malaria [115].

The recommendations differ regarding the "minimum time to access medical care" at the destination, which should guide the ESM prescriber in assessing whether to prescribe ESM.
F recommends 12 hours, G recommends 48 hours, and the other recommendations advise 24 hours.

The German Society for Tropical Medicine, Travel Medicine and Global Health (Deutsche Gesellschaft für Tropenmedizin, Reisemedizin und Globale Gesundheit e.V. (DTG)) has decided to extend the recommendation from 24 to 48 hours to prevent unnecessary prescription of ESM.
The German board felt that with the relatively short 24-hour period for people to access medical care, many prescribers were unsure and tended to overprescribe ESM to be on the safe side, e.g. for South East Asian countries like Thailand or Vietnam with excellent medical infrastructure and an overall declining malaria risk [104]. It was felt that too liberal prescribing of ESM might lead to delayed diagnosis of much more prevalent febrile infections like dengue [116] and an erroneous intake of ESM [104].

Quite different standards may have been used in France, as the population composition is very different from that in Germany.
One reason for this may lie in the colonial history of the country, as many of the former French colonies were located in West and Central Africa, the region of the world with the overall highest malaria incidences. Due to its history, France has a large community of citizens with family roots in this region who run a high risk of acquiring malaria when visiting friends and relatives in their ancestral countries.
A cross-sectional study from 2019 of 43,333 malaria cases imported into France showed that the proportion of malaria cases among African individuals increased significantly from 1996 through 2016 (53.5% vs 83.4%) [117]. This large high-risk community and the high number of

imported cases may have played a role in the decision to set a minimum time for the access to medical care to 12 hours.
French data on imported malaria do not categorise the reason for travel, but where information is available, over 75% of malaria cases had not used chemoprophylaxis at all [118].

These findings may prompt decision makers to reconsider their guidelines and, instead of making recommendations ever stricter, place more effort to encourage those who do not take chemoprophylaxis at all to change their habits.

Table XXXVII:

Comparison of national data of imported malaria cases Germany/ France from 2019 [5, 119]

Country	**G**	**F**
Inhabitants	approx. 83,000,000	approx. 67,000,000
Imported cases of malaria	993 (85% P. *falciparum*)	5,540 (88% *P. falciparum)*
Data on the distribution of the imported cases	- travellers of German origin: 46%, of which VFRs: 38% - travellers with other origin: 54%, of which VFRs: 85% VFRs altogether: 63%	travellers of African origin: 84%

In summary: A variety of expert opinions combined with different cultural and political backgrounds of their countries, play a major role in this discussion. Additionally, the destinations of the own population and the travel behaviour are very different in the individual European countries.

However, it is important to note that the majority of imported malaria cases are not the result of ineffective medication but rather the result of travellers not taking or incorrectly administering chemoprophylaxis and/or emergency standby therapy [114, 115, 118]. This should trigger a discussion on improving traveller education and teaching simplified strategies.

Another problem is that many travellers (especially from the VFR group) [117] have not received any counselling. Here, too, extended educational initiatives would need to be created by the policymakers.

D.2.6 Use of antimalarials during pregnancy and breastfeeding

Malaria during pregnancy is very dangerous for both pregnant mother and child [120]. It is linked with an increased risk of (severe) malaria for the mother and a three to four times elevated risk of miscarriage and stillbirth. In malaria-endemic countries, approximately 10% of maternal deaths are estimated to result from *P. falciparum* infection [121].

All recommendations therefore advise not to travel to malaria-endemic areas during pregnancy. They also agree that there is no certainty about the absolute safety of any of the antimalarials

during pregnancy. If a journey is unavoidable all recommendations recommend to follow strict mosquito protection rules and to use repellents.

There are only few publications on malaria prophylaxis for pregnant travellers. Therefore the following studies on malaria prophylaxis for pregnant women from malaria-endemic areas are to be seen as a proxy for pregnant travellers:

D.2.6.1 Use of antimalarials for chemoprophylaxis in pregnant or breastfeeding travellers

For chemoprophylaxis in pregnant or breastfeeding travellers all recommendations advise M as first choice, with one exception of F, which recommends AP as first line treatment for chemoprophylaxis during breastfeeding.
In general, there is insufficient information on the safety, efficacy and pharmacokinetics of most antimalarial substances during pregnancy, especially during the first trimester [122].

A drug safety database analysis using the F. Hoffmann-La Roche global drug safety database on pregnancy and fetal outcomes after exposure to M demonstrated that the prevalence of birth defects and fetal loss was comparable to background rates. The analysis evaluated 2506 cases of individuals travelling during 1986 to 2010 in the pre- and periconception period and during pregnancy to malaria-endemic areas [123].
A systematic literature review on the safety and tolerability of M during pregnancy did not identify any increased risk for the unborn child, including during the first trimester. This review included studies which had evaluated both the use of M for malaria chemoprophylaxis in pregnant travellers and intermittent preventive treatment in pregnant women (IPTp) from endemic areas. Due to the increased risk of side effects observed, the authors concluded that the use of M for the prevention of malaria should be weighed against the risk of infection and the undesirable side effects [124, 125].

In summary, M seems to be safe for chemoprophylaxis in all trimesters of pregnancy. However, as there is an increased risk of side effects, it should be weighed in a risk-benefit analysis before use in pregnant travellers.

Regarding chemoprophylaxis during breastfeeding F recommends against M, arguing that M passes into breast milk and should be avoided as a precautionary measure. The French recommendations note that breast milk contains low concentrations of M, approximately 3 to 4% of a maternal dose (as observed in two women) and that the absence of any reported adverse event in breastfed children has led the WHO to consider its use as potentially possible. However, F emphasises that there is an increased risk of psychiatric side effects compared to

the general population, particularly during the postpartum period when psychological disorders occur more frequently [60].
The product information of the drug “Lariam” (active substance: M) informs that M passes into breast milk in small amounts, whereby the effect on the child is unknown. Guidance on the use of M during breastfeeding should be obtained from national and international recommendations [126].

F recommends AP as the first-line treatment for chemoprophylaxis during breastfeeding when the breastfed child weighs at least 5 kg. F posits that the recommended restrictions on its use during breastfeeding, which are justified as a precautionary measure since only a few data are available so far, could be ignored if chemoprophylaxis is urgently required and if the risk-benefit ratio for the child is taken into account [60].
The product information of the drug “Malarone” (active agent: AP) reports that in a study in rats, 30% of the maternal plasma concentration of atovaquone was measured in milk. However, it is not known whether atovaquone passes into breast milk in humans. Proguanil passes into human breast milk in small amounts. Furthermore, the product information states that AP is not recommended for breastfeeding women because of uncertain data situation [38].

In summary, the lack of data on malaria medication in pregnancy and breastfeeding [127] results in a high degree of uncertainty regarding which drugs may be safely recommended. For reasons of liability, manufacturers are particularly cautious about the use of the active substances during pregnancy and breastfeeding.
The scope for interpretation of the recommendations for travellers by national regulatory authorities and professional societies is considerable [55]. Currently, due to a confusing situation regarding drug approval processes in Europe (see chapter D.5), different interpretations and professional opinions become particularly evident. The “weighing up of risks and benefits” during pregnancy and breastfeeding is particularly challenging in view of the limited scientific data.

D.2.6.2 Use of antimalarials for ESM in pregnant or breastfeeding travellers

The recommendations for emergency standby treatment in pregnant travellers compared in this thesis are not consistent:
Some of the recommendations advise the use of quinine plus clindamycin in the first trimester and AP or AL from the second trimester, which is consistent with the previous WHO recommendations for pregnant women for the treatment of uncomplicated malaria, which were valid until 2022 [15, 122]. The other recommendations do not advise emergency standby

treatment during pregnancy, but do suggest the use of chemoprophylaxis even in low-risk malaria areas.

The emerging question here is whether a pregnant woman, for whom travel to a low or moderate-risk area is unavoidable, should be exposed to a malaria risk without chemoprophylaxis.
All recommendations that favour chemoprophylaxis over ESM for low to moderate-risk areas advise the use of M. However, M is often not well tolerated due to the increased risk of side effects, as the above-mentioned studies show [124, 125]. This can result in poor compliance.

For all recommendations favouring ESM over chemoprophylaxis the key issue before the year 2023 was the use of antimalarials during the first trimester of pregnancy. Due to the intolerability of M in chemoprophylaxis [124, 125] and the poorer tolerability and efficacy of quinine compared to artemisinin-based combination therapy (ACT) [128], there have been repeated discussions whether ACT could be used safely from the first trimester onwards.
A meta-analysis of five studies involving 30,618 first-trimester pregnancies in sub-Saharan Africa and Thailand, which compared artemisinin derivatives to quinine or no antimalarial treatment, found that a 3-day ACT regimen was preferable to the adverse consequences of inadequately treated malaria due to poor compliance with 7-day oral quinine treatments in early pregnancy [129]. The Malaria Policy Advisory Committee of the WHO [130] considered this analysis to endorse ACTs in the first trimester.

Subsequent studies involving pregnant women exposed to ACTs during the first trimester revealed no significant association with low birth weight, small gestational age, risk of miscarriage, stillbirth, or adverse effects on fetal growth [131-133].

Meanwhile, in 2022/3, the WHO conducted a comprehensive review of the latest evidence and concluded that AL should be recommended for the treatment of uncomplicated malaria, even in the first trimester of pregnancy. Other ACTs (artesunate-amodiaquine, artesunate-mefloquine and DP) may be considered if first-line AL is not recommended or not available [15, 50].
This may assist decision-makers in travel medicine in drawing an analogy to the use of AL as ESM in pregnant travellers during all trimesters.
The use of ACTs during the first trimester of pregnancy represents a significant change to the previously recommended quinine plus clindamycin (as ESM) or M (as chemoprophylaxis). Both quinine and M carry an increased risk of side effects, which can lead to poor compliance among pregnant women. For pregnant travellers, these side effects are particularly unpleasant to endure.

D.2.6.3 Use of chloroquine during pregnancy, breastfeeding and before conception in travellers

Although there are only a few areas left in the world where chloroquine-sensitive *P. falciparum* is prevalent [134], the majority of the recommendations still advocate the use of C in travel medicine (see chapter D.2.3).

The recommendations for the use of C during pregnancy, breastfeeding and before conception are discussed in contrasting ways.

All but one recommend the use during all trimesters of pregnancy and breastfeeding. F, however, discusses the contrary stating that C should not be used in pregnant women due to its genotoxic potential. It is therefore necessary to use contraception in men and women of childbearing age during treatment and for up to 8 months after its discontinuation. Additionally, F states that during breastfeeding C is contraindicated due to the excretion of up to 12% of the maternal daily dose in the breast milk, and its genotoxic potential [60].

According to the product information for C regarding pregnancy, data from animal studies have indeed shown reproductive toxicity. It is also mentioned that there is a potential genotoxic risk reported in some preclinical test systems and that C crosses the human placental barrier and may cause organ damage in the fetus. Furthermore, it is emphasised that pregnancy must be ruled out before taking C, and effective contraception must be maintained during its intake and for 3 months afterward.

In addition, the product information includes a contraindication for C during breastfeeding. This is because approximately 2 to 4% of the active substance passes into breast milk. Due to its long half-life, there is a risk of the active substance accumulating in the child. While it is mentioned that no adverse reactions to any child have been reported thus far, breastfeeding is not recommended due to insufficient experience.

Furthermore, the product information recommends conducting a risk-benefit assessment for the use of C in the treatment of malaria, particularly in patients residing in endemic areas, as the malaria infection itself can harm the fetus. It should be noted that the amounts absorbed by a breastfed child through breast milk are insufficient to provide protection against malaria [43, 135, 136].

F and the product information of C agree not to recommend C during pregnancy and breastfeeding, but they seem to use different sources, as they provide very different information on the amount of the active substance that passes into breast milk. It is likely that the

manufacturer is being cautious for liability reasons when advising against the use of the active substance during pregnancy and breastfeeding in the product information.

Conversely, C is a very old drug, developed in the 1930s [10] about which there is much experience and many post-authorisation studies discussed below:
The pharmacovigilance - and advisory centre for embryonic toxicology of the Charité-Universitätsmedizin Berlin “Embryotox” advises that malaria prophylaxis and therapy must be carried out in pregnancy according to the indication. In the absence of resistance (which is only the case in a few areas in the world [134]), Embryotox recommends C as the drug of choice for pregnancy [137].
“Embryotox” used the following studies for assessment [138]:

- A study analysing the outcome of 169 births in women taking 300 mg chloroquine base once a week for malaria chemoprophylaxis demonstrated that the proportion of birth defects was not significantly different from the control group not exposed to C [139].
- Two further studies from yielded similar results, leading the authors to conclude that the therapeutic doses of quinine and chloroquine are safe to use during the first trimester of pregnancy [134, 140].
- A comparative study of pregnant women in the first trimester taking C+P, M, or pyrimethamine-sulfadoxine prophylaxis found that the three groups exhibited comparable rates of spontaneous abortion and birth defects [141].
- A review investigated the ocular toxicity in the offspring during pregnancy. The review included 588 children born to mothers treated with C. The authors found no evidence of fetal ocular toxicity associated with C during pregnancy [142].
- A study examined antenatal records of 17,613 women in their first trimester at the Thai-Burmese border from 1986 to 2010. A similar risk of miscarriage was observed among women treated with chloroquine (92/354 = 26%), quinine (95/355 = 27%), or artesunate (20/64 = 31%) [143].

In conclusion, two opposing perspectives warrant consideration:
From the perspective of the manufacturer, studies indicate reproductive toxicity in animals and a potential genotoxic risk of C in certain preclinical test systems. For liability reasons, the manufacturer is particularly cautious about the use of the active substance during pregnancy and breastfeeding.
Conversely, post-authorisation studies on C, reflecting decades of observations and assessments, did not indicate an increased risk of miscarriage or stillbirth. These studies were interpreted as safe in all three trimesters of pregnancy.

The national regulatory authorities and professional societies have great scope for interpretation in the recommendations for travellers. It becomes evident that F supports the manufacturer's position with its recommendations, while the other countries align with the findings of the post-authorisation studies. These contrasting perspectives reflect, once again, the uncertainty of the authorities regarding pregnancy and breastfeeding (see also chapter D.2.6.1).

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D.2.7 Methodology of the definition of malaria risk areas

The definition of malaria risk areas and their graduation show many differences between the recommendations.

WHO has defined the Annual Parasite Index (API) as the “number of confirmed new malaria cases registered in a specific year, expressed per 1,000 individuals under surveillance, for a given country, territory, or geographic area. API refers to high and moderate malaria transmission risk areas” [63]. Additionally, there are two further indices distinguishing between incident cases by different parasite species: the Annual *Falciparum* Index or *P. falciparum* Annual Parasite Index (AFI or *Pf*API) and the Annual *Vivax* Index (AVI). Both are defined as the number of confirmed *P. falciparum* or *P. vivax* cases, respectively, per 1,000 population at moderate and high risk [64, 144]

The selected recommendations differ significantly in the methodology applied: some use the API combined with the number of documented malaria cases among 100,000 travellers per year, while others name the references, which are based on the country risk assessment and data on imported cases of their individual country. Only one uses mainly the AFI.

The main point of discussion is certainly whether to use the API to map malaria regions, which reflects the general malaria situation in the malaria-endemic area, or to focus on the AFI, which only shows the distribution of the most dangerous malaria species, *P. falciparum.*
For this purpose, both the efficacy of the medication used in travel medicine for chemoprophylaxis and emergency standby treatment and the distribution of reported malaria cases by species should be considered.

All drugs currently used and licensed for chemoprophylaxis and emergency standby treatment of malaria in Europe only protect against *P. falciparum* infection and are effective against the first episode of *P. vivax* and *P. ovale* infections [32]. They are inactive against hypnozoites in the dormant liver stage and therefore not effective in preventing *P. vivax* and *P. ovale* relapses [32-36]. Primaquine is effective against hypnozoites, but is also active against the liver schizonts of all malaria species [37]. In Europe it is used only for antirelapse therapy [11], whereas in the

USA it is also used for (primary) chemoprophylaxis in areas with predominant *P. vivax* malaria [7, 33, 35].

Looking at the distribution of the different *Plasmodium* species in the affected regions of the world shows that the API on the African continent is almost equal to the AFI, since *P. vivax (and other Plasmodium* species*)* are very rare and therefore the AVI is very low.
The distribution of *Plasmodium falciparum* to *Plasmodium vivax* varies in the regions of the Americas, Eastern Mediterranean, Asia, and Western Pacific. Here the API differs from the AFI very clearly (see Table XXXVIII).

Table XXXVIII:

Distribution of the parasites *P. falciparum* and *P. vivax* in the WHO world regions [8]

World region	***P. falciparum***	***P. vivax***
West Africa	100%	< 1%
Central Africa	100%	---
East and Southern Africa (High transmission regions)	100%	< 1%
East and Southern Africa (Low transmission regions)	96%	4%
Region of the Americas	76%	24%
Eastern Mediterranean Region	73%	27%
South-East Asia Region	53%	46%
Western Pacific Region	68%	32%

In summary, for WHO malaria world regions other than the African continent, it is necessary to reconsider the use of the AFI instead of the API. This is because in Europe the API better accounts for the utility of prescribing antimalarial drugs for travellers, thus allowing drugs to be used more effectively.
The situation is different in the USA, where primaquine or tafenoquine may also be used for (primary) chemoprophylaxis in areas with a higher proportion of vivax malaria. However, one must rule out G6PD deficiency in any patient for whom primaquine or tafenoquine is being considered, as it could otherwise induce haemolysis. The effort and costs to rule out G6PD deficiency in a busy travel clinic would be considerable [7, 11, 33, 34]. In other settings, such as occupational medicine or for providers working with long-term travellers it may be an effort worthwhile.

The methodological differences between the seven selected recommendations for travellers are also reflected in the data on the distribution of *Plasmodium species* in the six countries studied, Ethiopia, Kenya, Cambodia, India, Brazil, and Colombia. The divergence is particularly evident in the data from Cambodia on the ratio of the distribution of *Plasmodium falciparum* to *Plasmodium vivax* (see Table XXXIX).

Table XXXIX:

Distribution of the parasites *P. falciparum (Pf)* and *P. vivax (Pv)* in Cambodia according to the World Malaria Report (WMR) in different years [8] and according to the recommendations under review

Distribution by year (WMR)	***Pf* distribution in%**	***Pv* distribution in%**	**Mixed cases distribution in%** **Other species distribution in%**
2019	15%	85%	1%
2018	24%	73%	3%
2017	55%	41%	4%
2016	52%	42%	6%
2015	49%	36%	8% 7%
Distribution by countries			
G (Edited 2020)	25%	74%	***P. knowlesi*** rarely
NL (Edited 2019)	64-86%	12-36%	***P. knowlesi*** rarely
E (Edited 2019/ updated 2020)	58%	41%	----------

The other remain four countries of the selected recommendations do not discuss the topic of parasite distribution in Cambodia.

All seven countries refer to the World Malaria Report (WMR) [8], but the figures are not complete here. The national numbers of cases imported into the country in question are also processed. This makes it difficult to determine the source of the discrepancies.
(As an example of incomplete data in the WMR, here are the figures of the distribution of the different *Plasmodium species* of Cambodia from 2017 [8].
Indigenous cases: 76 804
Total *P. falciparum:* 20 328
Total *P. vivax:* 15 207
Total mixed cases: 1 397
Total other species: ---
The addition of all malaria cases of *P. falciparum, P. vivax*, total mixed case and total other species is 36 932. The figures for all indigenous cases of 76 804 in relation to the total number of cases disaggregated by species vary by a difference of 39872, which is greater than the total number of all individually disaggregated cases per se.)

