Imported malaria in pregnant women: A retrospective pooled analysis

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Abstract: BACKGROUND Data on imported malaria in pregnant women are scarce. METHOD A retrospective, descriptive study of pooled data on imported malaria in pregnancy was done using data from 1991 to 2014 from 8 different collaborators in Europe, the United States and Japan. National malaria reference centres as well as specialists on this topic were asked to search their archives for cases of imported malaria in pregnancy. A total of 631 cases were collated, providing information on Plasmodium species, region of acquisition, nationality, country of residence, reason for travel, age, gestational age, prophylactic measures and treatment used, as well as on complications and outcomes in mother and child. RESULTS Datasets from some sources were incomplete. The predominant Plasmodium species was P. falciparum (78.5% of cases). Among the 542 cases where information on the use of chemoprophylaxis was known, 464 (85.6%) did not use chemoprophylaxis. The main reason for travelling was "visiting friends and relatives" VFR (57.8%) and overall, most cases of malaria were imported from West Africa (57.4%). Severe anaemia was the most frequent complication in the mother. Data on offspring outcome were limited, but spontaneous abortion was a frequently reported foetal outcome (n = 14). A total of 50 different variants of malaria treatment regimens were reported. CONCLUSIONS Imported cases of malaria in pregnancy are mainly P. falciparum acquired in sub-Saharan Africa. Malaria prevention and treatment in pregnant travellers is a challenge for travel medicine due to few data on medication safety and maternal and foetal outcomes. International, collaborative efforts are needed to capture standardized data on imported malaria cases in pregnant women.

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Imported malaria in pregnant women: A retrospective pooled analysis

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Summary *Background:* Data on imported malaria in pregnant women are scarce.
Method: A retrospective, descriptive study of pooled data on imported malaria in pregnancy was done using data from 1991 to 2014 from 8 different collaborators in Europe, the United States and Japan. National malaria reference centres as well as specialists on this topic were

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Travel;
Treatment

asked to search their archives for cases of imported malaria in pregnancy. A total of 631 cases were collated, providing information on *Plasmodium* species, region of acquisition, nationality, country of residence, reason for travel, age, gestational age, prophylactic measures and treatment used, as well as on complications and outcomes in mother and child.
Results: Datasets from some sources were incomplete. The predominant *Plasmodium* species was *P. falciparum* (78.5% of cases). Among the 542 cases where information on the use of chemoprophylaxis was known, 464 (85.6%) did not use chemoprophylaxis. The main reason for travelling was "visiting friends and relatives" VFR (57.8%) and overall, most cases of malaria were imported from West Africa (57.4%). Severe anaemia was the most frequent complication in the mother. Data on offspring outcome were limited, but spontaneous abortion was a frequently reported foetal outcome (n = 14). A total of 50 different variants of malaria treatment regimens were reported.
Conclusions: Imported cases of malaria in pregnancy are mainly *P. falciparum* acquired in sub-Saharan Africa. Malaria prevention and treatment in pregnant travellers is a challenge for travel medicine due to few data on medication safety and maternal and foetal outcomes. International, collaborative efforts are needed to capture standardized data on imported malaria cases in pregnant women.

1. Introduction

Malaria in pregnancy is an important cause of maternal and foetal morbidity and is a potentially life-threatening infection [1]. In particular, non-immune pregnant women have an increased risk of both complications and a more severe course of the infection [2,3]. Additionally, pregnant women are more attractive to *Anopheles* mosquitoes compared to non-pregnant women although the mechanisms for this are poorly understood [4]. More than 80 million travellers visit malaria-endemic areas annually [5]. A significant proportion of travellers are women of childbearing age. In 2012, pregnant women constituted 6% of the women with imported malaria in the United States [6]. Pregnant travellers to malaria risk areas should use personal protection measures and in high-risk areas, chemoprophylaxis is also indicated. In general, few data exist on the number and proportion of pregnant travellers or women who become pregnant while visiting malaria endemic areas; on the geographic region where they acquired their malaria; the reason for travel; chemoprophylaxis, preventive measures and malaria treatments used. For ethical and safety reasons, there are few studies on malaria treatment in pregnant women and there is little information on outcomes for mother and foetus in the context of imported malaria defined as malaria presenting in a non-endemic area, having being acquired during travel or associated with immigration from a malaria-endemic region.

The goals of our study were to evaluate cases of imported malaria in pregnant women and to ascertain maternal and child outcomes, as well as the type of travel associated with infection acquisition (Visiting Friends and Relatives (VFR), tourism, immigration) and the preventive measures and treatments used.

2. Methods

We conducted a retrospective descriptive analysis of pregnant women who were diagnosed with laboratory confirmed malaria in non-endemic, industrialized countries. In order to create a comprehensive database, we asked authors of papers on the subject of malaria, as well as national malaria reference centres if they would search their archives for cases of malaria in pregnant women. Cases were contributed by two reference centres; the Centers for Disease Control and Prevention in the United States and the Malaria Reference Laboratory in the UK and from single centres in France, Spain, Sweden, Japan, Austria and the Netherlands. The cases provided by the reference centres were cases of imported malaria in pregnant women that had been reported by physicians countrywide. The cases provided by the single centres were locally collated data of cases presenting to that particular centre. Some of these cases have been previously published. This concerns the data provided from Madrid as well as some of the cases from Marseille [33,46].

We requested the following data elements; number of pregnant women with imported malaria; age; *Plasmodium* species, country of infection acquisition and the patient's nationality; the week of gestation at time of onset of malaria symptoms; complications concerning the mother (such as cerebral malaria; pulmonary oedema or acute respiratory distress syndrome; circulatory collapse; acute renal failure; hepatic failure; coagulopathy and/or disseminated intravascular coagulation (DIC); severe anaemia; hypoglycaemia; metabolic acidosis); pregnancy outcome (foetal death, low birth weight, intrauterine growth retardation, stillbirth, spontaneous or therapeutic abortion, pre-term, congenital malaria, healthy). Furthermore we inquired about the reason for travel (tourism; visiting friends and relatives (VFR); immigration; business etc.) and preventive measures used during travel (details of chemoprophylaxis; bed nets; protective clothing; repellents) as well as information on the antimalarial treatment used. Cases reported in the period 1991—2014 were included. All data were anonymised.

