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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 1977 to 2014 from 8 different collaborators in Europe, the United States and Japan. Most cases were from the period 1991–2014. 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 632 cases were collated, providing information on *Plasmodium* species, region of acquisition, nationality, country of residence, reason for travel, age, gestational age,

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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* in 72% of cases. Among the 543 cases where information on the use of chemoprophylaxis was known, 471 (74.5%) did not use chemoprophylaxis or used incorrect or incomplete chemoprophylaxis. The main reason for travelling was “visiting friends and relatives” VFR (48.6%) and overall, most cases of malaria were imported from West Africa (85.9%). Severe anaemia was the most frequent complication in the mother. Data on offspring outcome was limited, but spontaneous abortion was a frequently reported foetal outcome (n = 14). A total of 50 different variants of malaria treatment regimens were reported.

Conclusion—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.

Keywords

Imported malaria; Pregnancy; Chemoprophylaxis; Travel; Treatment; Complications

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]. Additionally, pregnant women are more attractive to *Anopheles* mosquitoes compared to non-pregnant women, although the mechanisms for this are poorly understood [3]. More than 80 million travellers visit malaria-endemic areas annually [4]. 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 [5]. 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, most malaria treatments have not been tested in pregnant women and there is little information on outcomes for mother and foetus in the context of imported malaria.

Methods

We conducted a retrospective descriptive analysis of pregnant women who were diagnosed with laboratory confirmed malaria in non-endemic, industrialized countries after having visited an endemic area. 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; 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. 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 to 2014 were included, with the exception of France (Marseille), where cases were extracted from two publications dating from the years 1977–2010.

The primary aims were to assess the outcome for the mother and child, as well as the type of travel associated with infection acquisition (VFR, tourism) and the preventive measures and treatments used.

Results

Number of cases (Table 1)

We collated a total number of 632 cases of imported malaria in pregnancy from areas where malaria is non-endemic; USA: n = 426, 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. It varied from 24.2 years in the Austrian case collection, where all 5 patients were migrants from Nigeria to 30.6 years in Japan, where apart from 1 patient all 9 women were of Japanese origin.

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.

Plasmodium species (Table 1)

The majority of cases (n = 455, 72% of all 632 cases) were diagnosed with *P. falciparum* malaria.

The second most frequent malaria species was *P. vivax* (n = 92, 14.5%).

The remaining cases were diagnosed with *P. ovale* (n = 15, 2.4%), *P. malariae* (n = 10, 1.6%) and 7 cases of mixed infection. The *Plasmodium* species listed by reporting centre is illustrated in Figure 1.

Region of Malaria Acquisition (Table 2)

Of the 611 patients for whom information was available on the geographic region of malaria acquisition (according to UN criteria; [6]), in 525 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 who were diagnosed with imported malaria in the United States and the United Kingdom fell in this category. In Marseille, however, most cases were imported from East Africa, more specifically from the Comoros, a former overseas territory of France.

86 women (14%) acquired malaria in East Africa (e.g. Comoros, Uganda, Kenya), followed by 68 cases (11.1%) of 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%).

Reason for travel

The most common reason for travel was visiting friends and relatives (n = 307, 48.6%). Another 130 women (20.6%) were refugees or recently immigrated. Twenty patients (3.2%) 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, 16%), the reason for travel was not stated in the clinical data.

Use of Chemoprophylaxis (Table 3)

Among the 543 pregnant patients, the majority (n = 471, 74.5%) either did not take any chemoprophylaxis at all, or were using incomplete or incorrect chemoprophylaxis. This was true for 314 (83.7% of 375) 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 72 women (13.2%) who were reported to have taken chemoprophylaxis, one woman had taken “herbs” as a prophylaxis. The preferred drug for malaria prevention was chloroquine (n = 22; 30.5% out of 72 patients who used chemoprophylaxis). Ten women (13.9%) 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 (2.8%) used doxycycline; one of whom suffered a miscarriage (gestational age unknown). In the other case, doxycycline was given postpartum. Other regimens used for chemoprophylaxis were pyrimethamine (n = 6), pyrimethamine/sulfadoxine (n = 4), chloroquine/proguanil (n = 2), proguanil (n = 2), artesunate (n = 2), primaquine (n = 1) and arthemeter/lumefantrine (n = 1). 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”.