The data on the distribution of *Plasmodium species* in Cambodia appear to refer to different years (see Table XXXIX). The recommendations from G from 2020 [57] refer to the WMR figures from 2018. The recommendations from E [61], which were edited in 2019 (but updated

in 2020), appear to refer to the figures from 2017. However, E indicated to use data from WMR of 2018 together with additional information from CDC regarding Cambodia [61] (see chapter C.8.1). The data of the recommendations of the NL from 2019 (the entire recommendation was edited in 2020 [58], but the maps and tables of the individual countries were published in 2019 [145]) cannot be traced by WMR data alone, and it appears that they refer additionally to other sources [145]. Furthermore, it can be observed in Table XXXIX that the numerical ratios of the WMR can reverse during individual years through overall small numerical differences.

These differences, which may appear to be minor in terms of parasite distribution, can have a significant impact on the recommendations for travellers as they may result in a completely different evaluation of the graduation of malaria risk areas. This can also have an impact on a completely different recommendation for travellers as to whether chemoprophylaxis or emergency standby treatment should be prescribed.
In summary, with regard to the distribution of *P. falciparum* and *P. vivax* in Asia, it can be stated that despite the lack of conclusive data from the WMR and the differing times at which the malaria figures were updated in the individual countries, the practical relevance is not so significant in view of the overall decline in the number of malaria cases.

D.3 Conclusions

A key factor in explaining the differences between European malaria recommendations for travellers is the lack of a standardised and transparent methodology. In addition, the use of national data on imported malaria cases and incomplete epidemiological data, particularly from developing countries, contributes to these differences. This often leads to varying interpretations among national professional societies and regulatory authorities, at both national and European levels, influenced by different expert opinions combined with diverse cultural and educational backgrounds. Improved communication between authorities, especially within Europe, is essential for effectively sharing data and achieving consistency.

In terms of instructions and application mode for the different antimalarials used for chemoprophylaxis and emergency standby therapy, as well as for repellents, there is a lack of consistency. Most antimalarial drugs are considerably old and have only been approved at the national level within the different European Union member states, resulting in a lack of standardised product information. Similarly, the approval of repellents also tends to be at the national level through licensing agreements of the authorities.

Due to limited data on the use of malaria medication in children, during pregnancy and breastfeeding, there is a considerable level of uncertainty. Manufacturers are cautious with

recommendations due to liability concerns, although studies often reach different conclusions based on long observation periods, sometimes over decades. This uncertainty leaves significant room for interpretation by national regulatory authorities and professional societies regarding travel recommendations. Assessing the "balance of risks and benefits" becomes particularly challenging in this context.

Two discrepancies in the recommendations were illuminated through research and by conducting a study:

Differences in repellents regarding age limits for children and use during pregnancy appear to depend more on the specific product as a whole and its co-formulants, which affect the absorption of the active substance in the body. The concentration of the biocidal active substance itself plays only a secondary role in this regard.

Furthermore, a study conducted in Mali demonstrated that wearing light-coloured clothing in tropical regions appears to be a sensible recommendation as a protective measure against mosquitoes, including the nocturnal Anopheline and *Culex* mosquitoes, as well as the diurnal *Aedes* mosquitoes [102].

Since 2022/23, Germany, Switzerland, the Netherlands, and Belgium have been striving to harmonise their country recommendations by issuing joint recommendations which may be an important step towards a uniform European guideline. The four countries use the same methodology to assess malaria risk in endemic areas and publish the same maps. As part of this process, the methodology was adapted to use different cut-off values for AFI (Annual *Falciparum* Index) and AVI (Annual *Vivax* Index) instead of the API (Annual Parasite Index) for mapping malaria risk areas, aiming to provide more precise recommendations for the appropriate prophylactic measures.
To promote further harmonisation of the recommendations, effective communication among professional societies and authorities across Europe is essential. This would involve establishing extensive data exchange to build up a comprehensive European database containing all relevant malaria-related information.

Nevertheless, it is crucial to highlight that the majority of imported malaria cases are not a result of ineffective medication and recommendation. Instead, it is the result of travellers not taking or incorrectly administering chemoprophylaxis and/or emergency standby therapy. This underscores the necessity for a discussion on improving education for travellers and the accessibility of information for all population groups. As the majority of imported malaria cases continue to be seen in VFRs who have not sought any guidance or counselling regarding

malaria prevention, it is necessary to develop expanded educational initiatives to address this risk group.

E. FUTURE RESEACH AREAS OF MALARIA

The authorisation of antimalarials and repellents is often limited to the national level in Europe, as previously described. Nationally collected data, among other sources, are used for the evaluation of scientific findings. This can result in different opinions among the authorities and professional organisations in the individual EU member states. Consequently, significant discrepancies may arise in the evaluation and implementation of recommendations and guidelines for the treatment of malaria.

The establishment of new areas of development in malaria research, organised from the outset at European level or through international collaborations, could help to establish a comprehensive data exchange to build a European database with all relevant information on malaria. Then, data on all malaria cases imported to Europe could be taken in account to harmonise European malaria recommendations.

E.1 Malaria vaccines

One of these areas of malaria research, where new development is currently taking place, is the area of vaccine research and development.

There are approximately 70 vaccine candidates which target different stages of the malaria parasite's lifecycle, each with specific modes of action [146, 147].

Pre-erythrocytic stage vaccines aim to prevent infections by acting against the parasite's development in the liver [148-150], blood stage vaccines focus on the prevention of the onset of the disease by acting against the parasites that multiply cyclically in the blood in the asexual stage [151-154]. Sexual stage vaccines aim to halt the transmission of the parasite by acting against the sexual forms of the parasite (gametocytes) [155], multi-stage vaccines take a comprehensive approach by targeting multiple phases of the parasite's lifecycle [156].

The pre-erythrocytic vaccines, which interfere with the liver cycle of the parasite, are currently studied best [146, 147]:

One of the two vaccines presently recommended by WHO for prevention of falciparum malaria is RTS,S/AS01 *(Mosquirix)* [147]. In phase III trials, after administration of three vaccine doses at 4-week intervals, RTS,S/AS01 demonstrated a vaccine efficacy of up to 56% against clinical malaria in children aged 5–17 months over the first year [157] and 36% after the fourth doses, over a median of 48 months of follow-up [149, 158].

RTS,S/AS01 is a recombinant pre-erythrocytic vaccine containing *P. falciparum* surface-protein circumsporozoite antigen, fused to hepatitis B virus surface antigen (HBsAg) and mixed with the adjuvant AS01 [150, 159]. In July 2015 the EMA published a positive scientific opinion [147,

160] and 4 years later, in 2019, RTS,S/AS01 became the first vaccine against malaria to undergo pilot implementation. Meanwhile, approx. 800,000 children in Malawi, Ghana, and Kenya [161, 162] have been vaccinated with the vaccine. Based on the results of this ongoing pilot program the WHO recommended in October 2021 the broad use of RTS,S/AS01 in children in sub-Saharan Africa and in other areas with moderate to high *falciparum* malaria transmission [162, 163]). A recent trial of Sahel and sub-Sahel regions showed that the administration of RTS,S/AS01 was noninferior to chemoprevention, but the combination of both interventions provided better protection than chemotherapy or vaccination alone [164].

In April 2021 another malaria vaccine candidate called R21/Matrix-M achieved a 77% efficacy in phase IIB trials, meeting the WHO's 75% efficacy goal. [147, 150, 165]: Developed by Oxford University researchers and partners, it is a pre-erythrocytic low-dose circumsporozoite protein-based vaccine candidate, fused to HBsAg [150] and mixed with Matrix-M, a saponin-based vaccine adjuvant produced by Novavax AB, Uppsala, Sweden [150, 166]. The trial in Burkina Faso involved 450 children aged 5-17 months, showing high efficacy over 12 months with no serious adverse events. The study, conducted until August 2019, included three initial doses at 4-week intervals before the malaria season, with a fourth dose a year later [150, 165], maintaining efficacy and immunogenicity over two years.[167]. By April 2023 R21/Matrix-M was licensed in Ghana and provisionally in Nigeria, even before the results of phase III trials could be published [168, 169]. Since October 2023 the WHO recommends R21/Matrix-M for malaria prevention in children [170].

The further evaluation with the phase III trial included different malaria transmission areas in Burkina Faso, Mali, Kenya, and Tanzania. It also included concurrent administration of seasonal malaria chemoprevention interventions and a wider age range with high malaria incidence. The results, published in February 2024, showed that the vaccine provided 75% protection against malaria in areas with seasonal transmission and 68% in areas with year-round transmission. The vaccine was more effective in children aged 5 to 17 months compared to those aged 18 to 36 months [171].

R21/Matrix-M is similar to RTS,S/AS01, both include fused HBsAg, but R21/Matrix-M does not have excess HBsAg. R21/Matrix-M provides a higher density of circumsporozoite protein epitopes on the surface of the particle than RTS,S/AS01, resulting in higher levels of malaria-specific antibodies [150]. In addition, the adjuvant differs.

A look at the future, with a further potential new vaccine candidate: The Mainz-based pharmaceutical company BioNTech wants to develop the world's first malaria vaccine based on mRNA technology, the same technology used for the first corona vaccine approved in the EU. First, they plan to investigate several mRNA vaccine candidates. A clinical trial with the most promising candidate was planned for the end of 2022 or the beginning of 2023 [172]. Additionally, the company states the intention to work with the WHO and the African Union Health Organisation (Africa CDC) to develop sustainable solutions for vaccine production and supply in Africa [172-174].

Certainly, the vaccine RTS, S/AS01, the work of Oxford University with R21/Matrix-M and the announced plans of BioNTech represent significant advances in malaria vaccine development. The use of the vaccine, at best combined with other interventions, can help reverse the current resurgence of malaria [175].The primary goal is to reduce the significant mortality from malaria in children under 5 years living in endemic malaria areas.

Whether these or indeed any other vaccines will ever be used in the field of travel medicine can only be seen as speculation at this point. To achieve this, the efficacy of a vaccine used in travel medicine would have to reach almost 100% to be at least as good as the gold standard chemoprophylaxis.

E.2 Monoclonal antibodies of malaria

CIS43LS is a monoclonal antibody against the sporozoites of *Plasmodium falciparum,* which was isolated from several subjects immunised with an attenuated *P. falciparum* whole-sporozoite vaccine (Sanaria *Pf* SPZ Vaccine). It has an extended half-life and targets a “junctional” epitope on the *P. falciparum* circumsporozoite protein (PfCSP), which is the major protein expressed on the surface of the sporozoites [176].

In a phase I clinical trial to assess the safety and pharmacokinetics of CIS43LS and its efficacy against infection with *P. falciparum,* it was demonstrated that administration of CIS43LS in nine healthy adults prevented malaria after controlled infection. Two participants only underwent the controlled infection after 36 weeks and did not show parasitaemia even later [177].

A phase II clinical trial was conducted in Mali under field conditions to assess the effectiveness of a single dose of 10 mg or 40 mg per kilogram of body weight CIS43LS administered intravenously (IV) to protect against *P. falciparum* infection. 40 mg per kg of CIS43LS provided up to 88.2% efficacy against *P. falciparum* infection in adults over a 6-month observational period. In contrast 78.2% of the participants in the placebo group developed malaria [178, 179].

Even though effective, IV administration will hamper the broad usage of CIS43LS, both under field conditions and in the pre-travel setting [178].

The new generation monoclonal antibody L9, which targets another conserved side of the junctional of PfCSP, is 2 to 3 times as potent as CIS43LS. It also has an increased half-life time, as it was modified with a LS mutation [178, 180]. Furthermore, it may be administered subcutaneously.

A phase I clinical trial of L9LS was conducted to assess the safety, pharmacokinetics, and efficacy against controlled human malaria infection in healthy adults. The antibody was administered intravenously or subcutaneously in different doses per kilogram body weight. It conveyed protection against malaria in a human challenge model following subcutaneous doses of 5 mg per kilogram, without evident safety concerns [181].

Currently in Kenya (ClinicalTrials.gov number NCT05400655) and Mali (NCT05304611) two phase II trials involving children are ongoing assessing the safety and efficacy of subcutaneously administered L9LS in year-round and seasonal transmission [178, 179].

In the field of travel medicine, subcutaneously administered monoclonal antibodies for malaria prevention in travellers could be a promising field for the future. Certainly, the efficacy under field conditions, the duration of protection, and tolerability in all age groups with and without pre-existing conditions still need to be tested. The cost calculation is still open, although an estimate of $50 per gram [182] has been mentioned, which is quite a positive outlook. However, it is first important to assess the level of protection that L9LS provides to children in Africa.

E.3 Pharmacokinetics and Pharmacogenetics in antimalarial drugs used in travel medicine

None of the analysed malaria recommendations address the topic of pharmacokinetics and pharmacogenetics/-genomics of antimalarial drugs across different ethnicities. Nevertheless, this could be of interest and importance for future travel medicine.
Many antimalarials have side effects or show incompatibilities when co-administered with other drugs [183, 184]. Studies show that travellers often become non-compliant with the prescribed prophylaxis or even discontinue it for these reasons, among others [185, 186]. A future vision for the antimalarial prophylaxis and treatment would be to adapt malaria drugs more precisely to the individual patient's metabolism on a dose-dependent basis, or even to develop new, better-tolerated drugs [187, 188].

Many antimalarial drugs used in both prophylaxis and therapy are metabolised with the involvement of the cytochrome P450 (CYP) enzyme system [188-190].
The human cytochrome P450 (CYP) system is a family of enzymes of membrane-bound haemoproteins [191], which is subdivided into a variety of isoenzymes. It catalyses biotransformation of phase I metabolism (by hydrolysis, dealkylation, deamination or oxidation) of drugs and degradation of many endogenous and exogenous substances [188, 192]. The nomenclature is as follows: CYPxyz*ab, where CYP=Cytochrome P450 and x=family (Arabic numeral), y=subfamily (Capital letter, if more than one exists), z=gene name (Arabic numeral), *a=allele (Arabic numeral), b=silent mutation or sub-allele (Capital letter) [188, 193].
Approximately 12 of 57 human CYPs, belonging to CYP families 1, 2 and 3, are responsible for the metabolism of almost 80% of all clinical drugs [188, 192, 194]. CYPs 3A4, 2C9, 2C8, 2E1, and 1A2 are the highest expressed forms in the liver, while 2A6, 2D6, 2B6, 2C19, and 3A5 are not so frequent. CYPs 2J2, 1A1, and 1B1 are mainly expressed extrahepatically. A combination of factors and mechanisms, such as genetic polymorphisms, induction or inhibition by xenobiotics, regulation by cytokines, hormones, disease states, gender, and age influence the expression of CYPs [192].
Genetic polymorphisms in CYP genes often depend on ethnicity and genetic diversity, which plays a considerable role in the field of tropical and travel medicine. They can cause different drug-drug-gene interactions, variation in adverse drug reactions, but also different treatment outcomes [188-190, 195]. They can also lead to different pharmacogenetic phenotypes defined as poor, intermediate, normal, and ultra-rapid metabolisers. Poor or intermediate metabolisers have two or one defective allele, normal metabolisers have two alleles with "normal activity", usually referred to as *1 (wild type), and ultra-rapid metabolisers exhibit duplicated or multiple duplicate gene copies of the same allele [188, 191, 192, 196].
Here are some examples of the effects of genetic polymorphisms on antimalarial drugs for travel medicine:
The drug transporter ATP-binding cassette ABCB1 c.3435CC genotype (wild type) of ABCB1 c.3435C>T single nucleotide polymorphism is associated with increased lumefantrine exposure and, consequently, a more favourable AL treatment outcome at the 28-day follow-up in patients with uncomplicated *falciparum* malaria. This genotype provides better protection against new infections compared to those with CT and TT genotype [197].

Drug transporter ATP-binding cassette ABCB1 c.1236TT genotype of ABCB1 c.1236C>T single nucleotide polymorphism had three times higher chances of successful treatment with mefloquine compared to those with genotypes CC (wild type) and CT [198].

CYP 2C8 (and to a lesser extent CYP 3A4/5) is known to metabolise chloroquine to N-desethylchloroquine, which has similar antimalarial activity [48, 199]. It was described that wild - type individuals with CYP 2C8*1 allele had a significant more rapid decrease in gametocytes than individuals with CYP 2C8*2, *3 and*4 alleles, which are associated with reduced enzyme activity [189, 200]. However, this is just an observation, but it has no clinical significance for the individual patient.

CYP 2C19 (and possibly CYP 3A4) is known to metabolise proguanil to cycloguanil, which is the active form of the drug [48, 188]. CYP 2C19*2 and CYP 2C19*3 alleles are associated with poor metabolism and the CYP 2C19*17 allele with (ultra)rapid metabolism of proguanil [188, 201-206]. However, under treatment with atovaquone/proguanil at the recommended dosage, proguanil metabolisation status does not appear to affect the malaria treatment or prophylaxis. Data suggest that proguanil's intrinsic efficacy against *falciparum* and *vivax* malaria remains significant, independent of cycloguanil. [207-209].

CYP 2D6 (and possibly CYP 3A4) is known to metabolise primaquine as a prodrug to at least six active metabolites, which are responsible for the anti-hypnozoite activity [210-213]. Apart from G6PD-deficiency, which can cause haemolysis [7, 11, 33, 34], there is evidence that individuals with poor-metaboliser CYP 2D6*4, *5, *10, *17 and *41 alleles may experience treatment failure when using primaquine [188, 214-216].

CYP 3A4 and CYP 3A5 enzymes overlap in their substrate activity, so that the majority of CYP 3A substrates are metabolised by both enzymes [217-219]. They are involved in the metabolism of many antimalarials used in travel medicine: artemether, chloroquine lumefantrine, mefloquine, piperaquine, primaquine, quinine. Pharmacogenetic studies have so far mainly focussed on the two active substances quinine and lumefantrine

CYP 3A4/5 are known to metabolise quinine as a substrate to 3-hydroxyquinine, which accounts for about 10% of the antimalarial effect of the parent compound [48]. Several studies show that there is a significant influence of CYP 3 A4*1B [220, 221], CYP3A4*22 [188] and 3A5*3, *6 or *7 alleles [221, 222], which are associated with low enzyme activity, low quinine metabolism, and high quinine adverse reactions [194, 222, 223]. Wild-type CYP 3A4*1 and CYP 3A5*1 alleles are associated with normal enzyme activity and normal quinine metabolism [223].

CYP 3A4/5 are known to metabolise lumefantrine to desbutyl-lumefantrine, which has an antiparasitic effect in vitro that is six to eight times higher than lumefantrine. [224]. Regarding artemether-lumefantrine, mefloquine and piperaquine, no significant association was found between CYP 3A variants and pharmacokinetic parameters in non-pregnant populations

described by two studies [197, 225] . However, two studies about malaria-positive pregnant women found significant associations between CYP 3A5 polymorphisms and day 7 plasma lumefantrine concentrations, being significantly higher in carriers of CYP 3A5*3, *6 or *7 alleles than in wild-type CYP 3A5*1 allele [226, 227]. High day 7 lumefantrine concentration is suggested as potent predictor of therapeutic response in pregnancy [226, 228, 229].
Further results showed that the majority of malaria-positive pregnant women with CYP 3A4*1B sub-alleles had significantly better adequate clinical and parasitological response (ACPR) than those with wild-type CYP 3A4*1 alleles after observation and examination on day 28 [226].
A study about malaria- HIV-coinfected women undergoing efavirenz therapy also showed a significant association of CYP3A5*3 carriers with a high maximum plasma concentration of lumefantrine, as well as longer half-life and thus with a very low to no enzyme activity [230].

