Persistence of imported Malaria into the UK: an epidemiological review of risk factors
and at risk groups

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Summary: After a decline in the early 2000's imported malaria has reached a plateau. Focus
on people returning to countries of origin as the at-risk population oversimplifies intervention
planning. Holiday and business reasons together exceed this as a risk factor.

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Abstract

Background: The UK documented a fall of over 30% in imported cases of malaria annually between 1996-2003 however there are still around 1700 cases and 5-10 deaths each year. Prophylaxis health messages focus on families returning to their country of origin as being at particular risk.

Methods: We reviewed 225 paper records including demographic data of patients seen in Addenbrooke’s hospital (Cambridge University Hospital Foundation Trust – CUHFT) a tertiary referral centre in Cambridge, England. All the records of the patients seen in CUHFT over the period 2002-2016 were analysed and assessed in the context of national figures from Public Health England.

Results: Over the period 2004-2016 there was no perceptible decrease in imported cases of malaria locally or nationally. Local figures largely reflected national trends. *P. falciparum* remains responsible for most imported infections (66.7%), *P. vivax* contributed 15.1%, *P. malariae* 4%, *P. ovale* 6.7% and 7.5% (17/225) patients had an incomplete record. Most cases were reported in people coming from West Africa. Sierra Leone and the Ivory Coast had the highest proportions of travellers being infected at 8 and 7 per 1000 respectively. Visiting family in the country of origin (27.8%) was the most common reason to have travelled to malarious countries. However, this was exceeded by the combined numbers travelling for work reasons and holidays, 22.5% and 20.1% respectively. 60% of patients took no prophylaxis. Of those that did, none of the patients finished their chemoprophylaxis regime.
Conclusions: A significant number of travellers to malarious countries still take no chemoprophylaxis. Health advice about prophylaxis pre-travel to malarious countries should be targeted not only at those visiting family in their country of origin but also to those travelling for holiday and work/business.

Keywords: malaria, imported, risk factors
Introduction

Malaria is a disease caused by the protozoan parasites of the genus \textit{Plasmodium} transmitted by the \textit{Anopheles} mosquito. The human types of malaria are \textit{Plasmodium falciparum} (\textit{P.falciparum}), which is the most serious and can be fatal, \textit{P.vivax}; \textit{P.malariae}, \textit{P.ovale} and rarely \textit{P.Knowlesii} which can each cause acute, severe disease but with a low mortality [1]. Worldwide in 2015 there were an estimated 214 million new cases of malaria with a 429 000 deaths (WHO Malaria factsheet, 2016). The WHO African region accounts for 90%, South East Asia 7% and the Eastern Mediterranean region 2% of these cases.

Malaria in the UK is always imported. At 1500 cases per year, it is the most common imported tropical disease [2, 3]. Much of this morbidity has been attributed to people returning to the country of origin of their family; this group was previously shown to report the least use of chemoprophylaxis [4]. Regional experience of imported malaria in the UK has not been reported since 2015 [5]. We were curious to know whether the epidemiology had changed and whether health advice messages were still being appropriately targeted. We undertook a review and analysis of the epidemiological data of malaria patients seen in Addenbrooke's hospital (Cambridge University Hospital Foundation Trust – CUHFT) from 2002 to 2016 and compared this with national data.
Methods

This was a retrospective review of patients with confirmed malaria seen in CUHFT from the year 2002 to 2016. Malaria infection was confirmed using a combination of antigen testing, clinical data and blood films. Whilst most of the patient records were paper based the patient records software, EPIC, was accessed for more detailed demographic data. National figures on imported malaria were kindly provided by Public Health England (PHE) Malaria Reference Laboratory.

Results

General Trend

225 patients had confirmed malaria between 2002 and 2016, with a mean of 15 cases per year. There was little evidence of any change in trend from 2004 onwards. Most of these infections were due to *P.falciparum* which accounted for 66.7% (150/225 cases) in this 15 year period, (Figure 1a).

UK malaria cases show a decline in malaria cases of 31.2% between 1996 and 2003, however this is not maintained as the numbers of malaria cases per year in the UK plateau thereafter (Figure 1b).

Age and Gender
Data on age and gender was available for 219 patients. There were more male cases of malaria at all ages except in the 10-14 age group. The highest number of malaria cases for men was in the 30-34 age group peaking at 29 cases; for females it was in the 20-24 age group peaking at 12 cases. (Figure 2).