Outcome of mother and child

No maternal deaths were reported but information on outcomes was largely incomplete. 43 women were classified as having ‘severe malaria’¹. In 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.

Some 235 women had no reported malaria complications (Table 5). Of a total of 52 reported maternal malaria complications (several complications possible per individual case), the most frequent were severe anaemia with a measured haemoglobin of 7 g/l 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. Two 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 to 11 g/L, n = 82); thrombocytopenia (platelet count < 150.000/μl; n = 28); thrombosis (n = 3); splenomegaly (n = 7) and/or hepatomegaly (n = 3). There were also 14 other complications noted, such as hypertension; gestational diabetes; and non-specified complications.

Concerning the offspring, few data were available (Table 6). 66 babies were reported to have reached term. In 51 cases the offspring was reported to be healthy. Among these 51 cases, in 7 cases, child health at birth was good. In an additional two cases, child health on follow-up at 3 months and 12 months respectively was also considered good. 10 children 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, 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

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

relatives. She was reported to have taken chemoprophylaxis before admission, but the exact drug remained unclear). Two cases of congenital malaria were documented.

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 = 53). Monotherapy with quinine or quinidine was administered in 49 cases. Quinine or quinidine plus tetracycline was given in 38 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.

Discussion

Our retrospective analysis included 632 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, both of which are hydrolysed to the active metabolite dihydroartemisinin. pregnant women were recently shown to have lower plasma concentrations of dihydroartemisinin compared to non-pregnant adults. This finding was accompanied by a lower cure-rate of the malaria infection [13].

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, 14]. Additionally, pregnant women often experience a more severe course of the infection than non-pregnant women [2]. *P. falciparum* and less often *P. vivax* and *P. knowlesi* 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, 15, 16, 17]. Little is known regarding the impact of *P. ovale* and *P. malariae* on pregnancy. In our study, there were 43 cases designated as “severe malaria” (mainly *P. falciparum* (36 cases) and 5 cases of single *P. vivax* infection and two unknown) and, although we have sparse detail information, a total of 64 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 43 cases of severe malaria were reported. In the four afore-mentioned 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 [18].

Prevention of malaria in pregnant women is problematic and travel should be deferred if possible [9]. Few studies have evaluated the safety of malaria chemoprophylaxis for pregnant women or the unborn child [19, 20].

While chloroquine (as monotherapy or in combination with proguanil) is considered safe and effective in all trimesters of pregnancy [20], 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* [16, 19], but its use in the first trimester has been reported in only two studies [21, 22] and in a case series [23] and no prospective studies have been performed 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 [19]. 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 [24].

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 [10]. 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 [25]. Other studies also suggest a transient inhibition of bone growth in the newborn and unborn child [26]. In the UK guidelines for malaria prevention [9],

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. This evaluation is supported by data from the Swedish medical birth register, where 1,809 women were exposed to tetracyclines during early pregnancy and where no excess of malformations was found compared to a control group with no exposure [27]. Primaquine is contraindicated in pregnancy, as it can cause acute hemolysis 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 subsequently diagnosed with malaria ($n = 471$, 86.7% of the women for whom this information was available) did not take any preventive measures at all or used incomplete chemoprophylaxis. 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 [28, 29, 30]. This was confirmed in our study, as VFR travellers account for a significant fraction of our study population (48.6%). VFR travellers may mistakenly believe that previous, partial immunity protects them from the disease [31] which is true with regard to protection against severe disease [32]. The cost of the chemoprophylaxis is also believed to be a discouraging factor for some VFRs [33]. 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 [5].

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 [34]. 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 [18].

Among the women in our study population who did use chemoprophylaxis, post 1990, chloroquine and/or proguanil was most 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 [35]. International guidelines on the use of chemoprophylaxis are depicted in Table 4.

Unfortunately, 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 [18, 36]. 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 but based on experience, DEET is recommended by experts even in the first trimester [7, 9].