3. Results

3.1. Number of cases (Table 1)

We collated a total number of 631 cases of imported malaria in pregnancy from areas where malaria is non-

Table 1 Demographic characteristics and *Plasmodium* species reported.

Variables		Number
Pregnant Women		n = 631[a]
Age	Unknown	n = 11
	Mean age[b] (years)	29.6
	Range (years)	13–51
Gestational Age	Unknown	n = 504
	1st Trimester	23.6% (n = 30)
	2nd Trimester	38.6% (n = 49)
	3rd Trimester	36.2% (n = 46)
	Post-Partum	1.6% (n = 2)
Plasmodium Species	Unknown	8.4% (n = 53)
	Plasmodium falciparum	72% (n = 454)
	Plasmodium vivax	14.6% (n = 92)
	Plasmodium malariae	1.6% (n = 10)
	Plasmodium ovale	2.4% (n = 15)
	Mixed *P. falciparum*/*P. vivax*	0.16% (n = 1)
	Mixed *P. falciparum*/*P. malariae*	0.32% (n = 2)
	Mixed *P. falciparum*/*P. ovale*	0.32% (n = 2)
	Mixed *P. vivax*/*P. ovale*	0.32% (n = 2)

[a] Includes 2 cases where malaria was diagnosed post-partum.
[b] Madrid and Marseille only provided the mean age for their patients.

endemic; USA: n = 425, UK: n = 113, Marseille: n = 40, Madrid: n = 19, Stockholm: n = 15, Japan: n = 9, Vienna: n = 5 and Amsterdam: n = 5. Availability of requested data parameters varied between sites. *Plasmodium* species identification was largely complete. Epidemiological and demographic data were available from 8 sites and some clinical obstetric data from 7 sites.

The mean age for the entire study population, where this information was available was 29.6 years.

Data were scarce with regard to the gestational age, but out of 127 women, 46 women (36%) were in their third trimester at malaria diagnosis, 49 women (38.6%) were in their second trimester and 30 women (23.6%) were in their first trimester. There were 2 cases of malaria diagnosed post-partum.

3.2. *Plasmodium* species (Table 1)

The majority of cases (n = 454, 78.5% of all 578 cases where this information was available) were diagnosed with *Plasmodium falciparum* malaria.

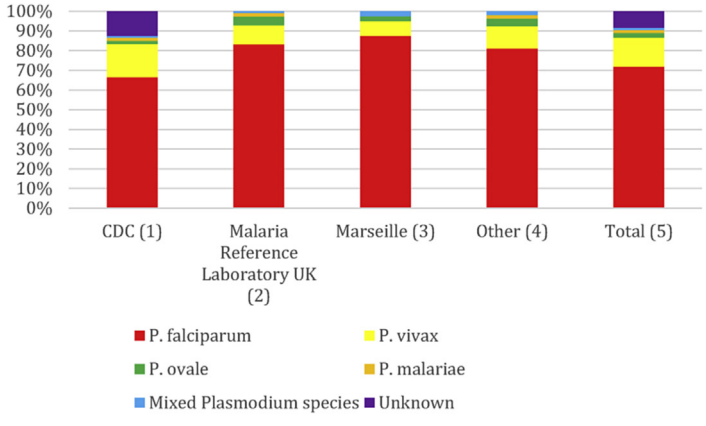
The second most frequent malaria species was *Plasmodium vivax* (n = 92, 15.9%).

The remaining cases were diagnosed with *Plasmodium ovale* (n = 15, 2.6%), *Plasmodium malariae* (n = 10, 1.7%) and 7 cases of mixed infection. The *Plasmodium* species listed by reporting centre are shown in Fig. 1.

3.3. Region of malaria acquisition (Table 2)

Of the 610 patients for whom information was available on the geographic region of malaria acquisition (according to UN criteria; [7]), in 524 cases (85.9%), Africa was the continent where they acquired their malaria; with West Africa (e.g. Nigeria, Ghana, Sierra Leone) being the UN-region with most infection acquisitions (n = 351, 57.4%). Most women diagnosed with imported malaria in the United States and the United Kingdom fell into this category. In Marseille, however, most cases were imported from East Africa, more specifically from the Comoros Union.

86 women (14%) acquired malaria in East Africa (e.g. Comoros, Uganda, Kenya), followed by 67 cases (10.9%) of



(1) CDC: n = 425
(2) PHE Malaria Reference Laboratory UK: n = 113
(3) Marseille: n = 40
(4) Other: Madrid: n = 19; Stockholm: n = 15; Japan: n = 9; Vienna: n = 5; Amsterdam: n = 5
(5) Total: n = 632

Fig. 1 *Plasmodium* species by reporting centre.

Table 2 Regions of malaria acquisition listed by reporting institutions.

	CDC n[a]	PHE MRL n	Marseille n	Other n	Total N = 610 n (%)
East Africa	26	16	37	7	86 (14.1%)
Middle Africa	47	5	0	15	67 (11.1%)
North Africa	4	1	0	0	5 (0.8%)
Southern Africa	5	0	0	0	5 (0.8%)
West Africa	250	71	3	27	351 (57.4%)
Caribbean	7	0	0	0	7 (1.1%)
Central America	24	0	0	0	24 (3.9%)
South America	4	0	0	1	5 (0.8%)
South Asia	39	8	0	0	47 (7.7%)
South-East Asia	1	0	0	1	2 (0.3%)
Melanesia	1	0	0	0	1 (0.16%)

[a] In 10 US-cases the continent Africa was stated as region of acquisition without being further specified.

infection acquisition in Middle Africa (e.g. Cameroon, Equatorial Guinea) and 47 cases (7.7%) in South Asia (e.g. India, Pakistan).