**Travel History**

Most of the malaria cases seen in CUHFT between 2002 and 2016 were imported from Africa, West Africa (in particular Ghana and Nigeria) contributed the most (66) cases. Some patients visited more than one malarious country and it was unclear where their malaria was acquired (Figure 3).

National data (Figure 3b) shows similar trends to those seen in CUHFT with Nigeria and Ghana also contributing the most malaria cases imported to the UK in this time period (7175 and 2567 reported cases respectively). India had the most people coming to the UK, with over 16 million people, however it had one of the lowest rates of imported infection at 8 cases per 100000 travellers nationally. This is in contrast to countries like Sierra Leone; Ivory Coast and Cameroon that had the highest proportions of infection at 7,8 and 5 cases per 1000 travellers respectively despite relatively fewer travellers. No malaria cases were recorded by the Malaria Research Laboratory (MRL) nationally as shown above from Egypt, Laos, Vietnam and Mauritius despite there being at least one case from each of these countries seen in CUHFT (Figure 3b); this disparity is unexplained. Based on country of birth the UK and Africa accounted for 64% of all cases (Figure 4b).
Reasons for Travel

Reasons for travelling to a malarious country were documented for 169 patients. Of these, the largest group were those visiting family in their country of origin 27.8% (47/169) however a large number of patients were also UK residents visiting malarious countries for holiday, 22.5% (38/169) and/or work reasons, 20.1% (34/169) including volunteer work and military attachments. Other reasons included UK citizens living abroad 2.4% (4/169), foreign students studying in the UK 13.0% (22/169), new entrants to the UK 8.3% (14/169) and foreign visitors falling ill in the UK 5.9% (10/169) (Figure 4a).

Chemoprophylaxis

To assess the effectiveness of health messages on the importance of anti-malarial chemoprophylaxis we examined the evidence for taking and adhering to chemoprophylaxis by this population over this 15-year period. This data was available for 193 patients. Of these, a staggering 60% (116/193) patients took no prophylaxis at all. Of the 40% (77/193) that took prophylaxis 32.5% (25/77) did not know what they had taken (‘unknown’) (Figure 5). The remaining 52 took a variety of drugs but none consistently so and none on return to the UK. The most common identified prophylactic drug used was doxycycline.
Treatment and Outcomes

Parasitaemia data was available for patients presenting with *P.falciparum* malaria in 109/150 patients. Most patients presented quite early on with low parasitaemia levels in the range 0.1-0.5% which may have contributed to the successful treatment outcomes (Supplementary Figure 1).

Heavier parasitaemia was observed in patients at the extremes of age with an average of 4.3% in the 5-9 age group and 5.35% in the 65-69 age group as shown in (Supplementary Figure 2).

Almost all of the patients treated in Addenbrooke’s hospital who presented with malaria between 2002 and 2016 recovered. Data on outcomes of treatment was obtained using Addenbrooke’s EPIC software and was available for 202 patients. Of these, 98.5% (199/202) recovered and 1.5% (3/202) succumbed to infection (Supplementary Figure 3).

UK national figures show a similar pattern of treatment outcomes as that shown in CUHFT. Most patients, 99.6% (24045/24149), who had malaria recovered, while 0.4% (104/24149) succumbed to infection.

Discussion
In this study, we set out to elucidate the trends of malaria in patients presenting to Addenbrooke’s hospital. The total malaria cases per year stayed relatively constant with an average of 15 cases every year. This is in line with data from the UK malaria report 2015 [2] which shows relatively static numbers from the year 2002 to 2015 following a steep decline from 2500 to 2050 cases annually seen between 1996 and 2001. This suggests that since this earlier fall current health messages about visiting malarious countries are having very little effect on combating imported malaria to the UK.

As in previous reports most of the cases seen in hospital were *P. falciparum* infection. This is consistent with data across the UK as reported in the UK Malaria report, 2015 [2]. Most of the cases of malaria infections in this study were in young men between the ages of 15 and 40. It is thought that men are less compliant with chemoprophylaxis [6] another plausible explanation is that more young men could be migrating to or emigrating from the UK for work related reasons.