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 [37], but difficult to evaluate in pregnant women for safety and ethical reasons. Data from animal studies suggest that high doses of artemisinin drugs in the first trimester are teratogenic [38, 39]. 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 [40].

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 [15]. Currently, in Europe, a pregnancy registry for dihydroartemisinin-piperaquine has been established, recording malaria treatment outcomes after use of this malaria treatment, in pregnant women and their babies up until the age of twelve months [41]. 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.

The number of cases where tetracyclines were used in treatment regimens stand out among all these different regimens ($n = 49$). Tetracyclines are considered to be contraindicated for pregnant women, because of their potential effects on the unborn: teeth discoloration and possibly also temporary inhibition of foetal bone growth [26].

Our limited data set did not permit the evaluation of child outcomes post-treatment.

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 sparse 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 overestimation of adherence to chemoprophylaxis.

The greatest limitation of the study, 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.

Conclusions

Our data show that malaria chemoprophylaxis and treatment in pregnant travellers are challenges for travel medicine with varying international 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.

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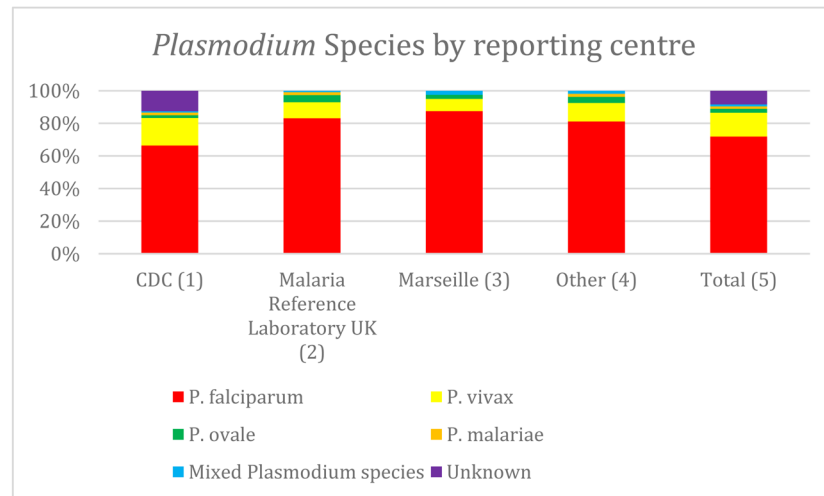


Figure 1.

(1) CDC: n = 426

(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 = 63

Table 1Demographic characteristics and *Plasmodium* species reported.

Variables		Number or Frequency
Pregnant Women		n = 632 ^a
Age	Unknown	n = 11
	Mean age ^b (years)	29.6
	Range (years)	13 – 64
Gestational Age	Unknown	N = 505
	1 st Trimester	23.6% (n = 30)
	2 nd Trimester	38.6% (n = 49)
	3 rd Trimester	36.2% (n = 46)
	Post Partum	1.6% (n = 2)
<i>Plasmodium</i> Species	Unknown	8.4% (n = 53)
	<i>Plasmodium falciparum</i>	72% (n = 455)
	<i>Plasmodium vivax</i>	14.6% (n = 92)
	<i>Plasmodium malariae</i>	1.6% (n = 10)
	<i>Plasmodium ovale</i>	2.4% (n = 15)
	Mixed <i>P. falciparum</i> / <i>P. vivax</i>	0.16% (n = 1)
	Mixed <i>P. falciparum</i> / <i>P. malariae</i>	0.32% (n = 2)
	Mixed <i>P. falciparum</i> / <i>P. ovale</i>	0.32% (n = 2)
	Mixed <i>P. vivax</i> / <i>P. ovale</i>	0.32% (n = 2)

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

Table 2

Regions of malaria acquisition listed by reporting institutions.