The distribution of allele frequency of CYP3A4*1B is 3% in Europeans, about 76% in Africans and none in Asians [231], of CYP 3A5*3 is 93% in Europeans, 30% in Africans and about 70.0% in Asians [232]. Further distributions of allele frequencies, which often differ significant between the various ethnic groups, can be looked up in Table XL.

It has been demonstrated that pharmacogenetic differences that occur in antimalarial drugs used in travel medicine may contribute to individual variability in desired drug effects as well as adverse effects and drug interactions, depending on ethnicity. Genotyping should be considered in patients who show or in the past have shown particularly severe adverse effects or reduced efficacy with the above agents.

In the future, the findings could also contribute to the development of modern and personalised treatment methods, leading to an improvement in patient safety for new drugs and therapy concepts.

Table XL:

Important variant and allele frequencies of the human CYP family [231, 232] *(Permission has been granted by the publishers)*

Allele	Allele frequencies in indicated populations (in%)						Functional consequence
CYP 2C8	**EUR**	**AFR**	**EAS**	**JP**	**SAS**	**AMR**	
***1**	82.9	81.6	99.3	100	92.5	89.7	normal
***2**	0.3	15.2	<0.1	0	1.9	0.8	decreased
***3**	11.3	2.0	<0.1	0	4.1	6.8	controversial
***4**	5.4	1.1	<0.1	0	1.5	2.7	decreased
CYP 2C19							
***1**	61.5	55.8	62.1	64.8	67.1	79.1	normal
***2**	14.7	17.8	30.8	26.7	32.4	10.1	inactive
***3**	<0.1	<0.1	6.3	8.6	0.4	<0.1	inactive
***17**	23.1	20.9	0.7	0	13.6	10.1	increased
CYP 2D6							
***1**	24.1	20.8	17.5	42	25.3	48.9	normal
***2**	33.6	22.5	14.6	15.8	38.0	26.0	normal
***4**	19.6	8.0	0.3	0	10.4	11.1	inactive
***5**	2.9	6.2	5.2	4.9	3.2	2.1	inactive
***10**	1.7	4.8	57.3	35.0	5.5	1.4	decreased
***17**	<0.1	20.5	0	0	0	0.7	decreased
***41**	9.3	2.6	3.2	0.7	13.6	4.0	decreased
CYP 3A4							
***1**	94.7	96.2	97.5	93.4	99.4	97.1	normal
***1B (sub-allele)[231]**	3.0	76.0	0	0	0	12.0	decreased
***22**	4.4	0.9	0	0	0.6	2.5	decreased
CYP 3A5							
***1**	6.4	47.0	28.6	25.0	33.2	19.5	normal
***3**	92.9	29.8	71.4	74.0	66.8	79.2	inactive
***6**	<0.1	12.9	0	0	<0.1	0.8	inactive
***7**	<0.1	10.2	<0.1	0	<0.1	0.5	inactive

AFR, Africans; AMR, admixed Americans; CYP, cytochrome P450; EAS, East Asians; EUR, Europeans; JP, Japanese; SAS, South Asians

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APPENDCICES

Appendix A

Table XLI:

Formal Aspects I

Formal aspects I	1. Institutional background	2. Authors/Editors	3. Year of publication/ last updates	4. Type of publication
UK	Public Health England (PHE)-Advisory Committee on Malaria Prevention (ACMP) Wellington House 133-155 Waterloo Road London SE1 8UG United Kingdom Tel: 020 7654 8000 E-Mail: ACMPSecretariat@phe.gov.uk https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/833506/ACMP_Guidelines.pdf	Chiodini, Peter Patel, Dipti Whitty, Christopher	2019	internet brochure
Germany	Deutsche Gesellschaft für Tropenmedizin, Reisemedizin und Globale Gesundheit (DTG) e.V. Ständige Ausschusss Reisemedizin der DTG (StAR) Bernhard-Nocht-Straße 74 20359 Hamburg Germany E-MAIL: dtg@bnitm.de https://dtg.org/images/Startseite-Download-Box/2020_DTG_Empfehlungen_Malaria.pdf	Rothe, Camilla; Rosenbusch, Deike; Alberer, Martin; Burchard, Gerd; Bühler, Silja; Erkens, Kai; Feldt, Torsten; Grobusch, Martin P.; Kapaun, Anette; Köhler, Carsten; Löbermann, Micha; Meischner, Karin; Metzger, Wolfram; Müller, Andreas; Nothdurft, Hans Dieter; Rieke, Burkhard; Schlaich, Clara; Schönfeld, Christian; Schulze, Marco H.; Siedenburg, Jörg; Steiner, Florian; Veit, Olivia; Weitzel, Thomas; Boecken, Gerhard	2020	journal article
Netherlands	Landelijk Coördinatiecentrum Reizigersadvisering (LCR)-independent foundation Postbus 1008 1000 BA Amsterdam Netherlands https://www.lcr.nl/	Malaria werkgroep of the LCR (https://www.lcr.nl/Over-het-LCR)	2020	LCR-membership brochure and web page
Belgium	Travelhealth - Institute of Tropical Medicine Antwerp Wanda-Travel in good health Kronenburgstraat 43 2000 Antwerpen Belgium https://www.wanda.be/en/	Crough, Mieke Maniewski-Kelner, Ula	last updates of the web pages between 2019-2021	web page
France	Haut Conseil de la santé publique (HCSP) Commission spécialisée Maladies infectieuses et Maladies émergentes 14 avenue Duquesne 75350 Paris 07 SP France https://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspa20200313_recommasanitaipourlesvoyageu.pdf	Camus, Daniel Chidiac, Christian	2020	two chapters of internet brochure
Spain	SOCIEDAD ESPAÑOLA DE MEDICINA TROPICAL Y SALUD INTERNACIONAL (SEMTSI) Sergio Hernández Theoria Congresos C/ Carreres Puchalt 6 46020 Valencia Spain Tel. (34) 960.728.212 Mail: secretaria_tecnica@semtsi.org o sergio.hernandez@theoriacongresos.com http://www.semtsi.es/0/activos/texto/wsemt_pdf_1602-I3GliR67BpA4wf2K.pdf	Morales, Raisa; Rodriguez, Natalia; Otero, Susana; Cabanas, Laia; Agüero, Fernando; Oliveira, Inés	2020	internet brochure
Italy	SOCIETÀ ITALIANA DI MEDICINA TROPICALE E SALUTE GLOBALE (SIMET) c/o Dipartimento di Malattie Infettive, Reparto di Malattie trasmesse da Vettori; Istituto Superiore di Sanità, Viale Regina Elena 299 00161 Roma Italy Tel. +39 06 49906102 Fax +39 06 49903561 http://www.simetweb.eu/document/3967	Calleri, Guido; Gobbi, Federico Giovanni; Napoletano, Giuseppina; Odolini, Silvia; Romi, Roberto; Rossanese, Andrea; Tomasoni, Lina Rachele	2018	internet brochure

Table XLII:

Formal Aspects II

Formal aspects II	UK	Germany	Netherlands	Belgium	France	Spain	Italy
5. Member list of the editing board	v (p.97)	v (p.163)	v "malaria working group" (https://www.lcr.nl/Over-het-LCR)	v only authors are named	v (p.2)	v (p.9-12)	v (preface of the guideline)
6. Declaration of conflict of interest	v (p.98)	v (p.181)	v (https://www.lcr.nl/Over-het-LCR)	x	v (p.2)	v (p.2)	x
7. Updates/ cycle of publication	annually (p.98)	annually (p.163)	v not clear information in which cycle, probably annually (https://www.lcr.nl/Over-het-LCR)	annually	annually (p.1)	annually	v every few years:(2003; 2013) and last update 2018
8. Chapter of key changes of updates	v chapter (p.8-9)	v chapter	x	x	v introduction; text markings (p.1)	v methodology chapter (p.8; 20-21)	v yellow marked sections through the whole guideline
9. Epidemiology	v table (p.14)	v chapter	v small paragraph within the introduction (p.1)	x	v chapter (p.26-28)	v two chapters (p.6-7; 56-69)	v in the VFR-chapter (p.24-25)
10. Reference list/literature list/bibliography	v (p.145-153)	v (p.181-182)	v (p.33-36)	x	v (p.89-91)	v by chapter/ chapterwise	v (p.29-33)
11. Malaria maps of key countries	v (p.107-144)	v (p.183-189)	v maps only accessible for LCR-members	v (https://www.wanda.be/en/landen/)	x	v (p.120-130)	v one world map (p.36)
12. Table of country recommendations	v (p.42-51)	v (p.190-197)	v (https://www.lcr.nl/Landen; LCR-landenlijst, only accessible for LCR-members)	v (https://www.wanda.be/en/landen/)	v (p.35-47)	v (p.23-54)	v table of world regions (p.34-35)
13.Template for risk assessment	v (p.101-105)	x	v (p.25-26)	x	x	x	x
14. Information leaflet of ESM	v (p.105-106)	x	v (https://lcr.nl/Bestanden/Malaria%20folder%20nb%20mrt%202018.pdf)	v (https://www.wanda.be/en/a-z-index/emergency-treatment-for-malaria)	x	x	x
15. List of repellent products	x	v (p.166)	x	x	v (p.52)	v (p.73)	x
16. Map of rain period areas	x	x	x	x	x	v (p.58)	x
17.Table of handling long term travels	x	v (p.177)	x	x	x	x chapter with list (p.103)	x

Appendix B

Table XLIII:

General Aspects I

General Apsects I	How to give advice/checklist/ risk assessment	Risk exposure/when and where do mosquitos bite information	Risk exposure/when and where do mosquitos bite: Altitude	Risk exposure/when and where do mosquitos bite: Rain periode
UK	v ABCD- rules (p.12-13), template of risk assessment (p.101-105); information leaflet of ESM (p.105-106)	v (p.19-20)	v > 2000m malaria is rarely found, some countries reported up to 2500m (p.19)	v (p.19)
Germany	v checklist (p.172)	v (p.164-165; 174; 177-178; 180; 190-197)	v > 2000m malaria is rarely found (p.174; 190-196)	v (p.164;174; 178; 190-197)
Netherlands	v checklist (p.25-26; 28)	x	x	v (p.22)
Belgium	x	v (https://www.wanda.be/en/a-z-index/travellers-with-higher-malaria-risk)	x	x
France	v checklist (p.30)	v (p.29)	v > 1500m malaria is rarely found in Africa, > 2500m malaria is rarely found in America and Asia (p.29)	v (p.29,34)
Spain	v checklist for long term traveller´s advice (p.101)	v (p.57-58; 70; 93; 102-103)	v > 1500m malaria is rarely found, some countries reported up to 2500m (p.57)	v (p.58; 70; 103)
Italy	v ABCD- rules (p.6), CP advice (p.16)	v (p. 4-5)	v > 2000m malaria is rarely found (p.4)	v (p.4)

Table XLIV:

General Aspects II

General Apsects II	Risk exposure/when and where do mosquitos bite: Temperature	Risk exposure/when and where do mosquitos bite: Rural/ urban	Risk exposure/when and where do mosquitos bite: Dusk to dawn (differences btw. Africa/ South America-South East Asia)
UK	v high humidity and a temperature in the range 20 to 30°C, does not occur in regions with temperatures below the 16°C (p.19)	v in Africa 8 times higher in villages than in towns (p.19)	v peaks at and just after midnight in Africa/ peaks in the evening in South America-South East Asia (p.21; 57)
Germany	x	v (p.164; 174, 177; 190-197)	v no differences mentioned between Africa/ South America-South East Asia (p.165; 180)
Netherlands	x	v Asia, South America towns free from malaria, Africa towns often with malaria (p.21; 23; 27)	v no differences mentioned between Africa/ South America-South East Asia (p.1)
Belgium	x	v (https://www.wanda.be/en/a-z-index/travellers-with-higher-malaria-risk)	v higher risk in rural areas (https://www.wanda.be/en/a-z-index/travellers-with-higher-malaria-risk)
France	x	v Asia, South America towns often free from malaria (p.29)	v no differences mentioned between Africa/ South America-South East Asia (p.29; 35)
Spain	x	v VFR higher risk as they tend to travel to rural areas (p.93, 102-103)	v no differences mentioned between Africa/ South America-South East Asia (p.70)
Italy	v high humidity and a temperature in the range 20 to 30°C, does not occur in regions with temperatures below the 16°C (p.4)	v in Africa 8 times higher in villages than in towns (p.4)	v no differences mentioned between Africa/ South America-South East Asia (p.4)

Appendix C

Table XLV:

Bite Protection: DEET

Bite Protection: DEET	DEET recommended concentration	DEET and duration of protection	DEET and sunscreen	DEET and children	DEET and pregnancy/breastfeeding
UK	v 20-50% DEET recommended (p.21-23)	1 to 3 hours for 20%, up to 6 hours for 30% and up to 12 hours for 50% DEET. There is no further increase in duration of protection beyond a concentration of 50%. (p.22)	v DEET should be applied after the sunscreen, 30 to 50 SPF sunscreen should be applied to compensate for DEET-induced reduction in SPF (p.22)	v <= 50% DEET approved for children >= 2 months (p.22-23)	v <= 50% DEET recommended in all stages of pregnancy and while breastfeeding (p.22-23; 57)
Germany	v 30-50% DEET recommended (p.166-167)	The concentration correlates with the duration of action. There is no further increase in duration of protection beyond a concentration of 50%. (p.167)	v DEET should be applied 20-30 min after the sunscreen (p.165; 167; 175)	v <= 50% DEET approved for children >= 2 years (p.165-167)	v <= 50% DEET recommended in all stages of pregnancy and while breastfeeding (p.167)
Netherlands	v 30-50% DEET recommended (https://lcr.nl/Bestanden/Muggenwering%20op%20reis%20folder%20sept%202018.pdf)	There is no further increase in duration of protection beyond a concentration of 50%. Use DEET 20% 5 times a day; 30% 4 times, 40% 3times and 50% twice a day. (https://lcr.nl/Bestanden/Muggenwering%20op%20reis%20folder%20sept%202018.pdf)	v DEET should be applied after the sunscreen (https://lcr.nl/Bestanden/Muggenwering%20op%20reis%20folder%20sept%202018.pdf)	v <= 50% DEET approved for children >= 2 years, <= 30% DEET for children < 2 years (https://lcr.nl/Bestanden/Muggenwering%20op%20reis%20folder%20sept%202018.pdf)	v <= 30% DEET recommended for pregnancy (https://lcr.nl/Bestanden/Muggenwering%20op%20reis%20folder%20sept%202018.pdf)
Belgium	v 30-50% DEET recommended (https://www.wanda.be/en/a-z-index/deet)	DEET 20 to 30% offers 4-6 hours of protection; DEET 40 to 50% offers approx. 8 hours of protection. (https://www.wanda.be/en/a-z-index/deet)	v DEET should be applied after the sunscreen, 30 or higher SPF sunscreen should be applied to compensate for DEET-induced reduction in SPF (https://www.wanda.be/en/a-z-index/deet)	v 20- 30% DEET approved for children >= 6 months (https://www.wanda.be/en/a-z-index/deet)	v 20-30% DEET recommended for pregnancy (https://www.wanda.be/en/a-z-index/deet)
France	v 30-50% DEET recommended (p.52)	no specification	v DEET should be applied >= 20min after the sunscreen (p.50)	v 30-50% DEET approved for children >= 2 years; 10-20% approved for children < 2 years (p.52)	v <= 50% DEET recommended in all stages of pregnancy and breastfeeding, (p.52)
Spain	v 20-50% DEET recommended (p.71)	The concentration correlates with the duration of action. There is no further increase in duration of protection beyond a concentration of 50%. (p.71) DEET concentration of 20-35% has a duration of protection of 6-12hrs (p.72)	v DEET should be applied 20-30 min after the sunscreen (p.72)	v <= 50% DEET approved for children >= 2 months (p.71; 94-95)	v <= 50% DEET recommended in all stages of pregnancy and also while breastfeeding (p.71; 89)
Italy	v 5->30% DEET; > 30% DEET only in high-risk areas (p.9)	The concentration correlates with the duration of action. There is no further increase in duration of protection beyond a concentration of 30-50% (p.9)	x	v 10% DEET; synthetic repellents approved for children >= 2 years (p.9; 22)	v low doses possible, 10% DEET (p.10; 22)

Table XLVI:

Bite Protection: other repellents

Bite Protection: other repellents	Icaridin/Picaridin	IR3535	Eucalyptus citriodora oil, hydrated, cyclized (PMD)	Oil of citronella
UK	v >= 20% is recommended (p.23)	v less efficiency than DEET (p.23)	v 30% in studies recommended, no information about age limits (p.23)	v unsuitable for malaria areas because of short-lived protection (p.23)
Germany	v >= 20% concentration approved for children >= 6 months (p.167)	v less efficiency for malaria areas; 2nd choice repellent (p.165; 167)	v recommended for children >= 3 years (p.165); products with 5-30% approved for children >= 3 months available (p.166-167)	v limited efficiency for malaria areas (p.165)
Netherlands	v 15% concentration approved for children >= 13 years; not recommended for pregnancy (https://lcr.nl/Bestanden/Muggenwering%20op%20reis%20folder%20sept%202018.pdf)	x	x	x
Belgium	v 20-25% concentration approved for children >= 2 years; can be used during pregnancy (https://www.wanda.be/en/a-z-index/picaridin)	v >= 30% recommended, 20% approved for pregnancy and children >= 6 months (https://www.wanda.be/en/a-z-index/ir3535)	v recommended for children>= 6 months; products 20-25% recommended (https://www.wanda.be/en/a-z-index/citriodiol)	v not recommended (https://www.wanda.be/en/a-z-index/insect-repellents)
France	v >= 20-25% concentration approved for children >= 2 years; 20% concentration can be used during pregnancy (p.52)	v 20% concentration approved for children >= 6 months and during pregnancy, 25-35% approved for >= 2years (p.52)	v <= 20% concentration approved for children >= 6 months and during pregnancy, 25% approved for >= 2years (p.52)	v unsuitable for malaria areas because of short-lived protection (p.50)
Spain	v >= 20% is recommended (p.71)	v less efficiency than DEET, approved for children >= 1 year (p.71; 73)	v recommended for children>= 3 years; products >=20% recommended (p.72-73)	v unsuitable for malaria areas because of short-lived protection (p.72)
Italy	v up to 40-45%; approved for children>= 2years (p.10)	v less toxic (p.10)	v new product, less experience (p.10)	x

Table XLVII:

Bite Protection: insufficient methods

Bite Protection: insufficient methods	UK	Germany	Netherlands	Belgium	France	Spain	Italy
Insufficient methods	v (p.25-26)	v (p.165; 167)	v (p.31)	v (https://www.wanda.be/en/a-z-index/insect-repellents)	v (p.33; 48; 51)	v (p.73)	v (p.10)
Herbal products	v (p.25)	V warning about products of the plant artemisia (p. 172)	x	v warning about products of the plant artemisia or medication as monotherapy (https://www.wanda.be/en/a-z-index/emergency-treatment-for-malaria)	v special warning about products of the plant artemisia or medication as monotherapy (p.33; 48)	x	x
Homeopathy	v (p.25)	x	v (p.31)	x	v (p.50)	v "Ledum palustre" (p.73)	x
Buzzer	v (p.25)	v (p.165)	x	v (https://www.wanda.be/en/a-z-index/insect-repellents)	v (p.50)	v (p.73)	x
Vitamins B1, B12	v (p.25)	v (p.165; 167)	x	v (https://www.wanda.be/en/a-z-index/insect-repellents)	v (p.50)	v (p.73)	v (p.10)
Garlic	v (p.25)	v (p.165;167)	x	x	x	v (p.73)	v (p.10)
Yeast extract	v (p.25)	x	x	x	x	v (p.73)	x
Tea tree oil	v (p.26)	x	x	x	v (p.50)	v (p.73)	x
Essential oil (oil of eucalyptus lemon, Lotus flower, lavender)	v (p.26)	x	x	v (https://www.wanda.be/en/a-z-index/insect-repellents)	v (p.51)	v (p.73)	x