Twenty four pregnant women (3.9%) were infected in Central America (Honduras, Guatemala). Only a few cases of malaria acquisition occurred in the Caribbean (n = 7, 1.1%), South America (n = 5, 0.8%), North Africa (n = 5, 0.8%), Southern Africa (n = 5, 0.8%), South-East Asia (n = 2, 0.3%) and Melanesia (n = 1, 0.2%).

Table 3 Malaria chemoprophylaxis used by pregnant women diagnosed with malaria.

	Total N = 542 n (%)
No chemoprophylaxis	464 (85.6%)
Chemoprophylaxis used[a]	78 (14.4%)
Chloroquine	26 (4.8%)
Chloroquine + proguanil	2 (0.4%)
Proguanil	3 (0.6%)
Atovaquone + proguanil	1 (0.2%)
Mefloquine	10 (1.8%)
Doxycycline	2 (0.4%)
Primaquine[b]	1 (0.2%)
Pyrimethamine	6 (1.1%)
Sulfadoxine + pyrimethamine	4 (0.7%)
Artesunate*	2 (0.4%)
Artemether + lumefantrine*	1 (0.2%)
"Herbs"	1 (0.2%)
Chemoprophylaxis used but medication unknown	19 (3.5%)

* Used as "prophylaxis" not treatment.

[a] Including eleven cases where chemoprophylaxis was classified as incorrect or incomplete.

[b] Primaquine is contraindicated in pregnancy, as it can cause acute haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency and it is not feasible to test the unborn for G6PD deficiency.

3.4. Reason for travel

The most common reason for travel was visiting friends and relatives (n = 306, 57.8%). Another 130 women (24.6%) were refugees or recently immigrated. Twenty patients (3.8%) travelled for "tourism". Other reasons for travel were student or teacher activities (n = 16), business (n = 13), missionary duties (n = 6), military (n = 1) or working in an airline or ship (n = 1). In many cases (n = 102), the reason for travel was not stated in the clinical data.

3.5. Use of chemoprophylaxis (Table 3)

Among the 542 pregnant patients for whom this information was available, the majority (n = 464, 85.6%) did not use chemoprophylaxis. This was true for 313 (83.7% of 374) US-cases and for 74 women in the United Kingdom (91.4% of 81 cases for which this data were available). Among the 130 refugees or migrants, five reported use of chemoprophylaxis (chloroquine: n = 1, primaquine: n = 1, pyrimethamine: n = 1, drug unknown: n = 2). For 89 women it is unclear if chemoprophylaxis was taken.

Among the 78 women (14.4%) who were reported to have taken chemoprophylaxis, eleven women were classified to have used incorrect (n = 9) or incomplete (n = 2) chemoprophylaxis, including one woman who had taken "herbs" as a prophylaxis. However, our analysis showed among the women using chloroquine and/or proguanil, in an additional 24 cases, this can be considered "incorrect chemoprophylaxis" in view of the region of acquisition and the spread of chloroquine resistance.

The preferred drug for malaria prevention was chloroquine (n = 26; 33.3% out of 78 patients who used chemoprophylaxis). Ten women (12.8%) were taking mefloquine (one woman was at 15 weeks of pregnancy, in the other 9 cases the gestational age is unknown. No adverse pregnancy outcomes were documented among the 10 women using mefloquine prophylaxis). Two women (2.6%) used doxycycline; one of whom suffered a miscarriage (gestational age unknown). In the other case, doxycycline was given postpartum. In 1 case, prophylaxis with atovaquone/proguanil was used; this patient was at 20 weeks gestation and suffered a *P. vivax* relapse. The pregnancy outcome was documented as "good". Other regimens used for chemoprophylaxis were pyrimethamine (n = 6), pyrimethamine/sulfadoxine (n = 4), chloroquine/proguanil (n = 2), proguanil (n = 3), primaquine (n = 1) and in three cases, malaria treatment medications were incorrectly used as prophylaxis – artesunate (n = 2), and arthemeter/lumefantrine (n = 1).

3.6. Outcome of mother and child

No maternal deaths were reported but information on outcomes was largely incomplete. 46 women were classified as having 'severe malaria'.[1] In an additional 7 cases, the reason for being classified as severe malaria was not

[1] Severe malaria was defined according to WHO criteria [8].

Table 4 Guidelines on anti-malarial chemoprophylaxis for pregnant women by different countries/institutions.

	Centers for disease control and prevention [9]	Public Health England [10]	France [11]
Atovaquone-proguanil	Cannot be used for women who are pregnant or breastfeeding a child that weighs >5 kg.	Should not be used in pregnancy because of lack of evidence on safety in pregnancy. However, if there are no other options, use may be considered in second and third trimesters after risk assessment. Inadvertent use is no indication to consider termination of the pregnancy. Should be avoided by breastfeeding women but can be used if no suitable alternative antimalarial.	May be considered if travel to areas with chloroquine-resistance and areas with multidrug-resistance cannot be deferred.
Chloroquine	Can be used in all trimesters of pregnancy, but restricted to areas where there is no chloroquine or mefloquine resistance.	Safe in all three trimesters. Only in regions without drug-resistance.	Safe in pregnant women.
Doxycycline	Cannot be used in pregnant women and children <8 years.	Best avoided during pregnancy. But if required before 15 weeks' gestation it should not be withheld if other options are unsuitable. The regimen must be completed before 15 weeks' gestation though (including 4 weeks after travel) (UK National Teratology Information Service, see toxbase.org).	Contraindicated in the second and third trimester. Not recommended in the first trimester.
Mefloquine	Can be used in all trimesters of pregnancy. Cannot be used in areas with mefloquine-resistance. Cannot be used in certain neuropsychiatric disorders.	Caution in first trimester, but can be used in all trimesters for travellers to highly endemic areas. It seems unlikely that mefloquine is associated with adverse foetal outcomes. Inadvertent use does not constitute an indication to terminate pregnancy.	Recommended for pregnant women travelling to areas with elevated chloroquine-resistance and/or multidrug-resistance.
Primaquine	Cannot be used in pregnant women. Cannot be used in patients with G6PD-deficiency. Cannot be used in breastfeeding women unless baby has also been tested for G6PD-deficiency. Only for areas with principally *P. vivax*.	No information.	No information.
Proguanil	No information.	Caution in pregnancy. Folic acid 5 mg daily required at least during first trimester. Mostly used in combination with other drugs. As monotherapy, only for regions without chloroquine-resistance and if chloroquine cannot be used for that particular patient.	Combination chloroquine-proguanil recommended for pregnant women travelling to chloroquine-resistant areas.