	CDC n ^a	PHE n	MRL n	Marselle n	Other n	Total N = 611 n (%)
<i>Eastern Africa</i>	26	16	37	7	7	86 (14.1%)
<i>Middle Africa</i>	48	5	0	15	15	68 (11.1%)
<i>Northern Africa</i>	4	1	0	0	0	5 (0.8%)
<i>Southern Africa</i>	5	0	0	0	0	5 (0.8%)
<i>Western Africa</i>	259	71	3	27	27	351 (57.4%)
<i>Caribbean</i>	7	0	0	0	0	7 (1.1%)
<i>Central America</i>	24	0	0	0	0	24 (3.9%)
<i>South America</i>	4	0	0	1	1	5 (0.8%)
<i>Southern Asia</i>	39	8	0	0	0	47 (7.7%)
<i>South-Eastern Asia</i>	1	0	0	1	1	2 (0.3%)
<i>Melanesia</i>	1	0	0	0	0	1 (0.16%)

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

Table 3

Malaria chemoprophylaxis used by pregnant women diagnosed with malaria.

	Total N = 543 n (%)
No chemoprophylaxis	471 (74.5%)
Chemoprophylaxis used	72 (11.4%)
Chloroquine	22 (4.1%)
Chloroquine + proguanil	2 (0.4%)
Proguanil	2 (0.4%)
Atovaquone + proguanil	1 (0.2%)
Mefloquine	10 (1.9%)
Doxycycline	2 (0.4%)
Primaquine ^a	1 (0.2%)
Pyrimethamine	6 (1.1%)
Sulfadoxine + pyrimethamine	4 (0.7%)
Artesunate	2 (0.4%)
Arthemeter + lumefantrine	1 (0.2%)
“Herbs”	1 (0.2%)
Chemoprophylaxis used but medication unknown	18 (3.3%)

^aPrimaquine is contraindicated in pregnancy, as it can cause acute hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency and it is not feasible to test the unborn for G6PD deficiency.

Table 4

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

	Centers for Disease Control and Prevention [7]	Public Health England [9]	France [10]
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 <i>P. vivax</i> .	No information.	No information.
Proguanil		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 5Clinical features of *P. falciparum* malaria in the mother.

Type of complication	n
No complications	235
Neurological impairment/coma	2
Prostration	2
Pulmonary oedema/acute respiratory distress syndrome (ARDS)	13
Respiratory distress, hyperventilation	1
Acute renal Failure (Creatinine > 265 µmol/l)	5
Severe anaemia (Hb < 7 g/dl)	22
Jaundice	4
Coagulopathy and/or disseminated intravascular coagulation	2
Circulatory shock (systolic blood pressure < 70 mm Hg)	1
Severe malaria	43

* There were no data available on complications in the mother from UK data.

Table 6

Outcome of offspring *.

No information	537
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

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

Table 7Antimalarial treatments or combinations including sequential combinations used ²

Treatment	Number n
No information	195
No treatment	3 (1 refused treatment)
Quinine	14
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 + clindamycin + artesunate	1
Quinine + clindamycin + 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	17
Chloroquine	53
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

Treatment	Number n
Mefloquine + quinine/quinidine	3
Mefloquine + quinine/quinidine + tetracycline	1
Atovaquone + proguanil	14
Atovaquone + proguanil + doxycycline	2
Atovaquone + proguanil + quinine + quinidine	1
Atovaquone + proguanil + chloroquine	1
Atovaquone + proguanil + clindamycin	1
Pyrimethamine	2
Sulfadoxine + pyrimethamine	1
Artemisinin + lumefantrine	7
Artemeter followed by artesunate	1
Artesunate	3
Artesunate followed by artemeter + lumefantrine	2
Artesunate + clindamycin	2
Primaquine	1

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 [11]
Uncomplicated falciparum malaria in 1st trimester	First line: quinine + clindamycin or quinine monotherapy if clindamycin is not available	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	First line: artesunate	First line: i.v. quinine
Complicated falciparum malaria in 2nd and 3rd trimester	First line: artesunate ^b	First line: i.v. artesunate Second line: i.v. quinine
<i>P. ovale</i>, <i>P. malariae</i> und <i>P. vivax</i>	Oral chloroquine in uncomplicated <i>P. vivax</i> cases, no further specific information in pregnant women	First line: in all trimesters oral chloroquine Second line: in 2 nd and 3 rd trimester oral ACT

^aExcluded 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]