Table XLVIII:

Bite Protection: mechanical barriers

Bite Protection: mechanical barriers	Impregnated mosquito net/ air condition	clothing	Permethrin/pyrethrum
UK	v insecticide-treated mosquito nets /v (p.24)	v impregnated clothes with long sleevesno evidence that the colour of clothing is relevant to mosquitoes (p.24)	v to kill resting mosquitos in a room, to impregnate clothes and mosquito net (p.24)
Germany	v with permethrin treated/ v (p.165)	v impregnated clothes with long sleeves, light colours (p.165-166; 175)	v to impregnate clothes and mosquito net (p.165-166)
Netherlands	v (p.2)/v (leaflet: https://lcr.nl/Bestanden/Malaria%20folder%20antimug%20mrt%202018.pdf)	v impregnated clothes with long sleeves (leaflet: https://lcr.nl/Bestanden/Malaria%20folder%20antimug%20mrt%202018.pdf)	x
Belgium	v insecticide-treated mosquito nets /v (https://www.wanda.be/en/a-z-index/impregnated-mosquito-net/)	v impregnated clothes with long sleeves (https://www.wanda.be/en/a-z-index/mosquito-repellent-measures)	v to impregnate clothes and mosquito net (https://www.wanda.be/en/a-z-index/mosquito-repellent-measures)
France	v insecticide-treated mosquito nets /v (p.50; 51)	v impregnated clothes with long sleeves (p.50)	v/x not special mentioned, but included in the word "insecticides"
Spain	v insecticide-treated mosquito nets (p.16; 70; 72; 89; 95; 102) /v (p.16; 94)	v impregnated clothes with long sleeves, light colours (p.70; 94)	v to impregnate surfaces, clothes and mosquito net (p.70; 72)
Italy	v insecticide-treated mosquito nets (p.6; 10)/v (p.8)	v impregnated clothes with long sleeves, light colours (p.8)	v to impregnate surfaces, clothes and mosquito net (p.6; 10-11))

Appendix D

Table XLVIX:

Chemoprophylaxis (CHP)

Chemoprophylaxis (CHP)	CHP (adults)	CHP (children)	Vomiting antimalarials
UK	v AP, D, M, C+P (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p.38)	v AP (5-< 11 Kg: off-label-use), D (>= 12 years), M (>= 5 kg), C+P (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p.39-40)	v vomiting < 30 min after taking antimalarial: take full dose again (p.52; 106) vomiting 30-60 min after taking antimalarial: take half dose again (p.52; 106))
Germany	v AP, D (off-label-use), M (p.169)	v AP (5-< 11 Kg: off-label-use), D (>= 8 years, off-label-use), M (>= 5 kg) (p.169; 175)	v vomiting < 30 min after taking antimalarial: take full dose again (p.172-173) vomiting 30-60 min after taking antimalarial: AP, AL take full dose again; M take half dose again (p.172-173)
Netherlands	v AP, D, M C+P (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p.5-14; 17)	v AP (5-< 11 Kg: off-label-use), D (8-<12 years: off-label-use), M (5-< 15 kg: off-label-use), C +P (C: <10 kg: off-label-use; chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p. 5-14; 17; 19)	v vomiting < 60 min after taking antimalarial: take full dose again (p.3-4)
Belgium	v AP, D, M (https://www.wanda.be/en/a-z-index/malaria-tablets)	v AP, D, M (https://www.wanda.be/en/a-z-index/malaria-tablets-dose-for-children)	v ESM: AP: vomiting < 3 hours after taking AP: take full dose again (https://www.wanda.be/en/a-z-index/emergency-treatment-for-malaria)
France	v AP, D, M, C (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p.30-32)	v AP (5-< 11 Kg: off-label-use), D (>= 8 years), M (5-<15 kg: off-label-use:), C (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p.30-32)	x
Spain	v AP, D, M, C+P (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p.23-54; 86)	v AP (5-< 11 Kg: off-label-use), D (>= 8 years), M (>= 5 kg), C+P (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p.23-54; 95-96)	v vomiting < 60 min after taking AP: take full dose again (p.108)
Italy	v AP, D, M, C (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p. 12-16)	v AP (>=11 Kg), D (>= 8 years,>= 25kg), M (>= 5 kg), C (chloroquine sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep) (p. 12-16)	x

Table L:

Chemoprophylaxis (AP and M: dosage and recommendations) ***---next page---***

CHP (AP and M: dosage and recommendations)	Atovaquone/proguanil combination preparation (AP) Efficiency Usual amount per tablet of atovaquone/proguanil (mg) Prophylactic regimen Dosage(adults/children)	Mefloquine (M) Efficiency Usual amount per tablet (mg) Prophylactic regimen Dosage (adults/children) with weight adaption
UK	v 5-<11 kg: off-label-use (p.36-38; 40; 68) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; chloroquine-resistant areas; 250/100 and paediatric 62.5/25 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 7 days after leaving 5-< 8kg: 1/2 tablet (62.5/25); off-label-use 8-< 10 kg :3/4 tablet (62.5/25); off-label-use 10-< 20 kg: 1 tablet (62.5/25) 20-< 30 kg: 2 tablets (62.5/25) 30-< 40 kg: 3 tablets (62.5/25) >= 40kg: 1 tablet (250/100)	v for justified medical indication, stringent risk assessment (p.31-34;38-39) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP; chloroquine-resistant areas without the mefloquine resistant areas in Asia 250 weekly, starting 1-3 weeks before entering the malaria area, continuing through the time and for 4 weeks after leaving 6-< 16 kg: 1/4 tablet * 16-< 25 kg: 1/2 tablet 25-< 45 kg: 3/4 tablet >= 45 kg : 1 tablet no further weight adjustment * can be used for>= 5kg->10 kg: 1/4 tablet (p.39)
Germany	v 5-<11 kg: off-label-use (p.168-169; 175) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas 250/100 and paediatric 62.5/25 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 7 days after leaving 5-< 9 kg: 1/2 tablet (62.5/25); off-label-use 9-< 11 kg :3/4 tablet (62.5/25); off-label-use 11-< 21 kg: 1 tablet (62.5/25) 21-< 31 kg: 2 tablet (62.5/25) 31-< 40 kg: 3 tablet (62.5/25) >= 40kg: 1 tablet (250/100)	v not licensed in Germany, but can be imported on-label-use for justified medical indication (p.169-170; 175; 197) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP ; all malaria areas without the mefloquine resistant areas in Asia 250 weekly, starting 1-3 weeks before entering the malaria area, continuing through the time and for 4 weeks after leaving 5-< 9 kg: 1/8 tablet 9-< 15 kg : 1/4 tablet 15-< 19 kg: 1/4 + 1/8 tablet 19-< 31 kg: 1/2 tablet 31-< 45 kg: 3/4 tablet 45-< 90 kg: 1 tablet
Netherlands	v 5-<11 kg: off-label-use (p.4-7;17) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas 250/100 and paediatric 62.5/25 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 7 days after leaving 5-< 9 kg: 1/2 tablet (62.5/25); off-label-use 9-< 11 kg :3/4 tablet (62.5/25); off-label-use 11-< 21 kg: 1 tablet (62.5/25) 21-< 31 kg: 2 tablets (62.5/25) 31-< 40 kg: 3 tablets (62.5/25) >= 40kg: 1 tablet (250/100)	v not licensed in Netherlands for children 5-< 15kg (< 2years): off-label-use (p.4; 10-13; 17); if side effects appear: weekly dosage may be divided in half of the dosage twice a week (p.29) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP; all malaria areas without the mefloquine resistant areas in Asia 250 weekly, starting 3 weeks before entering the malaria area, continuing through the time and for 4 weeks after leaving,* 5-< 11 kg: 1/4 tablet off-label-use 11-< 21 kg : 1/4 tablet ;off-label-use 21-< 31 kg: 1/2 tablet 31-< 45 kg: 3/4 tablet >= 45 kg: 1 tablet ;no further weight adjustment; *One tablet per day for 3 consecutive days, followed by 1 tablet on day 9 and then 1 tablet per week (off-label advice for loading dose for <10 days before arrival in malaria area)
Belgium	v tablets for adults can be cut using a tablet cutter (https://www.wanda.be/en/a-z-index/malaria-tablets-dose-for-children)(https://www.wanda.be/en/a-z-index/malaria-tablet) Pf, Plasmodium non falciparum ; ESM, CHP; all malaria areas 250/100 and paediatric 62.5/25 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 7 days after leaving 5-< 7 kg: 1/2 tablet (62.5/25); 8-< 11 kg :3/4 tablet (62.5/25); 11-< 21 kg: 1 tablet (62.5/25) or 1/4 tablet (250/100) 21-< 31 kg: 2 tablets (62.5/25) or 1/2 tablet (250/100) 31-< 40 kg: 3 tablets (62.5/25) or 3/4 tablet (250/100) >= 40kg: 1 tablet (250/100)	v warning card with the doctor´s contact details should be taken with the patient (https://www.wanda.be/en/a-z-index/malaria-tablets)(https://www.wanda.be/en/a-z-index/malaria-tablets-dose-for-children) Pf, Plasmodium non falciparum; CHP ; all malaria areas without the mefloquine resistant areas in Asia 250 weekly, starting 3 weeks before entering the malaria area, continuing through the time and for 4 weeks after leaving 5-< 11 kg: 1/8 tablet 11-< 21 kg : 1/4 tablet 21-< 31 kg: 1/2 tablet 31-< 45 kg: 3/4 tablet >= 45 kg: 1 tablet no further weight adjustment
France	v 5-<11 kg: off-label-use, first choice medication (p.30-32; 35) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas 250/100 and paediatric 62.5/25 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 7 days after leaving 5-< 8 kg: 1/2 tablet (62.5/25); off-label-use 8-< 11 kg :3/4 tablet (62.5/25); off-label-use 11-< 21 kg: 1 tablet (62.5/25) 21-< 31 kg: 2 tablet (62.5/25) 31-< 40 kg: 3 tablet (62.5/25) >= 40kg: 1 tablet (250/100)	v not licensed in France for children 5- < 15kg: off-label-use; generally on-label-use for justified medical indication (p.30-32; 35) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP; all malaria areas without the mefloquine resistant areas in Asia 250 weekly, starting 2 weeks before entering the malaria area, continuing through the time and for 3 weeks after leaving children dose: 5 mg/kg 5-< 15 kg: 1/8 tablet ;off-label-use 15-19 kg : 1/4 tablet >19-30 kg: 1/2 tablet > 30-45 kg: 3/4tablet > 45 kg: 1 tablet
Spain	v 5-<11 kg: off-label-use (p.76-78; 86) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; chloroquine and mefloquine resistant areas 250/100 and paediatric 62.5/25 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 7 days after leaving 5-< 9 kg: 1/2 tablet (62.5/25); off-label-use 9-< 11 kg :3/4 tablet (62.5/25); off-label-use 11-< 21 kg: 1 tablet (62.5/25) 21-< 31 kg: 2 tablets (62.5/25) 31-< 40 kg: 3 tablets (62.5/25) >= 40kg: 1 tablet (250/100)	v not licensed in Spain, but can be imported on-label-use for justified medical indication (p.78-80; 86) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP; chloroquine-resistant areas without the mefloquine resistant areas in Asia 250 weekly, starting 1 week before entering the malaria area, continuing through the time and for 4 weeks after leaving 5-< 11 kg: 1/8 tablet 11-< 21 kg : 1/4 tablet 21-< 31 kg: 1/2 tablet 31-< 45 kg: 3/4 tablet >= 45 kg: 1 tablet no further weight adjustment
Italy	v children >=11 kg, first choice medication (p. 12-13) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas, chloroquine-resistant areas 250/100 and paediatric 62.5/25 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 7 days after leaving 11-< 21 kg: 1 tablet (62.5/25) 21-< 31 kg: 2 tablets (62.5/25) 31-< 40 kg: 3 tablets (62.5/25) >= 40kg: 1 tablet (250/100)	v approved for children from >=5kg (p.14-15; 28) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); C; all malaria areas without the mefloquine resistant areas in Asia 250 weekly, starting 1 week before entering the malaria area, continuing through the time and for 4 weeks after leaving children dose: 5 mg/kg adults: 1 tablet weight adjustment: >90- 120 kg: 1.5 tablets; > 120 kg: 2 tablets (p.28)

Table LI:

Chemoprophylaxis (D, C and P: dosage and recommendations) ***---next page---***

CHP (D, C and P: dosage and recommendations)	Doxycycline (D) Efficiency Usual amount per tablet (mg) Prophylactic regimen Dosage(adults/children)	Chloroquine Efficiency Usual amount per tablet (base) Prophylactic regimen Dosage (adults/children)	Proguanil (P) Efficiency Usual amount per tablet (mg) Prophylactic regimen Dosage (adults/children) with weight adaption
UK	v approved for children >= 12 years (p.34-36; 38-39) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP; chloroquine-resistant areas 100 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 4 weeks after leaving 25-< 45 kg: 1 tablet* (approved for children > 12 years) >= 45 kg: 1 tablet dose adjustment: 2 tablets, if simultaneously co-medication carbamazepine, phenytoin (p.36) *The adult dose is necessary when doxycycline is only available in capsule form and 3/4 is not feasible	v contraindication: epilepsy, psoriasis, myasthenia gravis, retinopathy while long term use (p.29-30; 38-40) Pf, Plasmodium non falciparum (not against hypnozoite episodes); CHP; chloroquine-sensitive areas: Central America north of Panama Canal and Haiti and Dom. Rep. 155 base weekly, starting 1 week before entering the malaria area, continuing through the time and for 4 weeks after leaving, only taken in co-medication with proguanil <=6 kg: 1/4 tablet 6-< 10 kg: 1/2 tablet 10-< 16 kg:3/4 tablet 16-< 25 kg: 1 tablet 25-< 45 kg: 1 1/2 tablets >= 45kg: 2 tablets	v (p.31; 38-39) Pf, Plasmodium non falciparum (not against hypnozoite episodes); CHP; chloroquine-sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep. 100 daily, starting 1 week before entering the malaria area, continuing through the time and for 4 weeks after leaving, only taken in co-medication with chloroquine <=6 kg 1/4 tablet 6-< 10 kg: 1/2 tablet 10-< 16 kg:3/4 tablet 16-< 25 kg: 1 tablet 25-< 45 kg: 1 1/2 tablets >= 45 kg: 2 tablets
Germany	v off-label-use, not registered in Germany for malaria; approved for children >= 8 years (p.169-170; 175) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP; all malaria areas 100 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 4 weeks after leaving 25-< 36 kg: 1/2 tablet (approved for children >= 8 years) 36-< 50 kg: 3/4 tablet >= 50 kg: 1 tablet dose adjustment: 2 tablets, if simultaneously co-medication rifampicin, barbiturates, carbamazepine, diphenylhydantoin, or chronic alcohol abuse is taken with an enzyme induction (p.170; 180)	v not recommended anymore (p.172)	x
Netherlands	v for children from 8-11 years: off-label-use (p.4; 8-10; 17) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP; all malaria areas 100 daily, starting on the day of arrival in the malaria area, continuing through the time and for 4 weeks after leaving < 45 kg: 1/2-1 tablet or 2 mg/ kg (approved for children >= 12 years; children 8-11 years: off label-use) >= 45 kg: 1 tablet no further weight adjustment	v <10kg: off-label-use; contraindication: epilepsy, psoriasis, myasthenia gravis, retinopathy while long term use (p.4; 7-8; 17) Pf, Plasmodium non falciparum (not against hypnozoite episodes); CHP; chloroquine-sensitive areas: Central America north of Panama Canal and Haiti and Dom. Rep. 100mg/ base weekly: starting on the day of arrival in the malaria area daily for 2 days, then after theses 2 days once a week (off-label-advice), continuing through the time and for 4 weeks after leaving, only taken in co-medication with proguanil < 5 kg 1/4 tablet or 5 mg/kg; off-label-use 5-< 11 kg: 1/2 tablet or 50 mg; off-label-use 11-< 21 kg: 1 tablet or 100 mg 21-< 30 kg: 1 1/2 tablets or 150 mg 31-< 45 kg: 2 1/2 tablets or 250 mg >= 45kg: 3 tablets or 300 mg	v not licensed in Netherlands, but can be imported on-label-use (p.4; 13-14; 17) Pf, Plasmodium non falciparum (not against hypnozoite episodes); CHP; chloroquine-sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep. 100 daily, starting on the day of arrival in the malaria area continuing through the time and for 4 weeks after leaving, only taken in co-medication with chloroquine < 5 kg: 1/4 tablet or 25 mg 5-< 11 kg: 1/4 tablet or 25 mg 11-< 21 kg:1/2 tablet or 50 mg 21-< 31 kg: 2x 1/2 tablet or 100 mg 31-< 45 kg: 2x 3/4 tablets or 150 mg >= 45 kg: 2x1 tablet or 200 mg; adjustment of dosages: dosage should be halved at clearance 30-60 ml/min (p.13)
Belgium	v approved for children >= 8 years (https://www.wanda.be/en/a-z-index/malaria-tablets-dose-for-children(https://www.wanda.be/en/a-z-index/malaria-tablets) Pf, Plasmodium non falciparum ; CHP; all malaria areas; 100 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 4 weeks after leaving 1,5 mg/ kg to a maximum of 100 mg per day (approved for children >=8 years) adults: 1 tablet no further weight adjustment	x	x
France	v approved for children >= 8 years; first choice medication (p.30-32; 35) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria) ; CHP; all malaria areas; 100 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 4 weeks after leaving < 40 kg: 50mg (approved for children >= 8 years) >= 40 kg: 100 mg adults: 1 tablet no further weight adjustment	v contraindicated: pregnancy, breastfeeding; after treatment 8 months contraception (p.31-32; 35; 74) Pf, Plasmodium non falciparum (not against hypnozoite episodes); CHP; chloroquine-sensitive areas: Central America north of Panama Canal and Haiti and Dom. Rep 100mg daily, starting on the day of arrival in the malaria area, continuing through the time and for 4 weeks after leaving, children dose: 1,7mg/kg (< 50 kg) <10 kg: 12,5 mg >=10-16 kg: 25 mg >16-33 kg: 50mg >33-45 kg: 75mg >45kg: 100mg adults: 1 tablet (>= 50 kg)	x
Spain	v approved for children >= 8 years (p.81-82; 86) Pf (multiresistant), Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); CHP; chloroquine and mefloquine resistant areas 100 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 4 weeks after leaving 1,5-2 mg/ kg (approved for children >9 years) adults: 1 tablet no further weight adjustment	v contraindication: epilepsy, psoriasis, retinopathy while long term use, therapy with gold salt (p.82-84; 86) Pf, Plasmodium non falciparum (not against hypnozoite episodes); CHP; chloroquine-sensitive areas 150 base weekly, starting 1 week before entering the malaria area, continuing through the time and for 4 weeks after leaving, only taken in co-medication with proguanil < 36 kg: 5mg/kg 36-< 46 kg: 1 1/2 tablets 46-< 61 kg: 2 tablets 61-75 kg: 2 1/2 tablets > 75kg: 3 tablets*	v not licensed in Spain, but can be imported (p.84-85; 86) Pf, Plasmodium non falciparum (not against hypnozoite episodes); CHP; chloroquine-sensitive areas: Central America north of Panama Canal and Haiti & Dom. Rep. 100 daily, starting 1 day before entering the malaria area, continuing through the time and for 4 weeks after leaving, only taken in co-medication with chloroquine < 55 kg: 1 tablet >55 kg: 2 tablets
Italy	v off-label-use, not registered in Italy for malaria, approved for children >8 years (p.13-14; 25) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria; CHP; all malaria areas, chloroquine-resistant areas 100 daily, starting 1-2 days before entering the malaria area, continuing through the time and for 4 weeks after leaving 1,5mg/ kg (approved for children >8 years and >= 25 kg) adults: 1 tablet	v contraindication: epilepsy, psoriasis, retinopathy while long term use (p.15-16) Pf, Plasmodium non falciparum (not against hypnozoite episodes); CHP; chloroquine-sensitive areas (Central America and Middle East) 150 base weekly, starting 1 -2 weeks before entering the malaria area, continuing through the time and for 4 weeks after leaving children dose: 5mg/ kg >45 kg: 2 tablets	v not licensed in Italy and therefore not recommended (p.16; 37)