Table 5 Clinical features of *P. falciparum* malaria in the mother.[a]

Uncomplicated malaria	Number n
No complications reported	235
Jaundice	2
Prostration	2
Complicated malaria	**Number n**
Severe malaria[b]	46
Neurological impairment/coma	2
Pulmonary oedema/acute respiratory distress syndrome (ARDS)	13
Acute renal Fl Fis ualsly women?cliniciansf which 44 had severe malaria?immigrantsn since here only includes thos who turned up as cases ailure (Creatinine >265 μmol/l)	5
Severe anaemia (Hb <7 g/dl)	22
Coagulopathy and/or disseminated intravascular coagulation[c]	2
Circulatory shock (systolic blood pressure <70 mm Hg)	1
Hypoglycemia (above WHO cut-off level for severe malaria)	4
Respiratory distress, hyperventilation (without acidosis)	1

[a] There were no data available on complications in the mother from UK data.
[b] In an additional 7 cases, the reason for being classified as severe malaria was not apparent as no complications were reported, but the women were treated with i.v.-quinidine which was used as a treatment for complicated malaria.
[c] In 1 case, disseminated intravascular coagulation was considered to be associated with stillbirth rather than the malaria episode.

apparent as no complications were reported, but the women were treated with i.v.-quinidine which was used as a treatment for complicated malaria.

Some 235 women had no reported malaria complications (Table 5). Of a total of 54 reported maternal malaria complications (several complications possible per individual case), the most frequent were severe anaemia with a measured haemoglobin of 7 g/dl or less (n = 22).

One patient suffered from circulatory shock with a systolic blood pressure <70 mm Hg. The patient survived but no details were available. Four cases of hypoglycaemia were reported, but they were asymptomatic and above the WHO cut-off for severe malaria (glucose >40 mg/dl). One patient was reported to have tachypnoea, but neither pulmonary oedema/ARDS nor metabolic acidosis were reported for this patient. Hyperparasitaemia over 5% was reported in eight cases, with another seven cases with a parasitaemia within the range of 1–4%.

Other laboratory and clinical findings were mild or moderate anaemia (Hb 7–11 g/dl, n = 82); thrombocytopenia (platelet count <150.000/μl; n = 38); thrombosis (n = 3); splenomegaly (n = 7) and/or hepatomegaly (n = 3).

There were also 12 other complications noted, such as hypertension; gestational diabetes; thrombosis; and non-specified complications.

Concerning the offspring, few data were available (Table 6). Among the 95 cases where data on outcome of the offspring was available, 51/95 (53%) children were considered healthy. In 9/95 (9.5%), cases child health at birth was documented as good. 10/95 children (10.5%) were delivered pre-term, one by caesarean section in the 35th gestational week because of threatening intrauterine asphyxia; the baby was reported to have continuing bradycardia and there was a lack of uterine contractions. In three cases, intrauterine growth retardation occurred and one baby was reported to have a low birth weight <2500 g. Of 16 abortions (16.8% of 95 cases), 14 occurred spontaneously whereas 2 were therapeutically induced. One of the therapeutic abortions was unrelated to the malaria episode, the other was conducted because of foetal malformations: the mother suffered severe *P. falciparum* malaria in the 18th week of pregnancy some two days after returning from a 35-day trip to Zambia to visit friends and relatives. She was reported to have taken chemoprophylaxis before admission, but the exact drug remained unclear. Two cases of congenital malaria were documented.

3.7. Treatment (Table 7)

Fourteen women received blood transfusions and an additional two women were supported by exchange transfusion therapy.

Amongst the 50 different treatment regimens reported in this study population, the most frequent was the combination of quinine or quinidine plus clindamycin (administered 160 times). Chloroquine as monotherapy was the second most frequent (n = 56). Monotherapy with quinine or quinidine was administered in 84 cases. Quinine or quinidine plus tetracycline was given in 37 cases. Mefloquine (n = 24), atovaquone plus proguanil (n = 14) and chloroquine plus primaquine (n = 13); in five cases, it was clearly stated that primaquine was administered post-partum. The other therapeutic regimens and combinations are listed in Table 7.

4. Discussion

Our retrospective analysis included 631 women who presented with travel-associated malaria in 8 non-endemic countries. Although data are incomplete, they show that the main species was *P. falciparum*, the main source of malaria was sub-Saharan Africa, that the majority of the women did not use chemoprophylaxis and that there was no standardization of treatment as shown by a total of 50 different treatment regimens.

The treatment of malaria in pregnant travellers or in women who become pregnant whilst travelling to a malaria-endemic region poses important challenges for clinicians. Safety is an issue and data on the pharmacokinetics of therapeutic drugs in pregnancy are incomplete. Due to an increased volume of distribution and other physiological changes in pregnancy, there may be altered drug metabolism and therefore the need to optimize dosages for pregnant women. This is exemplified by dihydroartemisinin and artemether. Pregnant women both were shown to have lower plasma concentrations of dihydroartemisinin (active metabolite) compared to non-

Table 6 Outcome of offspring.[a]

Type of complication	Number n
No information	536
Healthy	51
Intrauterine foetal death	1
Intrauterine Growth Retardation (IUGR)	3
Low birth weight <2.5 kg	1
Pre-Term	10
Stillborn	1
Therapeutic Abortion	2
Spontaneous Abortion	14
Foetal distress	2
Congenital malaria	2

[a] No outcome data were available from the UK. Also, in many other cases there was no information available on the outcome of the offspring.

pregnant adults. This finding was accompanied by a lower cure-rate of the malaria infection [14].