Table LII:

Side effects, CYP 450, Interactions, Contraindications, Precautions: AP

Side effects, CYP450, Interactions, Contraindications, Cautions: AP	UK	G	NL	B	F	E	IT
Side-effects				x	x		
headache	v	v	v			v	v
gastrointestinal upsets	v (p.38)	v	v			v	v (rarely hepatotoxicity)
Rarely: palpitations, dizziness, insomnia, unusual dreams	x	v	v			v	x
depression	x	v (p.168)	v (p.6)			x	x
mouth ulcers	x	x	v			v (p.77)	x
hair loss	x	x	*v (https://lcr.nl/Bestanden/Malaria%20folder%20profylaxe%20mrt%202018.pdf)*			x	x (p.13)
CYP 450	*atovaquone inhibits CYP 3A4 (p.62; 83)*	*v (p.179)*	v resistance because of varying bioavailability (p.4), *P is converted in the liver mainly by CYP2C19, but also by CYP3A, to the active cycloguanil. (p.30)*	x	x	x	*atovaquone inhibits CYP 3A4, therefore enhance anticoagulation (DOC) (p.26)*
Interactions				x			
proguanil:	**proguanil:**	**proguanil:**	**proguanil:**		**proguanil:**	**proguanil:**	***proguanil:***
warfarin (anticoagulant effect of warfarin ↑)	v	v	v		v vitamin k anatgonist, check INR (p.32)	v	*v (p. 25)*
pyrimethamine (antifolate effect ↑)	v (p.31)	x	x		x	x	*x*
PI´s and ritonavir may inhibit P metabolism to cycloguanil (active form) (effect of P↓)	x	x	*v (p.30)*		x	*v (p.98)*	*v (p.26)*
atovaquone:	**atovaquone:**	**atovaquone:**	**atovaquone:**		**atovaquone:**	**atovaquone:**	***atovaquone:***
rifabutin; rifampicin (level of atovaquone ↓);	v	v	v		x	v	*x*
NNRTI, protease inhibitors (level of atovaquone ↓);	v	*v (p179)*	v (interactions, but no clinical relevance)		x	v	*v (p.26)*
tetracycline (level of atovaquone ↓; avoid concomitants)	v	v	x		x	v	*x*
metoclopramide (level of atovaquone ↓; avoid concomitants)	v	v (p.169)	v (p.6)		x	v	*x*
antiretroviral drugs (interaction)	v (p. 37)	x	*v (may increase the level of zidovudine) (p.30)*		x	v	*x*
oral typhoid vaccine; distance of 3 days before starting prophylaxis	x	x	x		x	v	*x*
aurothioglucose (gold salts) contraindicated	x	x	x		x	v	*x*
trimethoprim-sulfamethoxazole (level of trimethoprim-sulfamethoxazole↓)	x	x	x		x	v	*x*
antacids and antidiarrheals 2-3 hours distance (absorption of AP↓)	x	x	x		x	v (p.78)	*x*
Contraindications				x			
allergry to proguanil or atovaquone;	v	x	x		x	x	x
pregnancy (use only in 2nd and 3rd trimester)	v *add 5mg folic acid* (p.37; *59*)	x	v pregnancy all trimesters		x	v	v pregnancy all trimesters
breastfeeding (use only if no alternative antimalarial);	v	x	v possible use for breastfeeding mothers with children >=5kg		x	v	v contraindicated breastfeeding
diarrhoea or vomiting	v (p.37)	x	x		x	x	x
renal impairment: GFR of less than 30mL/ minute	v (p.37;65)	*v + dialysis (p.178)*	v		x	v	v (p.13) *+ dialysis (p.27)*
children <5kg	v	v	v (p.5-6)		v (p.31-32)	v (p.77)	v children < 11kg (p.13)
aurothioglucose (gold salts) contraindicated	x	x	x		x	v (p.78)	x
Cautions				x			
pregnancy (considered under strict risk assessment)	x	*v (p.176)*	x		v (p.31-32)	x	x
renal impairment: GFR of less than 30mL/ minute	x	*x*	x		x	v	x
hepatic impairment	x	*x*	x		x	v (p.77)	x

Table LIII:

Side effects, CYP 450, Interactions, Contraindications, Precautions: M

Side effects, CYP450, Interactions, Contraindications, Cautions: M	UK	G	NL	B	F	E	IT
Side-effects				x			
neuropsychiatric problems	v	v	v		v	v	v
vestibular disorders	v (p.34)	x (p. 170)	v		v(p.32)	v	v
nausea, vomiting	x	x	v (p.11)		x	v (p.79)	v (p.15)
CYP 450	substrate of CYP 3A4; *also inhibits CYP 3A4* (p.34; *61; 83*)	v depenent on CYP 3A4 metabolism (p.170)	x	x	x	M inhibits CYP3A4 (p.80)	*M inhibits CYP 3A4, therefore enhance anticoagulation (DOC) (p.26)*
Interactions				x			
use with halofantrine contraindicated (p.33)	v	x	v		x	v + chloroquine, lumefantrine	*x*
antiepileptics (anticonvulsant effect of antiepileptics ↓)	v	v	v		x	v	*x*
cardiac conducted drugs (arrhythmias ↑)	v	v	v		x	v	*v (p.27)*
ritonavir (level of ritonavir↓)	v	x	x		x	*v (p.98)*	*x*
inhibitors of CYP3A4: itraconazole (level of M ↑)	v	v (p.170)	x		x	v	*x*
inducers of CYP3A4: rifampicine ; NNRTI, PI (level of M ↓)	v (p.34; *64*)	v (p.170)	v (p.12) *(no interaction between PI´s and M) (p.30)*		x	*v (p.98)*	*v (p.26)*
substrates of CYP 3A4 :DOCs: apixaban; rivaroxaban (level of DOCs, bleeding ↑)	*v (p.61; 83)*	*v (p.179)*	v		x	v	*v (p.26)*
antidiabetics (check blood sugar)	x	v	x		x	x	*x*
vitamin K antagonists/ coumarins(check INR, anticoagulation effect ↑)	x	v (p.170)	v		v (p.32)	v	*v (p.25)*
rabies vaccine, oral live typhoid vaccine (antibody response possibly↓)	x	x	v (p.12)		x	v (p.80)	*x*
aurothioglucose (gold salts) contraindicated	x	x	x		x	v	*x*
alcohol: caution 48 hours later	x	x	x		x	v	*x*
antiemetics: ondansetron	x	x	x		x	v	*x*
triptans: zolmitriptan	x	x	x		x	v	*x*
concomitant use with isotretinoin: neuropsychiatric side effects and hepatotoxicity	x	x	x		x	v (p.80)	*x*
Contraindications				x			
allergy to mefloquine, quinine;	v	x	v		x	v	v
epilepsy, psychiatric disorder	v	v (psychiatric and many neurological conditions)	v		v (p.32)	v	v
blackwater fever	v	x	v		x	x	x
use with halofantrine	v (p.32)	x (p.170)	x		x	x	x
children< 5 kg	x	x	v		x	x	x
severe hepatic impairment	x	x	v (p. 10-11)		x	v (p.79)	x
aurothioglucose (gold salts) contraindicated	x	x	x		x	v (p.80)	x
Long QT syndrome	x	x	x		x	v (p.86)	x
Cautions				x			
cardiac conduction;	v	v	x		x	v	*v (p.27)*
children < 5 kg	v (p.33)	x	x		x	v (p.79)	v
travellers with activities requiring unimpaired attention and fine motor skills	x	v (p.170)	v		v (p.32)	v (p.80)	v
pregnancy first trimester possible to take but caution	*v (p.58)*	x	v		x	x	v pregnancy first trimester possible but caution (p.15)
NNRTI, PI	*v (p.64)*	x	x (p.11)		x	x	x
renal impairment no dosage adjustment	*x*	x	x		x	v	x
severe hepatic impairment	*x*	x	x		x	v (p.79)	x

Table LIV:

Side effects, CYP 450, Interactions, Contraindications, Precautions: D

Side effects, CYP450, Interactions, Contraindications, Cautions: D	UK	G	NL	B	F	E	IT
Side-effects				x			
oesophagigis and gastritis	v	v (oesophageal ulcers and nausea)	v		x	x	v
photosensitivity	v	v	v		v (p.31-32)	v	v
vaginal candidiasis	v (p.36)	v	v		x	v	v
ndigestion	x	v	x		x	v (p.81)	v
elevated liver enzymes	x	v (p.169)	x (p.9)		x	x	x (p.14)
Interactions				x			
carbamazepine, phenytoin (metabolism of D ↑)	v increase the dose of D to 200mg (p.35, 89)	v + rifampicin, barbiturates, chronic alcohol abuse; increase the dose of D to 200mg	v (nothing said about increase of dosage of D)		x	v (nothing mentioned about dosage)	*v (dosage must be adjusted for carbamazepine, phenytoin, barbiturates (metabolism of D ↑)*
coumarins (anticoagulant effect of coumarins ↑)	v	v	v		v (p.32)	v	*v (p.25)*
ciclosporin (level of ciclosporin ↑)	v	*v + other calcineurin inhibitors (pimecrolimus, tacrolimus) (p.179)*	x		x	x	*x*
oral typhoid vaccine (efficiency of vaccine ↓)	v (p.36)	x	x		x	v	*x*
insulin, sulphonyl urea derivatives (effect of insulin↑)	x	v	x		x	x	*x*
contraceptives (effect of contraceptives ↓)	x	v (p.170)	x		x	v	*x*
antacids and iron-containing medicines (effect of D↓)	x	x	v		x	v	*x*
didanosine (RTI) D should be taken 2 hours before didanosine	x	x	v (p.9)		x	v	*x*
retinoids (isotretinoin)risk of pseudotumor cerebri, not recommended	x	x	x		x	v	*x*
rifampicin (level of D↓)	x	x	x		x	v	*x*
alcohol consumption (level of D↑)	x	x	x		x	v	*x*
methotrexate(toxicity of methotrexate ↑)	x	x	x		x	v (p.82)	*x*
Contraindications				x			
allergy to tetracyclines	v	x	v		x	v	v
children < 12 years/8 years	v < 12 years	v < 8 years;	v < 8 years		v < 8 years (p.31-32)	v < 8 years	v < 8 years
pregnancy after 15th week of gestation; breastfeeding	v(p.35)	v pregnancy (mostly second half of pregnancy); breastfeeding (p.170)	v pregnancy (all trimesters); breastfeeding		v pregnancy (2nd and 3rd trimester); breastfeeding (p.31-32)	v pregnancy; breastfeeding (p.82)	v pregnancy (all trimesters); breastfeeding
porphyriasis	*v (p.66)*	x	x		x	x	x
severe hepatic and renal impairment	x	x	v (p.9)		x	x	v (p.14)
Cautions				x			
hepatic impairment	v	x	v		x	v	v (p.27)
renal impairment;	v	x	v		x	v (p.82)	v (dosage adjustment of D necessary) (p.27)
myasthenia gravis;	v	x	x		x	x	x
lupus erythematosus	v (p.35)	x	x (p.9)		x	x	x
pregnancy 1st trimester	v (p.35)	v (p.170)	x		v (p.31-32)	x	x

Table LV:

Side effects, CYP 450, Interactions, Contraindications, Precautions: C

Side effects, CYP450, Interactions, Contraindications, Cautions: C	UK	G	NL	B	F	E	IT
Side-effects		not recommended/mentioned		x	x		
gastrointestinal disturbances	v		v			v	v
headache	v		v			v	v
convulsions	v		v			x	v
skin reactions	v (p.30)		x			v	v
hypoglycaemia	x		v (p.8)			x	x (p.16)
psoriatic crisis	x		x			v	x
possible hearing loss	x		x			v	x
retinopathy with accumulated doses	x		x			v (p.83)	x
CYP 450	x	not recommended/mentioned	*Chloroquine is approximately 50% metabolised by the cytochrome P450 system as substrate; CYP3A and CYP2D6 are probably involved.(p.30)*	x	x	x	*x*
Interactions		not recommended/mentioned		x	x		
concomitant use with amiodarone contraindicated	v		x			x	*x*
ciclosporin (toxicity of ciclosporin ↑)	v		x			v	*v (p.27)*
digoxin (concentration of digoxin↑)	v		x			x	*x*
mefloquine (convulsions ↑)	v		x			x	*x*
moxifloxacin (ventricular arrhythmias ↑)	v		x			x	*x*
rabies vaccine (antibody response ↓)	v (p.30)		v			x	*x*
HIV medication (interactions, but no clinical relevance)	x		v (p.8)			v	*v (p.26)*
antacids and antidiarrheals (level of C↓)	x		x			v	*x*
antipsychotics, antidepressants (risk of long QT syndrome ↑)	x		x			v	*x*
antibiotics: quinolones, telithromycin, clarithromycin (risk of long QT↑)	x		x			v	*x*
metronidazole not recommended	x		x			v	*x*
cimetidine: ranitidine or omeprazole is recommended instead	x		x			v	*x*
levothyroxine (effect of levothyroxine↓)	x		x			v	*x*
ampicillin, praziquantel (effect of C↓)	x		x			v	*x*
aurothioglucose (gold salts) contraindicated	x		x			v (p.84)	*x*
ritonavir (level of ritonavir↓)	x		x			*v (p.98)*	*x*
Contraindications		not recommended/mentioned		x			
allergy to chloroquine;	v		v		x	x	v
concomitant use with amiodarone	v (p.29)		x		v (risk of cardiotoxicity) (p.32)	x	x
epilepsy	*v (p.62)*		x		x	v	v
retinopathy	x		v		x	v	v (p.16)
myasthenia gravis	x		v (p.7)		x	x	x
pregnancy, breastfeeding; after treatment 8 months contraception	x		x		v (p.31-32)	x	x
psoriasis	x		x		x	v	x
aurothioglucose (gold salts) contraindicated	x		x		x	v (p.83)	x
liver failure	x		x		x	x	v (p.16)
Cautions		not recommended/mentioned		x			
epilepsy	v		v		x	x	x
psoriasis, porphyria	v		v		x	x	x
myasthenia gravis	v		x		x	x	x
hypoglycaemia,	v		x		x	x	x
retinopathy risk	v (p.31)		x		x	x	x
possible interaction with warfarin	*v (p.60)*		x		x	x	*x (no interaction with warfarin) (p.25)*
risk of haemolysis in some G6PD-deficient individuals in treatment dose	*v (* p.63)		x		x	x	*v (p.26)*
renal impairment: dose reduction in severe stage	*v (p.65)*		x (p.7)		x	v (no dose adjustment necessary if GFR >10 ml/min)	*v (severe renal impairment: reduction of dosage of C) (p.27)*
risk of cardiotoxicity	x		x		v (p.32)	x	x
hepatic impairment: no administration in severe hepatic insufficiency	x		x		x	v (p.83)	x
neuropathy	x		x		x	x	v (p.16)

Table LVI:

Side effects, CYP 450, Interactions, Contraindications, Precautions: P

Side effects, CYP450, Interactions, Contraindications, Cautions: P	UK	G	NL	B	F	E	IT
Side-effects				x	x		not recommended/mentioned
gastric intolerance and diarrhoea	v	v (p.168)	x			v	
mouth ulcers	v (p.31)	x	v			v	
severe renal impairment (clearance < 30 ml/min)	x	x	v (p.13)			x	
hair loss	x	x	v (p.14)			v (p.85)	
CYP 450	x	x	*P is converted in the liver mainly by CYP2C19, but also by CYP3A, to the active cycloguanil. (p.30)*	x	x	x	not recommended/mentioned
Interactions				x	x		not recommended/mentioned
warfarin (anticoagulant effect of warfarin ↑)	v	v	v			v	
pyrimethamine (antifolate effect ↑)	v (p.31)	v (p.169)	x			x	
HIV medication (interactions, but no clinical relevance)	x	x	v			v	
oral live typhoid vaccine (antibody response possibly↓)	x	x	v (p.14)			v	
PI´s and ritonavir may inhibit P metabolism to cycloguanil (active form) (effect of P↓)	x	x	*v (p.30)*			x	
aurothioglucose (gold salts): increases risk of blood dyscrasias	x	x	*x*			v (p.85)	
Contraindications		x		x	x		not recommended/mentioned
allergy to proguanil	v (p.31)		x			x	
dialysis	*v (p.65)*		v severe renal impairment (clearance < 30 ml/min) (p.13)			v (p.85)	
aurothioglucose (gold salts): increases risk of blood dyscrasias	x		x			v (p.85)	
Cautions		x		x	x		not recommended/mentioned
renal impairment	v		renal impairment (clearance 30-60 ml/min), the dosage must be halved (p.13)			renal impairment no adminstration GFR of less than 30mL/ min	
pregnancy	v (p.31)		x			x	
hepatic impairment	x		x			v (p.85)	

Table LVII:

Chemoprophylaxis (*non-falciparum* species*)*

CP (Plasmodium non falciparum)	Primaquine (Plasmodium vivax and ovale)	Plasmodium malariae	Plasmodium knowlesi
UK	v not licensed in the UK and for the routine use for (terminal) prophylaxis against hypnozoites and liver stage schizonts, only occasionally used for terminal prophylaxis; contraindicated: G6PD-deficiency (p.20; 28; 63; 89)	v P. knowlesi morphological similar to P. malariae (p. 18)	v form of malaria from South East Asia; P. knowlesi morphological similar to P. malariae; short cycle time of only 24 hours: high risk of rapidly developing complex malaria (p. 18); P. knowlesi is sensitive to chloroquine (p.19)
Germany	v not licensed in Germany, but can be imported; used for terminal prophylaxis (antirelaps therapy) against hypnozoites and the liver stage schizonts; contraindicated: G6PD-deficiency, lupus erythematosus, rheumatoid arthritis (p.171-172)	v in blood films P. knowlesi can easily be confused with P. malariae (p.173)	v form of malaria from South East Asia; in blood films P. knowlesi can easily be confused with P. malariae; short cycle time of only 24 hours: high risk of rapidly developing complex malaria (p.173-174)
Netherlands	v not licensed in Netherlands; dosage (btw.0,5-30mg Base/kg): used for terminal prophylaxis (p.31-32); cycle of Pv and Po: up to 5 years after prophylaxis symptoms may return, the hypnozoites are not destroyed by the other chemoprophylactics; contraindicated: G6PD-deficiency (p.27; 28; 31-32)	v benign infection, malaria quartana due to P. malariae, the least frequent form, and malaria tropica due to P. falciparum are both completely prevented by chemoprophylaxis. (p.1, 27-28)	v form of malaria from South East Asia (p.1; 27)
Belgium	x	x	x
France	v not licensed in France, prescription needs an approval with registration by the Agence nationale de sécurité des médicaments et des produits de santé (ANSM); recommended for treatment after first diagnose of Pv or Po	v P. malariae is rare; symptoms occur often several years after the stay and are not always clear; benign infection (p.29)	v form of malaria from South East Asia; P. knowlesi is moderate sensitive to C, less sensitive to M (p.29)
Spain	v big chapter about the development of malaria tertiana and use of primaquine; in Spain primaquine is not licensed for CP, only for treatment; 30 mg base per day in adults and 0.5 mg base/kg per day in children for 14 days; contraindicated: G6PD-deficiency, pregnancy and breastfeeding, children <= 6 months (p.76; 90; 111-115)	v P. malariae is very rare, limited experience (p.114)	v form of malaria from South East Asia; P. knowlesi is sensitive to artemisinin, moderate sensitive to C, less sensitive to M (p.114-115)
Italy	v not licensed in Italy and therefore not recommended; dosage (30mg/day for adults); used for prophylaxis for Pv, Po, also for Pf; contraindicated: G6PD-deficiency, pregnancy and breastfeeding (p.2;7; 37); CP: not recommended in areas with exclusively Pv a/o Po (p.7; 12)	v one report about chloroquine resistance of P. malariae (p.2-3)	v form of malaria from South East Asia, reports from chloroquine resistance in South East Asia (p.2; 35)

Tables LVIII:

Side effects, CYP 450, Interactions, Contraindications, Precautions: Primaquine

Side effects, CYP450, Interactions, Contraindications, Cautions: Primaquine	UK	G	NL	B	F	E	IT
Side-effects				x	x		
haemolysis in G6PD-deficiency	v (p.28; 62-63)	v	*v (p.32)*			v (p.76)	*v (p.37)*
gastrointestinal disturbances	x	v	*x*			*v (p.114)*	*x*
skin itching	x	v	*x*			x	*x*
headache	x	v (p.172)	*x*			x	*x*
Interactions	not mentioned		x	x	x	x	x
haemolytic drugs		v (p.172)					
Contraindications				x	x		
G6PD-deficiency (haemolysis)	v (p.28; 62-63)	v	*v (p.32)*			v (p.76)	*v (p.37)*
rheumatoid arthritis	x	v	*x*			x	*x*
lupus erythematosus,	x	v	*x*			x	*x*
use of potentially haemolytic drugs	x	v (p. 172)	*x*			x	*v (p.37)*
pregnancy/ breastfeeding	x	x	*x*			*v (p.114)*	*v (p.37)*
children < 6 months	x	x	*x*			*v* (p.114)	
Cautions	not mentioned		x	x	x	x	x
pregnancy		v (p.172)					

Appendix E

Table LVIX:

ESM: Emergency standby treatment

Emergency standby treatment	When to use emergency standby medication (ESM)
UK	v fever>= 38°C, which last >= 24 hours after >= 8 days stay in malaria area (p.105) medical attention >= 24 hours recommended for those taking CHP and visting remote areas, the agent of ESM should be different from the drugs used for CHP (p.51-52) complete ESM course and recommence CHP 1 week after taking the first treatment dose. if quinine is used as ESM, mefloquine should be resumed at least 12 hours after the last treatment dose (p.51-53; 105-106)
Germany	v fever>= 38°C, which last >= 24 hours after >= 7 days stay in malaria area medical attention >= 48 hours in moderate risk areas as initial treatment course (p.168; 173-174)
Netherlands	v fever>= 38,5°C, which last >= 24 hours (p.2) after >= 7days stay in malaria area medical attention >= 24 hours in moderate risk areas as initial treatment course (p.3; https://lcr.nl/Bestanden/Malaria%20folder%20nb%20mrt%202018.pdf)
Belgium	v fever>= 38°C, which last >= 24 hours after >= 7 days stay in malaria area with low to moderate risk medical attention >= 24 hours in moderate risk areas as initial treatment course (https://www.wanda.be/en/a-z-index/emergency-treatment-for-malaria)
France	v fever>= 38°C, which last >= 12 hours after >= 7 days stay in malaria area medical attention >= 12 hours should remain the exception, recommended for those visiting remote areas, the agent of ESM should be different from the drugs may be used for CHP (p.48)
Spain	v fever>= 38°C, which last >= 24 hours after >= 7 days stay in malaria area medical attention >= 24 hours in moderate risk areas as initial treatment course (p.19; 106) ((VFR) in high-risk areas: complete ESM/ treatment course and recommence CHP 1 week after taking the first treatment dose, if quinine is used as ESM, mefloquine should be resumed at least 12 hours after the last treatment dose (p.102)
Italy	v fever>= 37,5°C (p.6), which last >= 24 hours after >= 7 days stay in malaria area medical attention >= 24 hours (p.2) in moderate risk areas (p.19) in high-risk areas: complete ESM/ treatment course and recommence CHP 1 week after taking the first treatment dose (p.19)

Table LX:

ESM (AL, AP and DP: dosage and recommendations) ***---next page---***

ESM (AL, AP and DP: dosage and recommendations)	**Artemether/lumefantrine combination preparation (AL)** **Situation of use** **Usual amount per tablet of artemether/lumefantrine (mg)** **Standby treatment regimen** **Dosage (adults/children)**	**Atovaquone/proguanil combination preparation (AP)** **Situation of use** **Usual amount per tablet of atovaquone/proguanil (mg)** **Standby treatment regimen** **Dosage (adults/children)**	**Dihydroartemisinin-piperaquine combination preparation (DP)** **Situation of use** **Usual amount per tablet of dihydroartemisinin-piperaquine (mg)** **Standby treatment regimen** **Dosage (adults/children)**
UK	v no interactions are mentioned in this guideline, appears only in a table (p.53; 105) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; 2nd and 3rd trimester of pregnancy; all malaria areas, 20/120 dose of tablets given initially, followed by 5 further doses each given at 8, 24,36,48 and 60 hours adults: 4 tablets children dose: not mentioned	v (p.36-38; 53; 105) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas 4 tablets as a single dose on each of 3 consecutive days 250/100 and paediatric 62.5/25 adults: 4 tablets (250/100) children dose: not mentioned	v not recommended and not licensed (p.52)
Germany	v (p.169;171; 176) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; all malaria areas 20/120 dose of tablets given initially, followed by 5 further doses each given at 8, 24,36,48 and 60 hours 5-< 15 kg: 1 tablet 15-< 25 kg: 2 tablets 25-< 35 kg: 3 tablets >= 35 kg: 4 tablets	v (p.168-169; 176) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 250/100 and paediatric 62.5/25 5-< 9 kg: 2 tablets (62.5/25); 9-< 11 kg :3 tablets (62.5/25) 11-< 21 kg: 1 tablet (250/100) 21-< 31 kg: 2 tablets (250/100) 31-40 kg: 3 tablets (250/100) > 40kg: 4 tablets (250/100)	v not recommended (p.171)
Netherlands	v (p.3;14-17) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; all malaria areas 20/120 dose of tablets given initially, followed by 5 further doses each given at 8, 24,36,48 and 60 hours 15-< 25 kg : 2 tablets 25-< 35 kg: 3 tablet >= 35 kg: 4 tablets children < 5 years: CHP instead of ESM in moderate risk areas (p.17)	v (p.3;5; 16- 17) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 250/100 11-< 21 kg: 1 tablet (250/100) 21-< 31 kg: 2 tablets (250/100) 31-41 kg: 3 tablets (250/100) >= 41kg: 4 tablets (250/100) children < 5 years: CHP instead of ESM in moderate risk areas (p.17)	x
Belgium	v children dose: not mentioned, only for children >= 12 years (https://www.wanda.be/en/a-z-index/emergency-treatment-for-malaria) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; all malaria areas 20/120 dose of tablets given initially, followed by 5 further doses each given at 8, 24,36,48 and 60 hours adults and children >= 12 years: and >= 35 kg: 4 tablets	v first choice of ESM; children dose: not mentioned (https://www.wanda.be/en/a-z-index/emergency-treatment-for-malaria) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 250/100 and paediatric 62.5/25 children: adjusted dose adults: 4 tablets (250/100)	v children dose: not mentioned (https://www.wanda.be/en/a-z-index/emergency-treatment-for-malaria) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 320/40 and paediatric 160/20 adults: 36-< 75 kg: 3 tablets (320/40) 75- 100 kg: 4 tablets (320/40)
France	v children dose: not mentioned, because it should only be an exception to use it for children; first choice (p.48-49) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; all malaria areas 20/120 dose of tablets given initially, followed by 5 further doses each given at 8, 24,36,48 and 60 hours adults: >= 35 kg: 4 tablets	v children dose: not mentioned, because it should only be an exception to use it for children; second choice (p.48-49) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 250/100 and (paediatric 62.5/25) adults: > 40kg: 4 tablets (250/100)	v children dose: not mentioned, because it should only be an exception to use it for children; first choice (p.48-49) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 320/40 and paediatric 160/20 adults: 36-< 75 kg: 3 tablets (320/40) >=75 kg: 4 tablets (320/40)
Spain	v not licensed in Spain, but can be imported (p.108-109) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; all malaria areas 20/120 dose of tablets given initially, followed by 5 further doses each given at 8, 24,36,48 and 60 hours 5-< 15 kg: 1 tablet 15-< 25 kg : 2 tablets 25-< 35 kg: 3 tablet >= 35 kg: 4 tablets	v first choice in Spain (p.108-109) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 250/100 and paediatric 62.5/25 5-< 9 kg: 2 tablets (62.5/25); 9-< 11 kg :3 tablets (62.5/25) 11-< 21 kg: 1 tablet (250/100) 21-< 31 kg: 2 tablets (250/100) 31-40 kg: 3 tablets (250/100) > 40kg: 4 tablets (250/100)	v on-label use, but not much experience in Spain with ESM-therapy (p.108-110) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 320/40 and paediatric 160/20 5-< 7 kg: 1/2 tablet (160/20); 7-< 13 kg: 1 tablet (160/20) 13-< 24 kg: 1 tablet (320/40) 24-< 36 kg: 2 tablets (320/40) 36-< 75 kg: 3 tablets (320/40) 75-<100 kg: 4 tablets (320/40) > 100kg: no dates
Italy	v not licensed in Italy and therefore not recommended (p.19; 37)	v (p.19) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM, CHP; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 250/100 and paediatric 62.5/25 5-< 9 kg: 2 tablets (62.5/25); 9-< 11 kg :3 tablets (62.5/25) 11-< 21 kg: 1 tablet (250/100) 21-< 31 kg: 2 tablets (250/100) 31-40 kg: 3 tablets (250/100) > 40kg: 4 tablets (250/100)	v (p.19) Pf, Plasmodium non falciparum (not against hypnozoite episodes of vivax and ovale malaria); ESM; all malaria areas dose of tablets as a single dose on each of 3 consecutive days 320/40 and paediatric 160/20 5-< 7 kg: 1/2 tablet (160/20); 7-< 13 kg: 1 tablet (160/20) 13-< 25 kg: 1 tablet (320/40) 25-< 36 kg: 2 tablets (320/40) 36-< 75 kg: 3 tablets (320/40) 75-<100 kg: 4 tablets (320/40) > 100kg: no dates

Table LXI:

ESM (Quinine plus doxycycline, Quinine plus clindamycin: dosage and recommendations)

ESM (Quinine plus doxycycline, Quinine plus clindamycin: dosage and recommendations)	Quinine plus doxycycline Situation of use Usual amount per tablet of quinine plus doxycycline (mg) Standby treatment regimen Dosage (adults/children)	Quinine plus clindamycin Situation of use Usual amount per tablet quinine plus clindamycin (mg) Standby treatment regimen Dosage (adults/children)
UK	v no interactions are mentioned in this guideline, appears only in a table (p.53; 105) chloroquine or multi-drug resistant Pf 300 plus 100 quinine 2 tablets 3 times a day for 3 days, accompanied by 1 tablet of doxycycline twice daily for 7 days not further mentioned	v no interactions are mentioned in this guideline, appears only in a table (p.53; 105) first trimester of pregnancy 300 plus 150 quinine 2 tablets 3 times a day for 5-7 days, clindamycin 3 tablets 3 times a day for 5 days not further mentioned
Germany	x	x
Netherlands	x	v only ESM medication in pregnancy, no dosage mentioned (p.18)
Belgium	x	x
France	x	x
Spain	x	x
Italy	x	v v only ESM medication in pregnancy, no dosage mentioned (p.22)

Table LXII:

Side effects, CYP 450, Interactions, Contraindications, Precautions: AL

Side effects, CYP450, Interactions, Contraindications, Cautions: AL	UK	G	NL	B	F	E	IT
Side-effects	not mentioned			x	x	x	not recommended/mentioned
digestive disorders		v	v				
headache		v	v				
dizziness		v	v (p.15)				
delayed haemolysis		v (p.171)	x				
CYP 450	not mentioned	AL are both substrates of CYP 3A4 (p.171); *interaction with CYP 2D6 (p.179)*	v (p.15)	x	x	x	not recommended/mentioned
Interactions	not mentioned			x	x	x	not recommended/mentioned
inhibitors of CYP3A4 (erythromycin, ketoconazole, cimetidine, PIs, grapefruits juice)		v	x				
inducers of CYP3A4 :(NNRTIs, rifampicin, carbamazepine, phenytoin and St John's wort		v	v				
contraceptives (effect of contraceptives↓)		v (p.171)	x				
interaction with CYP2D6: metoprolol, imipramine, amitriptyline , clomipramine		*v (p.179)*	v (p.15)				
medicinal products that may cause long QTc interval and torsade de pointes tachycardia: class IA and III antiarrhythmic drugs, neuroleptics and antidepressants, antihistamines, macrolides, fluoroquinolones, imidazole, triazole antifungals (p.15)		v (compare with contraindication) (p.171)	v (p.15)				
Contraindications	not mentioned			x		x	not recommended/mentioned
family history of sudden cardiac death or congenital long QT syndrome		v	v		v (p.48)		*v*
children < 5 kg,		v	v		x		*x*
concomitant use of medicinal products that may cause long QTc interval and torsade de pointes tachycardia:		v	v		v		*v (p. 37)*
class IA and III antiarrhythmic drugs		v	v		v (p.48)		*x*
neuroleptics and antidepressants		v	v		x		*x*
antihistamines (e.g., terfenadine)		v	x		x		*x*
macrolides		v	x		x		*x*
fluoroquinolones		v	x		x		*x*
imidazole		v	x		x		*x*
triazole antifungals		v (p.171)	x		x		*x*
CYP 2D6: metoprolol, imipramine, amitriptyline, clomipramine		*v (p.179)*	x		x		*x*
Hypokalaemia and hypomagnesemia		*x*	v (p.15)		x		x
Cautions	not mentioned	x		x		x	not recommended/mentioned
severe hepatic and renal impairment			v (p.15)		x		
not recommended for pregnancy in the 1st trimester			x		v (p.49)		

Table LXIII:

Side effects, CYP 450, Interactions, Contraindications, Precautions: DP

Side effects, CYP450, Interactions, Contraindications, Cautions: DP	UK	G	NL	B	F	E	IT
Side-effects	not recommended	not recommended	x	x	x	x	x
Interactions	not recommended	not recommended	x	x	x	x	x
Contraindications family history of sudden cardiac death or congenital long QT syndrome concomitant use of medicinal products that may cause long QTc interval	not recommended	not recommended	x	x	 v v (p.48)	x	
Cautions Not recommended for pregnancy in the 1st trimester	not recommended	not recommended	x	x	 v (p.49)	x	x

Table LXIV

ESM (CHP and RDT)

ESM (CHP and RDT)	Restart CHP after ESM	Handling the rapid diagnostic test (RDT)
UK	v complete ESM course and recommence CHP 1 week after taking the first treatment dose; if quinine is used as ESM, mefloquine prophylaxis should be resumed at least 12 hours after the last treatment dose (p.52;106)	v recommended only in exceptional cases for trained, selected high-risk groups or medical staff, RDTs generally not recommended for travellers (p.55)
Germany	x	v recommended only in exceptional cases for trained patients or medical staff, RDTs generally not recommended for travellers (p.173-174)
Netherlands	v ESM medication should be different from the one used for CHP, exception: AP (p.29)	v RDT for travellers not recommended (p.3; 27; 29)
Belgium	x	v only for trained medical staff, RDTs generally not recommended for travellers (https://www.wanda.be/en/a-z-index/malaria#in_case_of_symptoms)
France	v ESM medication should be different from the one used for CHP (p.48)	v to the French law the tests are only available for medical laboratories (p.48)
Spain	v VFR: complete ESM/ treatment course and recommence CHP 1 week after taking the first treatment dose; if quinine is used as ESM, mefloquine prophylaxis should be resumed at least 12 hours after the last treatment dose (p.102)	x not further mentioned
Italy	in high-risk areas: complete ESM/ treatment course and recommence CHP 1 week after taking the first treatment dose (p.19)	recommended only in exceptional cases for trained patients or medical staff, RDTs generally not recommended for travellers (p. 18)

Appendix F

Table LXV:

Special groups I: pregnancy and children

Special groups I: pregnancy and children	Pregnancy and breastfeeding CHP ESM CHP prior to conception Breastfeeding	Children
UK	v (p. 53; 57-60; 85) CHP: M, C+P all trimester of pregnancy; contraindicated: AP (may be used: 2nd, 3rd trim.), D (may be used: 1st trim); ESM: quinine plus clindamycin in the first trimester, AL or AP in the second and third trimester of pregnancy CHP prior to conception: intervals after completing the course: M: 3 months, D: 1 week, AP: 2 weeks Breastfeeding: M; AP not recommended; contraindicated: D	v CHP: AP (5-<11 kg: off-label-use), M (>= 5 kg), D (>= 12 years), C+P for children of every weight; ESM: not mentioned (p.39;67-68; 87-88)
Germany	v (p.176) CHP: M from 1st trimester of pregnancy; contraindicated: AP, D (may be used: 1st trim); ESM: not recommended, CHP also in low-risk areas CHP prior to conception: not mentioned Breastfeeding same scheme for CHP/ ESM: M, AP not recommended, contraindicated: D	v CHP: AP (5-<11 kg: off-label-use), M (>= 5 kg), D (>= 8 years, off-label-use); ESM: AP, AL: >=5 kg (p.175)
Netherlands	v (p.5 ;7; 9; 11; 14; 18) CHP: M, C+P all trimesters of pregnancy; contraindicated: AP, D (p.18); ESM: not recommended, CHP also in moderate risk areas , BP in low risk areas (p.18); AL: use from 2nd trimester possible (p.15),quinine with clindamycin possible (p.18) CHP prior to conception: intervals after completing the course: D: 1week (p.18); AP: pregnancy after menstruation (p.18); Breastfeeding different scheme for CHP: M, C+P recommended, AP possible as off-label-use (for babies>=5kg), D contraindicated (p.19); Breastfeeding different scheme for ESM: AP, AL possible as off-label-use (for babies>=5kg) (p.6;19)	v CHP: AP (5-<11 kg: off-label-use), M (5 kg-< 15kg: off-label use), D (8 -< 12 years: off-label-use), C+P (C:< 10kg: off-label-use); ESM: AP, AL: >= 11kg/15kg (p.17) children < 5 years: CHP instead of ESM in moderate risk areas, children <5kg CHP: C+P, then >=5kg change to M or AP (p.19-20);
Belgium	v belongs to a group with higher risk (https://www.wanda.be/en/a-z-index/malaria-tablets) CHP: M all trimesters, contraindicated: AP (may be used if there is no alternative), D (may be used: 1st trim) ESM: not mentioned CHP prior to conception: not mentioned Breastfeeding different scheme for CHP: AP, M, contraindicated: D	v CHP: AP (>=5 kg)), M (>= 5 kg), D (>= 8 years), (https://www.wanda.be/en/a-z-index/malaria-tablets-dose-for-children) ESM: AL(>= 12 years),AP, DP(>= 36 kg): no further weight adjustment for children mentioned
France	v belongs to a group with higher risk (p.30-33; 48-49;74) CHP: M all trimesters, contraindicated: AP (may be used: 2nd, 3rd trim.), D (possible but not recommended:1st trim), C (after treatment 8 months contraception) ESM: AL, DP not recommended during 1st trimester (p.49) CHP prior to conception: C: 8 months (p.31) Breastfeeding different scheme for CHP: AP first choice, contraindicated: M, C, D (p.74)	v CHP: AP (5-<11 kg: off-label-use), M (>= 5 kg), D (>= 8 years), C for children of every weight ESM: AL, AP, DP: >= 5 kg (it should only be an exception to use it for children) (p.30-32; 48-49)
Spain	v (p. 77;79; 81; 83; 85; 88-91) CHP: M, C+P all trimester of pregnancy; contraindicated: AP (may be used: 2nd, 3rd trim.), D (may be used:1st trim); ESM: not mentioned CHP prior to conception: intervals after completing the course: M: 3 months, D: 1 week, AP: 2 weeks; C: none Breastfeeding: M ; C+P (p.79; 83; 85)); AP not recommended but may be used if baby >= 5kg (p.77; 90), contraindicated: D (p.81)	v CHP: AP (5-<11 kg: off-label-use), M (>= 5 kg), D (>= 8 years), C+P for children of every weight ESM: AL, AP, DP: >= 5 kg (p.93-96; 108-110)
Italy	v (p. 12-16 21-22)) CHP: M (mainly for 2nd and 3rd trim), C(+P) all trimester of pregnancy; contraindicated: AP, D ESM: quinine; M (2nd and 3rd trim, if no other option), AP (p.22) CHP prior to conception: intervals after completing the course: M: 3 months, D: 1 week, AP: 2 weeks; (p.22) Breastfeeding different scheme for CHP: M, C; contraindicated: D, AP (not recommended)	v CHP: AP (>=11 Kg), D (>= 8 years,>= 25kg), M (>= 5 kg), C for children of every weight (p.12-16; 23) ESM: AP, DP: >= 5 kg (p. 19)

Table LXVI:

Special groups II

Special groups II	Long term travellers Visiting friends and relatives (VFR) Expatriates Backpackers	Elderly travellers	Cruises	Oil rigs	Flight crew/ ship staff	Last minute travellers
UK	v AP, D, M, C+P possible; long term use: C+P: safe, AP: up to 1 year, D: up to 2 years; M: up to 3 years (p.73-80) v (p.71-72; 74) v (p.74)) v (p.74)	v good protection; special proof of interactions of co-medications (p.69)	v BP; overnight stay in a malaria area may require CHP (p.69; 81)	v CHP is advised on oil rigs based in river estuaries (p.70; 89)	x	AP, D starting 2 days before journey (p.71)
Germany	v AP, D, M possible; CHP for at least 3 months, during rain period; long term use: AP: 6 months or longer, D, M: up to years; (p.176-178) v (p.164; 177) v (p.178) v (p.177-178)	x	v passengers have to bring their own malaria medication on board (p.180)	x	v AP (civil aviation)/ AP (civil seafaring); D (military staff) (p.180)	v AP: first choice for last minute travellers (p.169)
Netherlands	v AP, D, M, C+P possible; long term use: C+P: safe, AP: up to 6 months, D: up to 2 years, M: up to 2,5 years (p.6; 10; 13-14); v (p.23; 30) v CHP at least for the first 3 months, during rain period (p.22) v (p.21)	v belongs to a group with higher risk (p.24)	x	x	v recommedation from the occupational health service (p.23)	v cosider ESM even for journeys < 7 days (p.23)
Belgium	v for a first stay: bridging period of 3 to 6 months (https://www.wanda.be/en/a-z-index/prolonged-or-frequent-stays-in-malaria-area) v group with increased risk (https://www.wanda.be/en/a-z-index/visiting-family-and-friends-in-foreign-countries) v (https://www.wanda.be/en/a-z-index/prolonged-stay-in-a-foreign-country-expats) x	v belongs to a group with higher risk (travellers >70years) (https://www.wanda.be/en/a-z-index/travellers-with-higher-malaria-risk)	x	x	x	x
France	v AP: longer than 3 months (p.31-32); CHP for 3 to 6 months, high risk zones longer; during rain period (p.34) v group with increased risk (p.34) v the group of expatriates is mentioned: long-term travellers advice in general (p,34) v (p.29)	v belongs to a group with higher risk (p.30)	x	v belong to a group with short and frequent stay; CHP: AP (p.34)	v belong to a group with short and frequent stay; CHP: AP (p.34)	v no CHP for journeys < 7 days (p.34)
Spain	v AP, D, M, C+P possible; long term use: C+P: safe, AP: up to 1 year, D: up to 2 years; M: up to 3 years (p.101-104) v (p.102) v high risk: CHP all time; moderate risk: during rain period and ESM (p.103) v high risk: CHP all time; moderate risk: during rain period and ESM (p.103-104)	x	x	x	v short and frequent stay: ESM recommended (p.101, 107))	x
Italy	v CHP for up to 6 months; during rain period; long term use: C: safe, AP: up to 1 year, D: up to 2 years, M: up to 3 years p.23-24) v (p.24-25) The risk of getting infected is 8 -10 times higher for VFR´s than for tourists (p.24) v the group of expatriates is not mentioned, but long-term travellers in general (p.23-24) x	v belongs to a group with higher risk (p.5)	x	x	x	v CHP or ESM as usual (p. 23-24)

Appendix G

Table LXVII:

Special medical condition I

Recommendations for special medical conditions I	Immunocompromised travellers Splenectomised travellers HIV Transplant patients	Renal impairment	Liver disease	heart disease
UK	v good protection, special examination of interactions; ciclosporin toxicity increases with chloroquine interaction (p.63-64; 66) v appropriate CHP,even in low-risk areas (p.66) v D has slightest potential of interactions, cave NNRTI´s and PI´s; www.hiv-druginteractions.org (p.64) v appropriate CHP, ciclosporin toxicity increases with chloroquine interaction (p.63)	v AP: contraindicated at eGFR less than 30 mL/minute/1.73 (p.37; 65); P: dose reduced like in table on p. 65 mentioned; D, M: may be used in severe renal failure	v mild impairment: C + P, D, AP, M; moderate impairment: D, P, AP, M possible; severe liver disease: D, AP (p.64-65)	x
Germany	v good protection, special examination of interactions; ciclosporin and tacrolimus toxicity increases with D, M (p.179) v appropriate CHP (p.179) v D has slightest potential of interactions, cave: NNRTI; all antimalarials: possible interaction with: NRTI, NNRTI, PI, INI (p.179) v (p.179)	v AP: contraindicated at a creatine clearance < 30ml/min; D, M: may be used in severe renal failure (p.178)	v Child-Pugh-Stage A and B: AP, D, AL (ESM) possible; Child-Pugh- Stage C: all antimalarials contraindicated (p.179)	v AL: contraindicated: cardiac arrhythmias, long QT syndrome, familial sudden cardiac death, co-medication: metoprolol, imipramine, amitriptyline; M: not recommended: cardiac pathology and co-medication with class 1 A antiarrhythmics (p.179)
Netherlands	v belongs to a group with high risk (p.1; 6, 8; 12; 14; 20-21) v belongs to a group with high risk; CHP in low and moderate risk areas, where normally BP or ESM is recommended (p.1; 20): v CHP instead of ESM in moderate risk areas, HIV medication interactions with AP,P, C, M possible but with no need to adjust the dose of malaria prophylaxis; www.hiv-druginteractions.org (p.21) x	v AP, P, AL: contraindicated at a creatine clearance < 30ml/min (p.5;13; 20); P: the dosage should be halved at clearance 30-60 ml/min (p.13); Recommended treatment in moderate risk areas: ESM: AL (relative contraindication) or CHP: M (p.20)	v D, M; AL: contraindicated for severe liver disease (p.9;11; 15)	v AL: contraindicated: long QT syndrome, familial sudden cardiac death, co-medication: metoprolol, imipramine, amitriptyline; (p.15)
Belgium	v belongs to a group with high risk (https://www.wanda.be/en/a-z-index/travellers-with-higher-malaria-risk) v belongs to a group with high risk (https://www.wanda.be/en/a-z-index/travellers-with-higher-malaria-risk) x x	x	x	x
France	v belongs to a group with high risk (p.30) v belongs to a group with high risk (p.30) v belongs to a group with high risk (p.30) x	v belongs to a group with higher risk (p.30)	x	v C: risk of cardiotoxicity (p.32)
Spain	v good protection, special examination of interactions; calcineurin inhibitors toxicity increases with CHP antimalarials (p.98-99) v belongs to a group with high risk (p.98) v D, (AP) first choice of CHP; www.hiv-druginteractions.org (p.98-99) v D, AP safest option; CHP antimalarial drugs may increase concentrations of calcineurin inhibitors (p.99)	v in chapter "quimioprofilaxis": AP, P: contraindicated at a creatine clearance < 30ml/min; M, D: no dose adjustment; C: no dose adjustment if creatinine clearance is >10 ml/min. (p.77; 79; 82-83; 85)	v in chapter "quimioprofilaxis": AP, D, P: no dose adjustment; contraindicated at severe stage: M, C (p.77; 79; 82-83; 85)	v in chapter "quimioprofilaxis": M: cautions in patients with cardiac pathology or alterations (p.79)
Italy	v belongs to a group with high risk (p. 26-27) v belongs to a group with high risk (p.27) v D has no significant interactions with HIV medication; interactions with AP, C, with M possible (p.26) v belongs to a group with high risk, ciclosporin toxicity increases with chloroquine interaction (p.27)	v AP: contraindicated at a creatine clearance < 30ml/min; M: no dose adjustment; C, D: dose adjustment (reduction) (p.27)	mild impairment: C, D (carefully), AP, M possible; moderate impairment: AP, M possible; severe liver disease: AP (p.27)	v M not recommend in patients with cardiac pathology or alterations (p.27)

Table LXVIII:

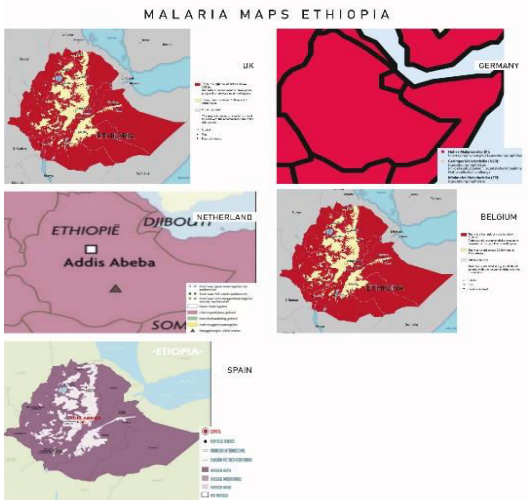
Special medical condition II

Recommendations for special medical conditions II	Anticoagulation Direct oral Anticoagulation (DOC)	Epilepsy	Glucose 6-phospate dehydrogenase deficiency	Sickle cell disease and thalassaemia	Acute porphyriasis	Psoriasis	smoking cessation
UK	v ensure their INR is stable; coumarins are possibly enhanced by AP, P, D (p.60-61; 82-83) v limited experience; DOC´s are possibly enhanced by M	v AP, D possible, but dose adjustment for D: 200mg with co-medication of carbamazepine, phenytoin, barbiturate; M, C unsuitable (p. 30; 32; 62;88)	v contraindication of primaquine: can lead to significant haemolysis with G6PD-deficiency (p.28; 62-63)	v need rigorous antimalarial protection because of haemolysis for homozygous form (p.63)	v D is unsafe in porphyria (p.66)	v C may exacerbate psoriasis (p.30;81)	v C, M should not be used as (p.57)
Germany	v ensure their INR is stable; coumarins are possibly enhanced by AP, P, D, M (p.179) v limited experience; DOC´s are possibly enhanced by M (p. 179)	v AP, D possible, but dose adjustment for D: 200mg with co-medication of carbamazepine, phenytoin, barbiturate; M unsuitable (p.180)	v contraindication of primaquine: can lead to significant haemolysis with G6PD-deficiency (p.172)	x	x	x	x
Netherlands	v ensure their INR is stable; coumarins are possibly enhanced by AP, P, D, M (p.6; 9; 14;24); CHP: AP possible, ESM: only AL recommended (p. 24) v DOC´s are possibly enhanced by P, D, M (p.6; 9)	v contraindicated: C, M (p.7; 10-13)	v contraindication of primaquine: can lead to significant haemolysis with G6PD-deficiency (p.32)	x	v precaution: C (p.7)	v C may exacerbate psoriasis (p.7)	x
Belgium	x	x	x	x	x	x	x
France	v ensure their INR is stable; coumarins are possibly enhanced by AP, D, M (p.32) x not mentioned	v contraindicated: M (p.31)	v G6PD deficiency is not a contraindication for any of the CHP drugs prescribed in France (p.30)	x	x	x	x
Spain	v in chapter "quimioprofilaxis": ensure their INR is stable; coumarins are possibly enhanced by AP, P, D, M, C (p.78; 80; 82; 86) v limited experience	v in chapter "quimioprofilaxis": contraindicated: M, C (p.79; 83; 86)	v contraindication of primaquine: can lead to significant haemolysis with G6PD-deficiency; pregnancy: it is not possible to determine this enzyme in the foetus during it (p.76; 90; 112-113)	x	x	v C may exacerbate psoriasis (p.83; 86)	x
Italy	v ensure their INR is stable; coumarins are possibly enhanced by AP, D, M (p. 25) v M, A (P) inhibit CYP 3A4, therefore enhance anticoagulation (p.26)	v AP, D possible, but dose adjustment for D: higher dosage with co-medication of carbamazepine, phenytoin, barbiturate; M, C contraindicated (p.25)	v contraindication of primaquine: can lead to significant haemolysis with G6PD-deficiency; there is no contraindication for any of the CHP drugs prescribed in Italy (AP, M, D, too low dose of C) (p.26; 37)	v needs rigorous antimalarial protection because of haemolysis for homozygous form (p.26)	x	x	x

Appendix H

Tables LXIX:

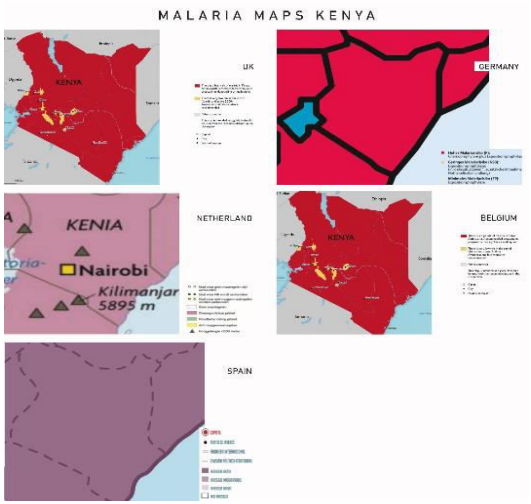
Comparison of Ethiopia



Common recommendations (Ethiopia)		**High risk** for malaria in the whole of Ethiopia below 2,000 m over the whole year. **No risk** of malaria in Addis Ababa. CHP and BP in high-risk areas should be performed. (AP/D/M)
Deviations of the Common recommendations	*Plasmodium* distribution	**G:** *Pf* 89%, *Pv* 11% **NL, B, F, E:** *Pf* 60-70%, *Pv* 30-40% **UK, IT:** distribution of *Plasmodium* not specified
	Regions	**G, NL: High risk** < 2,500 m (Addis Abeba is about 2,300 m above the sea level)
	Resistance	**F, E:** resistance of P. vivax to chloroquine

Tables LXX:

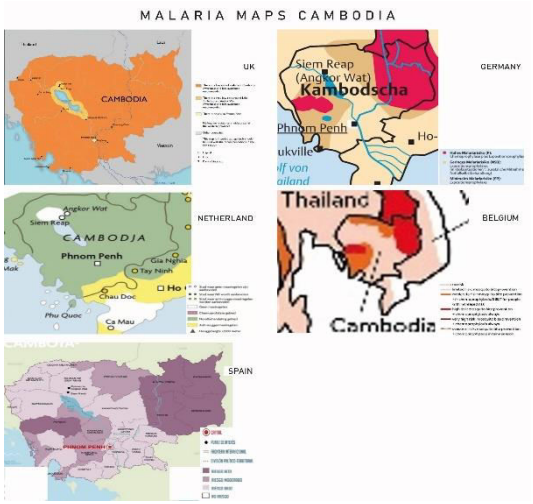
Comparison of Kenya



Common recommendations (Kenya)		**High risk** for malaria in the whole of Kenya below 2,500 m over the whole year. **Low risk** for malaria in the city of Nairobi and in the highlands above 2,500 m. CHP and BP should be performed in high-risk areas (AP/D/M), BP should be performed in the low-risk areas.
Deviations of the Common recommendations	*Plasmodium* distribution	**G, NL, F, E:** *Pf* >99%, predominant **UK, B, IT:** distribution of *Plasmodium* not specified
	Regions	**G: No risk** of malaria in Nairobi. (**B, F: Low risk** in Nairobi and in the elevated areas above 2,500 m in the following provinces: Central, Rift Valley, Eastern, Nyanza and Western Provinces.) **IT**: **Moderate risk** („very low risk “) the city of Nairobi (BP and ESM recommended). **No risk** of malaria in areas > 2,000 m around Mount Kenya.
	Resistance	**E:** resistance of chloroquine

Tables LXXI:

Comparison of Cambodia

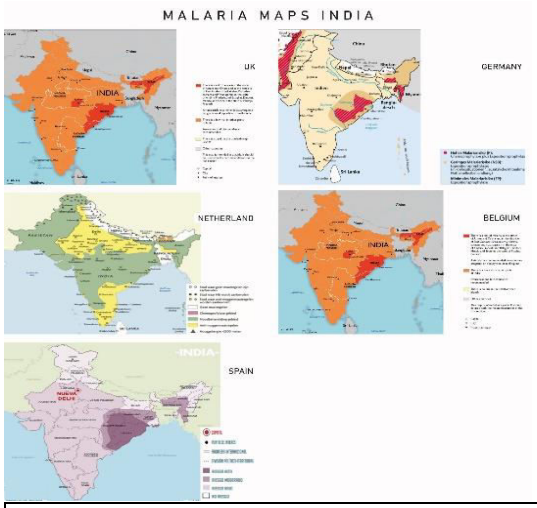


Common recommendations (Cambodia)		**High risk** for malaria in the northeast (E: Stung Treng, Ratanakiri, Mondulkiri and Kratie) and in the middle west (E: south of Pursat) of the country of Cambodia over the whole year. **Moderate risk** for malaria in the remaining northern and western regions (E: Tbong Khmum, Preah Vihear and northeast of Pursat, Kampong Chhnang, Kampong Speu, Kampot and Sihanoukville). **Low risk** for malaria in the southern Mekong region. **Low until very low risk** for malaria in the temple complexes of Angkor Wat and around Lake Tonle Sap, including Siem Reap. **No risk** of malaria in Phnom Penh. CHP and BP should be performed in high-risk areas (AP/D), ESM and BP should be performed in moderate-risk areas, BP should be performed in the low risk and very low-risk areas. Mefloquine resistance is widespread in the western provinces of Cambodia bordering Thailand
Deviations of the Common recommendations	*Plasmodium* distribution	**G:** *Pf* 25%, *Pv* 74%, rarely *P. knowlesi* **NL:** *Pf* 64-86%, *Pv* 12-36%, rarely *P. knowlesi* **E:** *Pf* 58%, *Pv* 41% **UK, B, F, IT:** distribution of *Plasmodium* not specified