Diagnosis of falciparum malaria in pregnancy can be confounded by sequestration of parasites in the placenta, which can lead to a parasite count in the peripheral blood below the threshold for microscopic detection in blood films, with possible delayed diagnosis [1,15]. Additionally, pregnant women often experience a more severe course of the infection than non-pregnant women [2,3]. *P. falciparum* and less often *P. vivax* are known to cause adverse pregnancy outcomes, such as miscarriages, low birth weight due to intrauterine growth retardation or preterm delivery, and maternal anaemia [8,16–18]. While *Plasmodium knowlesi* malaria is rare during pregnancy, especially compared to *P. falciparum*, it may be associated with preterm delivery, low birth weight and maternal anaemia [19]. Little is known regarding the impact of *P. ovale* and *P. malariae* on pregnancy. In our study, there were 46 cases designated as "severe malaria" (mainly *P. falciparum* (36 cases) and 5 cases of single *P. vivax* infection and five unknown) and, although we have limited detailed information, a total of 54 complications were recorded including cerebral malaria, severe anaemia, pulmonary oedema and ARDS. Two of the women received exchange blood transfusion. Four patients were reported as being admitted to intensive care, which seems an underestimate as 46 cases of severe malaria were reported. In the four aforementioned cases, the reasons for admission to intensive care were disseminated intravascular coagulation, cerebral malaria, post-operative bleeding after caesarean section and hypotension.

Overall, *P. falciparum* was the main species to cause malaria in the study population. The highest percentage of vivax malaria was recorded in the United States, whereas the lowest was documented in France. This indicates greater importation of *P. vivax* malaria into the United States compared to European countries, reflecting a higher rate of acquisition of malaria in South and/or Central America and India since these are important travel destinations for US travellers. Most women acquired their malaria infection in sub-Saharan Africa, which in the context of non-imported malaria is still the region where the malaria burden is greatest [20].

Prevention of malaria in pregnant women is problematic and travel should be deferred if possible [10]. Few studies have evaluated the safety of malaria chemoprophylaxis for pregnant women or the unborn child [21,22]. Current international guidelines on the use of chemoprophylaxis are summarized in Table 4. While chloroquine (as monotherapy or in combination with proguanil) is considered safe and effective in all trimesters of pregnancy [22], its usefulness is limited to areas where *P. vivax* is predominant and remains sensitive to this drug. *P. falciparum*, which is the main agent responsible for causing severe and sometimes fatal malaria is resistant to chloroquine in many regions. Mefloquine can be recommended for pregnant women travelling to an area with chloroquine-resistant *P. falciparum* [9,10,21], but prospective use in the first trimester has been reported in only two studies in malaria-endemic areas [23,24]. Limited data are available from a retrospective case series [25]. No prospective studies have been done in travellers. However, a drug safety database analysis showed no excess of neonatal malformations or miscarriages after mefloquine exposure (in prophylactic doses) in early pregnancy [21]. Additionally, the US FDA reviewed non-published data sources and also arrived at the conclusion that mefloquine was safe in all trimesters of pregnancy. Mefloquine should not be prescribed in the presence of a history of neuropsychiatric disorders such as seizures, affective disorders or psychosis. For travel to the border of Thailand–Laos, Thailand–Cambodia, Myanmar–Laos and China–Myanmar there are currently no safe, effective chemoprophylactic drugs for pregnant women as these areas are considered multi-drug-resistant areas [26].

The use of atovaquone-proguanil in pregnancy is still subject to debate, although the data on the individual components are reassuring and in some countries this prophylaxis is recommended [11]. It is likely that there have been many instances of inadvertent atovaquone-proguanil use before the patient discovered that she was pregnant. Analysing the data on the birth outcomes from these instances would be useful to assess the safety of atovaquone-proguanil use during pregnancy. Doxycycline is considered contraindicated by most authorities, since it may cause discolouration of the child's primary teeth if given during pregnancy [27]. Other studies also suggest a transient inhibition of bone growth in the newborn and unborn child [28]. In the UK guidelines for malaria prevention [10], doxycycline is considered best avoided during pregnancy. However, it is not absolutely contraindicated and may be considered as a possible prophylaxis during the first 15 weeks, if other options are unsuitable. Importantly, it is emphasized that the regimen must be concluded before 15 weeks' gestation. In Sweden, doxycycline can be recommended as chemprophylaxis during the first trimester. This evaluation is supported by data from the Swedish medical birth register, where 1809 women were exposed to tetracyclines during early pregnancy and where no excess of malformations was found compared to a control group with no exposure [29]. Primaquine is contraindicated in pregnancy, as it can cause acute haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency and it is not feasible to test the unborn for G6PD deficiency.

Our data highlight infrequent use of chemoprophylaxis. The majority of the pregnant women travelling who were

Table 7 Antimalarial treatments or combinations including sequential combinations used.

Treatment	Number n
No information	155
No treatment	3 (1 refused treatment)
Quinine	49
Quinine/quinidine	35
Quinine + artesunate	1
Quinine + clindamycin	59
Quinidine + clindamycin	11
Quinine/quinidine + clindamycin	90
Quinine + primaquine	2 (in 1 case primaquine given after delivery)
Quinine + clindamycine + artesunate	1
Quinine + clindamycine + artemether + lumefantrine	1
Quinine + doxycycline + artesunate	1
Quinine/quinidine + primaquine + tetracycline	2
Quinine/quinidine + clindamycin + tetracycline	1
Quinine/quinidine + pyrimethamine	11
Quinine/quinidine + tetracycline	21
Quinine + doxycycline	16
Chloroquine	56
Chloroquine + quinine	1
Chloroquine + quinidine	1
Chloroquine + quinine/quinidine	3
Chloroquine + quinine + clindamycin	2
Chloroquine + quinine/quinidine + clindamycin	5
Chloroquine + quinine + quinidine + clindamycin	1
Chloroquine + quinine/quinidine + pyrimethamine	2
Chloroquine + quinine/quinidine + clindamycin + pyrimethamine	1
Chloroquine + primaquine + mefloquine	1
Chloroquine + primaquine + quinine/quinidine	2
Chloroquine + primaquine + doxycycline	1
Chloroquine + primaquine	13 (in 5 cases primaquine given postpartum)
Chloroquine + mefloquine	2
Chloroquine + clindamycin	1
Chloroquine + pyrimethamine	2
Tetracycline	3
Clindamycin	3
Mefloquine	24
Mefloquine + clindamycin	1
Mefloquine + clindamycin + quinine/quinidine	2
Mefloquine + primaquine	2
Mefloquine + quinine/quinidine	3
Mefloquine + quinine/quinidine + tetracycline	1
Atovaquone + proguanil	16
Atovaquone + proguanil + doxycycline	2
Atovaquone + proguanil + quinine + quinidine	1
Atovaquone + proguanil + chloroquine	1
Atovaquone + proguanil + clindamycin	1
Pyrimethamine	2
Sulfadoxine + pyrimethamine	1
Artemisinine + lumefantrine	7
Arthemeter followed by artesunate	1
Artesunate	3
Artesunate followed by arthemeter + lumefantrine	2
Artesunate + clindamycin	2
Primaquine	1

subsequently diagnosed with malaria did not use chemoprophylaxis (85.6% of the women for whom this information was available). The reasons for this practice are probably caused by multiple factors. Some pregnant women may not have been aware of their pregnancy or may have foregone chemoprophylaxis because of concerns about possible adverse drug effects on the unborn child. Other risk factors may be socio-culturally determined: Travellers visiting friends and relatives in their country of origin (VFRs) have been shown to be a major risk group for imported malaria in several studies [30–33]. This was confirmed in our study, as VFR travellers account for a significant fraction of our study population (57.8%). VFR travellers may mistakenly believe that previous, partial immunity protects them from the disease [34] which is true with regard to protection against severe disease [35]. The cost of the chemoprophylaxis is also believed to be a discouraging factor for some VFRs [36].[2]

VFR travellers should be reminded that they need to take full preventive precautions. Since many VFRs do not seek pre-travel advice, they should also be targeted by the public health system including obstetricians. The Centers for Disease Control and Prevention recommends targeted messages for travellers according to peak travel seasons [6].

After VFRs, the second largest sub-group with imported malaria were refugee women or recent migrants. Screening may be an option here to detect malaria cases [37]. It should be taken into account that these women would not have used typical chemoprophylaxis regimen. However, in some countries with moderate or high malaria transmission, intermittent preventive treatment via administration of sulfadoxine/pyrimethamine (SP) during pregnancy is recommended by WHO [20].

Among the women in our study population who did use chemoprophylaxis, chloroquine and/or proguanil was most

[2] It should be noted that some of these medications are not recommended for use during pregnancy or are not actual recommended regimens or may have been used sequentially.

Table 8 International recommendations for malaria treatment in pregnancy.

	WHO [12]	ESGCP [13]
Uncomplicated falciparum malaria in 1st trimester	**First line:** quinine + clindamycin or quinine monotherapy if clindamycin is not available (artesunate + clindamycin if this treatment fails)	**First line:** quinine + clindamycin or quinine monotherapy if clindamycin is not available
Uncomplicated falciparum malaria in 2nd and 3rd trimester	Artemisinin-based combination therapy (ACT) known to be effective in the region where malaria was acquired[a] or artesunate + clindamycin or quinine + clindamycin	**First line:** artemether-lumefantrine **Second line:** quinine + clindamycin, quinine monotherapy or mefloquine
Complicated falciparum malaria in 1st trimester	Artesunate[b]	**First line:** i.v. quinine
Complicated falciparum malaria in 2nd and 3rd trimester	Artesunate[b]	**First line:** i.v. artesunate **Second line:** i.v. quinine
P. ovale, *P. malariae* und *P. vivax*	Chloroquine in uncomplicated cases. Artesunate for complicated *P. vivax* malaria. Primaquine for treatment of liver-stages of *P. ovale* and *P. vivax* is contraindicated during pregnancy	**First line:** in all trimesters oral chloroquine **Second line:** in 2nd and 3rd trimester oral ACT

[a] Excluded is dihydroartemisinin-piperaquine due to current insufficient data on use in pregnancy.
[b] If artesunate is not available in later pregnancy, WHO considers artemether preferable to quinine as quinine is associated with an elevated risk for hypoglycaemia [8].

frequently used. However, many of these women travelled to chloroquine-resistant *P. falciparum* and/or chloroquine-resistant *P. vivax* areas. A recent drug utilization study by Bloechliger et al. suggested that chloroquine-based regimens are disproportionally often prescribed by GPs relatively inexperienced in travel medicine [38]. It is however, important to point out that antimalarial prophylaxis recommendations and resistance patterns have changed during the time frame of the study (1991–2014).

Data on the use of protection against mosquito bites such as repellents, impregnated bed nets and clothing were largely unavailable. For pregnant women travelling to areas of drug-resistant *Plasmodium* species and for long-term travellers, personal protection measures against mosquitoes constitute a fundamental part of malaria prevention. The use of insecticide-treated bed nets and the application of DEET-repellents are considered safe and should be recommended to all pregnant travellers visiting malaria-endemic areas as well as protective clothing and air-conditioned or screened sleeping areas [20,39]. It should be noted that no studies exist on the use of DEET in women in the first trimester, or on the use of other repellents such as Icaridin or IR3535 in pregnancy [40], but based on experience, DEET is recommended by experts even in the first trimester [9,10].

A total of 50 treatment regimens were reported in our analysis. Data on the safety and efficacy of the use of malaria treatment in pregnant travellers are scarce. There are guidelines available (Table 8). Combinations of artemisinin or its derivatives with other antimalarials (ACT) are considered the most effective antimalarial drugs to date and are generally well tolerated [41], but difficult to evaluate in pregnant women for safety and ethical reasons. Data from animal studies suggest that high doses of artemisinins in the first trimester are teratogenic [42,43]. A recent observational study on first trimester exposure to artemether–lumefantrine did not indicate an excess of perinatal mortality, preterm deliveries or low birth weights compared to pregnant women who were exposed to sulfadoxine–pyrimethamine and/or quinine. Additionally, neurodevelopmental parameters up to twelve months were similar compared to the control-group [44].