	Regions	**UK: Moderate risk** of malaria in the whole of Cambodia, BP recommended. **Low risk** of malaria in Angkor Wat and around Lake Tonle Sap, including Siem Reap, BP recommended. **No risk** in Phnom Penh **G: No risk** of malaria in Siem Reap (Angkor Wat) **NL**: **Moderate risk** in the whole of Cambodia, except southern Mekong region and the cities of Siem Reap, Pnomh Penh and Ankor Wat and the Tonle Sap area, ESM recommended. **Low risk** for malaria in the southern Mekong region, BP recommended. **No risk** in Siem Reap, Pnomh Penh and Angkor Wat and the Tonle Sap area **B: Very low risk** in Phnom Penh, BP recommended **F: Low risk** of transmission in the whole of Cambodia all over the year in rural forested areas, BP recommended. **No risk** of malaria in Phnom Penh and around Tonle Sap (Siem Reap) and negligible area of Anghor Wat. **IT: High risk** in the whole of Cambodia (except Phnom Penh, Angkor Wat and Tonle Sap): CHP and BP recommended. **Moderate risk** in Phnom Penh, Angkor Wat and Tonle Sap: ESM and BP recommended.
	Resistance	**F, E, IT:** resistance of Pf to artesunate, mefloquine, lumefantrine and piperazine in western Cambodia and is spreading to central Cambodia; resistance of Pv to chloroquine

Tables LXXII:

Comparison of India

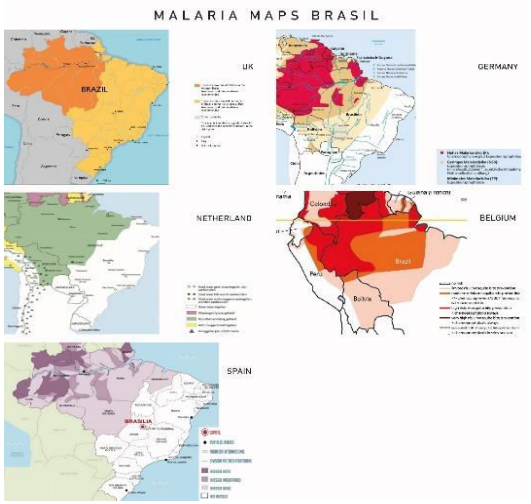


Common recommendations (India)		**High risk** for malaria in the states of Assam (northeast) and Orissa (east) and in some districts of Andhra Pradesh (East Godavari, Srikakulam and Vishakhapatnam) and Madhya Pradesh (Balaghat, Dindori, Mandla and Seoni) over the whole year **Low risk** for malaria for the rest of India below 2,000 m (including Goa, the Andaman and Nicobar Islands) **No risk** of malaria in areas above 2,000 m, in Himachal Pradesh, Jammu, Kashmir und Sikkim and on the Lakshadweep islands. CHP and BP should be performed in high-risk areas (AP/D/M), ESM and BP should be performed in moderate-risk areas, BP should be performed in the low risk and very low-risk areas.
Deviations of the Common recommendations	*Plasmodium* distribution	**G:** *Pf* 48%, *Pv* 52% **NL, B:** *Pf* 7-66%, *Pv* 34-93% **F:** *Pf* 40-50%; *Pv* 50-60% **E:** *Pf* 62%, *Pv* 37% **UK, IT:** distribution of *Plasmodium* not specified

	Regions	**UK, B:** no altitude mentioned **G (similar to F): Seasonal (may-November) high risk** and **(December April) moderate risk** for malaria in states of northeast of India (Meghalaya, Tripura and Mizoram) and east of India (Orissa and in district East Godavari of the state Andhra Pradesh) below 2,000 m, CHP or ESM recommended. **Low risk** for in the rest of northeast of India (Assam, Arunachal Pradesh, Nagaland and Manipur) and in the rest of east of India (Vishakhapatnam, Srikakulam and Bhubaneswar) and the Andaman and Nicobar Islands over the whole year, BP recommended. **No risk** ("very low risk") for malaria in the rest of India below 2,000 m, also in New Delhi, Rajasthan and Mumbai**, nothing recommended**. **NL: Moderate risk** for malaria below 2,000 m in the north-eastern states, Andaman and Nicobar Islands, Chhattisgarh, Gujarat, Jharkhand, Karnataka, Madhya Pradesh, Maharasthra, Orissa, Assam and West Bengal over the whole year, ESM recommended. **Low risk** for malaria in the rest of the India below 2,000 m, also in the cities of Bangalore, Goa, Mumbai, Nagpur, Nasik, Pune and Kolkata, BP recommended. **F: High risk** for malaria states of northeast of India (Tripura, Meghalaya, Mizoram) and also in the states of Orissa, Chhattisgarh, Jharkhand, Madhya Pradesh, Maharasthra over the whole year, CHP in rural areas recommended. **Low risk** for malaria in the rest of India below 2,00 0m, BP recommended. **No risk** above 2,000 m in the rest of India. **E: Seasonal high risk** for malaria in the eastern states of Chhattisgarh and Orissa, CHP recommended. **Moderate risk** for malaria below 2,000 m in the rest of the states of Orissa and Chhattisgarh, in the border areas of the states of Jarkhand, Madhya Pradesh, Andhra Pradesh and West Bengal, and in the north of the country in the states of Meghalaya, Assam and Mizoram, ESM recommended. **Low risk** in Rajasthan and in tourist areas in the north and southwest of the country, as well as in the Andaman and Nicobar Islands, BP recommended.
	Resistance	**UK:** In the exceptional circumstances when an antimalarial is recommended for a traveller to these areas, C+P would be an option, subject to individual risk assessment **E:** resistance of chloroquine

Tables LXXIII:

Comparison of Brazil

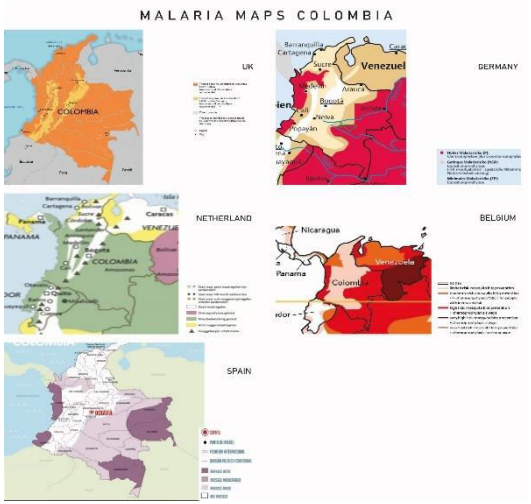


Common recommendations (Brazil)		**High risk** for malaria in the states of Acre, Amapá Amazonas and Roraima and especially high risk in the jungle mining areas, the agricultural settlements downstream from Manaus over the whole year. **Moderate risk** for malaria in Rondonia and Pará and in peri-urban regions of Santarem, Belem, Maraba and the city of Manaus **Low risk** for malaria in Maranhão, Mato Grosso and the Atlantic Forest in the states of Sao Paolo, Minas Gerais, Rio de Janeiro and Espirito Santa an. **No risk** of malaria in the cities of Brasilia, Rio de Janeiro, São Paulo, Recife, Fortaleza, Salvador and around the Iguaçu Falls CHP and BP should be performed in high-risk areas (AP/D/M), ESM and BP should be performed in moderate-risk areas, BP should be performed in the low risk and very low-risk areas
Deviations of the Common recommendations	*Plasmodium* distribution	**G, B, E:** *Pf* 10%, *Pv* 90% **NL:** *Pf* 15-16%, *Pv* 84-85% **UK, F, IT:** distribution of *Plasmodium* not specified

	Regions	**UK: Moderate risk** for malaria in the Amazon Basin of Brazil, including Manaus and a **low risk** for malaria in the rest of Brazil, BP recommended. **No risk** of malaria in Iguaçu Falls. **G: High risk** for malaria in the Amazon Basin (Acre, Amapá, Amazonas, Roraima, northern half of Rondônia and in southwest and northeast of Pará) over the whole year, CHP recommended. **Moderate risk** for malaria in the rest of Pará, northwest of Mato Grosso, the southern half of Rondônia and Manaus, ESM recommended. **Low risk** for malaria in the rest of Mato Grosso, Mato Grosso do Sul, Maranhão, in rural areas of Espirito Santo, Goiás, Minas Gerais, Piauí, Tocantins and in rural wooded areas of Rio de Janeiro and São Paulo States (Bahia: Wenceslaus Guimarães), EP recommend. There is **no risk** of malaria in the cities of Brasilia, Rio de Janeiro, São Paulo, Recife, Fortaleza and Salvador, Iguaçu Falls and east or south-east of the country if not mentioned above. **NL: Moderate risk** for malaria in Acre, Amapá, Amazonas, Maranhão (western part), Mato Grosso (northern part), Pará (except the city of Belém), Rondônia, Roraima and Tocantins (western part), ESM recommended. **Low risk** in Belém, BP recommended. **No risk** of malaria at the east coast including Fortaleza and Recife, and Iguazu Falls. **B: High risk** for malaria in the jungle mining areas, the agricultural settlements downstream from Manaus and in the northern parts of Amapa, Roraima and in Acre, Amazonas, Rondonia (also in Porto Velho), CHP recommended. **Moderate risk** for malaria in the other rural forested areas of the nine states of the “Legal Amazonia Region”: (Acre, Amapá, Amazonas, Maranhão, Mato Grosso, Pará Rondônia, Roraima and Tocantins) also in peri-urban regions of Santarem, Belem, Maraba and the city of Manaus, ESM recommended. **Low risk** for malaria in the forested areas at the Pacific Coast in the states of Sao Paolo, Minas Gerais, Rio de Janeiro, Espirito Santa and the Pantanal National Parc in the south of Mato Grosso, BP recommended. **No risk** of malaria in the rest of the country nor in large cities. **F: High risk** for malaria in the states of the "Legal Amazonia Region": Acre, Amapá, Amazonas, Maranhão, northern Mato Grosso, Pará (except the town of Belém), Rondônia, Roraima and Tocantins (western part), below 900 m, CHP recommended. **Variable risk** from one municipality to another, but it is higher in the jungle, especially in areas of mining production and rural settlement, in indigenous areas and in some urban areas on the outskirts of Cruzeiro do Sul, Manaus and Porto Velho. CHP recommended. **Low risk** for malaria in the regions of large cities such as Boa Vista, Macapá, Maraba, Rio Branco and Santarém. **Very low risk** for malaria in the Atlantic Forest in the states of São Paulo, Minas Gerais, Rio de Janeiro and Espirito Santo, BP recommended. **E: High risk** for malaria in the states of Acre, Amapá Amazonas and Roraima, CHP recommended. **Moderate risk** for malaria in parts of the states of Amazonas, Roraime, Rondonia and Pará, ESM recommended. **Low until very low risk** for malaria in the rest of Brazil, including the Iguaçu Falls, BP recommended **IT: Moderate risk** for malaria in the Amazon Basin and Maranhao, ESM recommended.
	Resistance	**F:** C or A/P or D or M in areas at risk of Pv **E:** resistance of chloroquine

Tables LXXIV:

Comparison of Colombia



Common recommendations (Colombia)		**High risk** for malaria in the areas at the Pacific Ocean (ESP: Chocó, Cauca and Nariño) and in the departments bordering Venezuela, Brazil and Peru (ESP: Vichada, Guainia, Vaupes and Amazonas) below 1,600/1,700 m over the whole year **Moderate risk** for malaria in Antioquia, Bolivar and Cordoba, and in areas adjunct to high-risk areas below 1,600/1,700 m **Low risk** for malaria at northern rural areas (Caribbean coast), in Valle del Cauca and Putumayo. **Very low risk** in the rest of the country below 1,600/1,700 m, BP recommended. **No risk** of malaria in urban areas, including Bogotá Cartagena, Medellín, at an altitude above 1,600/1,700 m and on the islands of the San Andrés y Providencia CHP and BP should be performed in high-risk areas (AP/D/M), ESM and BP should be performed in moderate-risk areas, BP should be performed in the low risk and very low-risk areas
Deviations of the Common recommendations	*Plasmodium* distribution	**G:** *Pf* 50%, *Pv* 50% **NL:** *Pf* 34-50% **B:** *Pf* 60% **F:** *Pf* 34%, *Pv* 66% **E:** *Pf* 58%, *Pv* 42% **UK, IT:** distribution of *Plasmodium* not specified

	Regions	**UK: Moderate risk** for malaria in rural areas of Colombia below 1,600 m, BP recommended. **Low risk** in areas above 1,600 m and in Cartagena, BP recommended. **G: High risk** for malaria on the Pacific coast, parts of the departments of Antioquia, Bolívar, Cordoba and tributaries of the Amazon (Guaviare / border departments to Venezuela, Brazil and Peru) below 1,700 m over the whole year, CHP recommended. **Low risk** for malaria in Valle del Cauca, Putumayo and in areas adjunct to high-risk areas below 1,700 m. **Very low risk** in in the rest of the country below 1,700 m, BP recommended. **No risk** of malaria in Bogotá, Cartagena, Medellín **NL: Moderate risk** for malaria in the whole country of Colombia below 1,700 m, except the big cities (Cartagena, Cali, Medellin) and rural areas in the north (Caribbean coast), ESM recommended. **Low risk** for malaria in northern rural areas (Caribbean coast), BP recommended. **No risk** of malaria for areas above 1,700 m and large cities (Cartagena, Cali, Medellin) and the islands: Providencia and San Andres. **B: High risk** for malaria in the areas at the Pacific Ocean and in the departments bordering Venezuela, Brazil and Peru, CHP recommended **Moderate risk** for malaria in the departments Antioquia and Cordoba at the Caribbean Coast, ESM recommended. **Low risk** for malaria in the northern coastal areas: Sucre, Bolivar, Atlántico, La Guairá, BP recommended. **No risk** of malaria in the areas above 1,700 m and in the cities of Bogota and Cartagena. **F: High risk** for malaria in the municipalities below 1,600 m of the following departments over the whole year: **Antioquia** (El Bagre, Vigía del Fuerte, Segovia, Tarazá, Zaragoza, Cáceres, Nechí, Murindó, Anorí, Remedios, Mutatá, Frontino, San Pedro de Urabá, Dabeiba, Valdivia, Caucasia), **Amazonas** (Tarapacá, La Pedrera, Puerto Nariño, Leticia, Miriti-Paraná, La Chorrera), **Bolívar** (Montecristo, Norosi, Tiquisio, San Pablo), **Cauca** (Timbiquí), **Chocó** (Bagadó, Nóvita, Lloró, Tadó, Río Quito, El Cantón del San Pablo, Río Iro, Atrato, Bojaya, San José del Palmar, Quibdó, Bajo Baudó, Medio San Juan, Carmen de Darien, Nuquí, Medio Baudó, Alto Baudó, Istmina, Bahía Solano, Medio Atrato, Juradó, Sipí, Unión Panamericana, Condoto, Certegui), **Córdoba** (Puerto Libertador, Tierralta), **Guainía** (Inirida, La Guadalupe), **Nariño** (Roberto Payán, Olaya Herrera, El Charco, Mosquera, Barbacoas, Santa Barbarba, Magüi, Francisco Pizarro, San Andrés de Tumaco), **Risaralda** (Pueblo Rico, La Virginia), **Valle del Cauca** (Cartago), **Vaupés** (Taraira, Yavarate) **Vichada** (Puerto Carreño, Cumaribo), CHP recommended. **Moderate risk** for malaria in the municipalities below 1,600 m of the following departments over the whole year: **Antioquia** (Urrao, Chigorodó, Apartadó, Necoclí, Yondo), **Amazonas** (El Encanto Puerto Santander**), Bolívar** (Santa Rosa del Sur Río Viejo), **Cauca** (Guapi, López), **Chocó** (El Litoral de San Juan), Riosucio, Acandí, Unguía), **Córdoba** (San José de Uré, La Apartada), **Guaviare** (San José de Guaviare, Miraflores, Calamar,El Retorno), **Nariño** (La Tola), **Vaupés** (Pacoa), CHP recommended. **Low risk** for malaria in some municipalities of Amazonas, Caqueta, Guaviare, Guainia, Meta, Putumayo, Vaupes and Vichada, BP recommended. **No risk** of malaria in urban areas, including Bogotá and its region, Cartagena, at an altitude above 1,600 m and on the islands of the San Andrés y Providencia. **E: High risk** for malaria in the coastal zone of the departments of Chocó, Cauca and Nariño, in parts of the departments of Vichada, Guainia, Vaupes and Amazonas, CHP recommended. **Moderate risk** for malaria in parts of the departments of Valle del Cauca, Cauca, Antioquia, Córdoba, Guaviare, Guainia, Vaupes and Amazonas, ESM recommended. **Low until very low risk** for malaria in Cartagena and the rest of the country, BP recommended. **No risk** of malaria in areas above 1,600 m. **IT: High risk** for malaria at Pacific coastal strip of Colombia, CHP recommended. **Moderate risk** for malaria at the Amazon region and Atlantic coast, ESM recommended. **Low risk** for malaria in the rest of Colombia (except Amazon region). BP recommended.
	Resistance	**E:** resistance of chloroquine

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Without you and your encouragement, I probably would not have been able to complete this project!

Your Ulla Benz

AFFIDAVIT/ DECLARATION OF AUTHORSHIP

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Eidesstattliche Versicherung

Benz, Ursula

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Internationaler Vergleich ausgewählter europäischer Malariaempfehlungen für Reisende-
International comparison of selected European malaria recommendations for travellers

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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Germering, 24.06.2024 — Ursula Benz

Ort, Datum — Unterschrift Doktorandin bzw. Doktorand

LIST OF PUBLICATIONS

March 2024-Journal Article: “Effect of textile colour on vector mosquito host selection: a simulated field study in Mali, West Africa”

Ursula Benz, Mohamad M Traore, Edita E Revay, Amadou S Traore, Alexey M Prozorov, Issa Traoré, Amy Junnila, Liwang Cui, Aidas Saldaitis, Aboubakr S Kone, Roman V Yakovlev, Younoussa Ziguime, Petrányi Gergely, Siriman Samake, Alou Keita, Günter C Müller, Thomas Weitzel, Camilla Rothe

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DOI: 10.1093/jtm/taae049

June 2023-Poster Publication: „Verringern helle Textilien die Stichrate von Vektor-Mücken? Eine simulierte Feldstudie aus Mali, Westafrika“

Ursula Benz, Mohamad M Traore, Edita E Revay, Amadou S Traore, Alexey M Prozorov, Issa Traoré, Amy Junnila, Liwang Cui, Aidas Saldaitis, Aboubakr S Kone, Roman V Yakovlev, Younoussa Ziguime, Petrányi Gergely, Siriman Samake, Alou Keita, Günter C Müller, Thomas Weitzel, Camilla Rothe

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