McGready and colleagues suggest that the potential risk of miscarriage with the use of artemisinin antimalarials in early pregnancy may be comparable with pregnant women treated with chloroquine or quinine and women who had no malaria during pregnancy [16]. Currently, in Europe, a pregnancy registry for the new EMA-registered malaria treatment, dihydroartemisinin-piperaquine has been established, recording malaria treatment outcomes after use in pregnant women and their infants up to the age of twelve months [45]. Included are women who take this combination within the time frame of one month before or at any time in pregnancy from conception onwards, and also women whose partner took this drug within one month before conception. If healthcare professionals are made aware of this registry and collaborate in reporting, then the register will be a valuable source of prospective surveillance data on the safety profile of this ACT in pregnancy – Pregnancy Register [45].

A major strength of our study is the large number of cases collected from various contributing institutions in non-endemic countries all over the world, and the pioneering character of this undertaking, as systematic data collections on this topic are scarce. One considerable limitation, however, was the largely incomplete datasets, especially on pregnancy outcomes. Additionally, follow-up until birth and thereafter to detect potential low birth

weight, malformations or gestational age at birth were practically non-existent and do not allow for a conclusion on possible adverse effects of chemoprophylaxis or treatment on the pregnancy. It can be speculated that most women would only have been seen by malaria/infectious disease specialists at the time of their infection, and thereafter returned to the care of their obstetricians for birth and follow-up. Also, a large number of our cases were contributed by national malaria reference centres, which often receive limited information on cases. Furthermore, information on the use of chemoprophylaxis is usually based on self-reporting by the pregnant women with the possibility of a recall bias and the risk of over-estimation of adherence to chemoprophylaxis.

The greatest limitation on this topic, however, is the absence of standardized data internationally and this is an area where collaboration between reference centres and national authorities should be pursued to achieve good quality reporting of malaria cases and outcomes in pregnancy.

5. Conclusions

Our data show that malaria chemoprophylaxis and treatment in pregnant travellers are challenges for travel medicine with varying national recommendations. The treatment of imported malaria in pregnant women does not appear to follow clear guidelines and over 50 treatment regimens were reported in this analysis. Efforts should be made to harmonize treatment recommendations. Prospective international surveillance databases on pregnant women using malaria chemoprophylaxis and/or treatments should be established to enable the evaluation of medication tolerability and foetal outcomes in this vulnerable group.

Conflict of interest

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References

[1] Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 2007 Feb;7(2):93—104.

[2] Kulcsar DD. Effects of malaria on pregnancy. Can Med Assoc J 1947 Oct;57(4):332—7.

[3] Rijken MJ, McGready R, Boel ME, Poespoprodjo R, Singh N, Syafruddin D, et al. Malaria in pregnancy in the Asia-Pacific region. Lancet Infect Dis 2012 Jan;12(1):75—88.

[4] Lindsay S, Ansell J, Selman C, Cox V, Hamilton K, Walraven G. Effect of pregnancy on exposure to malaria mosquitoes. Lancet 2000 Jun 3;355(9219):1972.

[5] United Nations World Tourism Organization (UNWTO). Annual report. 2013.

[6] Cullen DA, Arguin PM. Malaria surveillance-United States 2012. MMWR Surveill Summ 2014 Dec 5;63(12):1—22.

[7] United Nations Statistics Division. Geographical region and composition. 31.10.2013. Available from: [accessed on 22.02.15], http://unstats.un.org/unsd/methods/m49/m49regin.htm.

[8] World Health Organization. Management of severe malaria: a practical handbook. 3rd ed. 2012.

[9] Centers of Disease Control and Prevention (CDC). Health information for international travel, yellow book. 2014.

[10] Public Health England. Guidelines for malaria prevention in travellers from the UK. 2014.

[11] Recommandations sanitaires pour les voyageurs. Bulletin épidemiologique hebdomadaire. 2014. Nr 16—17/03.06.2014.

[12] World Health Organization. Guidelines for the treatment of malaria. 2nd ed. 2010.

[13] Askling HH, Bruneel F, Burchard G, Castelli F, Chiodini PL, Grobusch MP, et al. Management of imported malaria in Europe. Malar J 2012 Sep 17;11:328.

[14] Ward SA, Sevene EJP, Hastings IM, Nosten F, McGready R. Antimalarial drugs and pregnancy: safety, pharmacokinetics and pharmacovigilance. Lancet Infect Dis 2007 Feb;7(2):136—44.

[15] Rogerson SJ, Hviid L, Duffy PE, Leke RF, Taylor DW. Malaria in pregnancy: pathogenesis and immunity. Lancet Infect Dis 2007 Feb;7(2):105—17.

[16] McGready R, Lee SJ, Wiladphaingern J, Ashley EA, Rijken MJ, Boel M, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. Lancet Infect Dis 2012 May;12(5):388—96.

[17] McGready R, Ashley EA, Nosten F. Malaria and the pregnant traveller. Travel Med Infect Dis 2004 Aug-Nov;2(3—4):127—42.

[18] Nosten F, McGready R, Simpson JA, Thwai KL, Balkan S, Cho T, et al. Effects of plasmodium vivax malaria in pregnancy. Lancet 1999 Aug 14;354(9178):546—9.

[19] Barber BE, Bird E, Wilkes CS, William T, Grigg MJ, Paramaswaran U, et al. Plasmodium knowlesi malaria during pregnancy. J Infect Dis 2015 Apr 1;211(7):1104—10.

[20] World Health Organization. World malaria report. 2014.

[21] Schlagenhauf P, Blumentals WA, Suter P, Regep L, Vital-Durand G, Schaerer MT, et al. Pregnancy and fetal outcomes after exposure to mefloquine in the pre- and periconception period and during pregnancy. Clin Infect Dis 2012 Jun;54(11):e124—31.

[22] Villegas L, McGready R, Htway M, Paw MK, Pimanpanarak M, Arunjerdja R, et al. Chloroquine prophylaxis against vivax malaria in pregnancy : a randomized, double-blind, placebo-controlled trial. Trop Med Int Health 2007 Feb;12(2):209—18.

[23] Steketee RW, Wirima JJ, Slutsker L, Khoromana CO, Heymann DL, Breman JG. Malaria treatment and prevention in pregnancy: indications for use and adverse events associated

with use of chloroquine or mefloquine. Am J Trop Med Hyg 1996;55(1 Suppl.):50—6.
[24] Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, de Vries A, et al. The effects of mefloquine treatment in pregnancy. Clin Infect Dis 1999 Apr;28(4):808—15.
[25] Smoak BL, Writer JV, Keep LW, Cowan J, Chantelois JL. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. J Infect Dis 1997 Sep;176(3):831—3.
[26] Bundesamt für Gesundheit. Impfungen und Malariaschutz bei Auslandreisen. Empfehlungen Stand März. 2014. Available from: [accessed on 03.03.15], http://www.bag.admin.ch/impfinformation/06317/index.html?lang=de.
[27] Wallman IS, Hilton HB. Teeth pigmented by tetracycline. Lancet 1962 Apr 21;1(7234):827—9.
[28] Demers P, Fraser D, Goldbloom RB, Haworth JC, LaRochelle J, MacLean R, et al. Effects of tetracylines on skeletal growth and dentition. A report by the nutrition committee of the Canadian paediatric Society. Can Med Assoc J 1968 Nov 2; 99(17):849—54.
[29] Hellgren U, Rombo L. Alternatives for malaria prophylaxis during the first trimester of pregnancy: our personal view. J Travel Med 2010 Mar-Apr;17(2):130—2.
[30] Monge-Maillo B, Norman FF, Pérez-Molina JA, Navarro M, Díaz-Menéndez M, López-Vélez R. Travelers visiting friends and relatives (VFR) and imported infectious disease: travelers, immigrants or both ? A comparative analysis. Travel Med Infect Dis 2014 Jan-Feb;12(1):88—94.
[31] Checkley AM, Smith A, Smith V, Blaze M, Bradley D, Chiodini PL, et al. Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. BMJ 2012 Mar 27;344:e2116.
[32] Smith AD, Bradley DJ, Smith V, Blaze M, Behrens RH, Chiodini PL, et al. Imported malaria and high risk groups: observational study using UK surveillance data 1987—2006. BMJ 2008 Jul 3;337:a120.
[33] Botelho-Nevers E, Laurencin S, Delmont J, Parola P. Imported malaria in pregnancy: a retro-spective study of 18 cases in Marseille, France. Ann Trop Med Parasitol 2005 Oct;99(7):715—8.
[34] Wieten RW, Harting J, Biemond PM, Grobusch MP, van Vugt M. Towards improved uptake of malaria chemoprophylaxis among West African travellers: identification of behavioural determinants. Malar J 2013 Oct 10;12:360.
[35] Pistone T, Diallo A, Mechain M, Receveur MC, Malvy D. Epidemiology of imported malaria give support to the hypothesis of "long-term" semi-immunity to malaria in sub-Saharan African migrants living in France. Travel Med Infect Dis 2014 Jan-Feb;12(1):48—53.
[36] Neave PE, Jones CO, Behrens RH. Challenges facing providers of imported malaria-related healthcare services for Africans visiting friends and relatives (VFRs). Malar J 2014 Jan 9;13: 17.
[37] Monge-Maillo B, López-Vélez R. Migration and malaria in Europe. Mediterr J Hematol Infect Dis 2012;4(1):e2012014.
[38] Bloechliger M, Schlagenhauf P, Toovey S, Schnetzler G, Tatt I, Tomianovic D, et al. Malaria chemoprophylaxis regimens: a descriptive drug utilization study. Travel Med Infect Dis 2014 Nov-Dec;12(6 Pt B):718—25.
[39] McGready R, Hamilton KA, Simpson JA, Cho T, Luxemburger C, Edwards R, et al. Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. Am J Trop Med Hyg 2001 Oct; 65(4):285—9.
[40] Roggelin L, Cramer JP. Malaria prevention in the pregnant traveller. Travel Med Infect Dis 2014 May-Jun;12(3): 229—36.
[41] Lwin KM, Phyo AP, Tarning J, Hanpithakpong W, Ashley EA, Lee SJ, et al. Randomized, double-blind, placebo-controlled trial of monthly versus bimonthly dihydroartemisinin-piperaquine chemoprevention in adults at high risk of malaria. Antimicrob Agents Chemother 2012 Mar;56(3):1571—7.
[42] Clark RL, Lerman SA, Cox EM, Gristwood WE, White TE. Developmental toxicity of artesunate in the rat: comparison to other artemisinins, comparison of embryotoxicity and kinetics by oral and intravenous routes, and relationship to maternal reticulocyte count. Birth Defects Res B Dev Reprod Toxicol 2008 Aug;83(4):397—406.
[43] Longo M, Zanoncelli S, Torre PD, Riflettuto M, Cocco F, Pesenti M, et al. In vivo and in vitro investigations of the effect of the antimalarial drug dihydroartemisinin (DHA) on rat embryos. Reprod Toxicol 2006 Nov;22(4):797—810.
[44] Manyando C, Njunju EM, Virtanen M, Hamed K, Gomes M, Van geertruyden J-P. Exposure to artemether-lumefantrine (Coartem®) in first trimester pregnancy in an observational study in Zambia. Malar J 2015;14:77.
[45] Sigma-Tau Pregnancy Registry for Eurartesim®. Available from: [accessed on 03.03.15]. http://pregnancy-registry.net/index.php?Itemid=489&lang=en.
[46] Jiménez BC, Cuadros-Tito P, Ruiz-Giardin JM, Rojo-Marcos G, Cuadros-González J, Canalejo E, et al. Imported malaria in pregnancy in Madrid. Malar J 2012 Apr 11;11:112.