Malaria cases seen in CUHFT were acquired in a variety of countries but with the biggest contribution of malaria cases coming from West Africa, a well-documented source of imported malaria to the UK [4]. This could just reflect the relatively large numbers of people travelling to the UK from this region, there were over 4 million visitors to the UK between 2002 and 2016 from Nigeria and Ghana alone. This is in stark contrast to a country like Ivory Coast which had just over 67 000 visitors to the UK in the same time period but had the highest proportion infected with malaria at 8 per 1000 people. No malaria cases were recorded by the Malaria Laboratory nationally from Egypt, Laos, Vietnam and Mauritius despite there being at least one case from each of these countries seen in CUHFT. There are a number of possible explanations for this including inaccurate reporting/history in the
case of Egypt and Mauritius. This likely also reflects significant underreporting within the UK [7] although another plausible explanation is the difficulty in assigning a country of infection to people who travelled to more than one malaria endemic country on the same trip as we noted in a small number of our cases.

Over the 15 years covered by this study 52,239,837 million visits were made by UK residents to malarious countries (Figure 3b) and 22,053,510 million visits were made to the UK over the same time period from these areas. These figures are being maintained with potential malaria exposure occurring in an average of over 3 million UK residents travelling away from and over 1 million visitors coming to the UK every year (Supplementary Figures 4a and 4b).

From Figures 4a and b, it is clear that many people infected with malaria are visiting family in their own country of origin. This is a well observed phenomenon [2] [4] [8] and is associated with poor chemoprophylaxis use, as shown in figure 5. None of these patients reported using chemoprophylaxis as prescribed and in particular, none reported continuing the medication upon return, where a reason was given most of the patients cited side effects e.g. nausea as the reasons for stopping medication. Doxycycline was the most commonly used drug in those patients in whom prophylaxis was identified which may represent local advice as it was not the most commonly used nationally during this period. The Advisory Committee on Malaria Prevention (ACMP) recommends Atovaquone-Proguanil; Doxycycline or Mefloquine for most malaria endemic areas especially Sub-Saharan Africa [9]. Of the recommended drugs doxycycline is the cheapest and this may have influenced choice.
The ‘visiting family’ group of patients has been shown to report the least use of chemoprophylaxis which has been attributed to them visiting a familiar environment and being likely to underestimate loss of semi-immunity and the consequent risk of malaria [10]. Some travellers reported that they felt that even if they were to get ill they will be able to deal with it with ease while in their country of origin [11]. Therefore despite a lot of education on the importance of malarial chemoprophylaxis being targeted at this group of people it seems these efforts after a fall in the early years of the century as shown by [12] have now lost their impact [2]. Another potential contribution to this steep fall in cases could be more people visiting urban areas in malaria endemic areas where transmission is likely to be lower [12]. Lack of chemoprophylaxis use and lack of adherence to chemoprophylaxis regimen likely contribute to lack of continued significant decline in malaria cases after 2001 [4, 13, 14]. Chemoprophylaxis use as low as 7% in those travelling to visit friends and family and 24% in those travelling for other reasons has been recorded [4].

The contribution of people born in the UK going to malarious regions for holidays and work/business is significant and should be taken note of; this has also been noted by [15]. Some of the patients included in the category ‘work’ were soldiers with the British forces. This potentially highlights two more groups of people in which the message of the importance of chemoprophylaxis should be stressed. The UK malaria report 2015 [2] recommends targeting Africans i.e. those travelling to visit friends and family with pre-travel advice, this has recently been confirmed by [16] with highest rates of infection in those travelling to visit friends and family, black Africans in particular. Our data supports this but only in part since although the single largest group recording the highest malaria cases was the ‘visiting friends and family’ group (27.8%), however, British patients travelling for work (20.1%) and holiday (22.5%) contributed significantly with these 2 groups accounting for more malaria cases than those travelling to visit friends and family. Pre-travel prophylaxis
advice should thus also be targeted and emphasised to these two groups. Some malaria chemoprophylaxis including Mallof protect (Atovaquone and proguanil), Avloclor, Paludrine and Paludrine/Avloclor pack are now available without prescription over the counter in the UK [17]. This is a promising endeavour to improve access to chemoprophylaxis without the need to see a doctor. The issue that remains is bringing services like this to the attention of travellers and not only emphasising the importance of taking chemoprophylaxis but adhering to chemoprophylaxis regimen.

We noted a high average parasitaemia in extremes of age; 4.3% in the 5-9 age group and 5.4% in the 65-69 age group. At the younger age range it has been postulated that higher intrinsic susceptibility, combined with non-specific symptoms and potentially delayed diagnosis could contribute to higher average parasitaemias [10]. In the 65-69 age group factors such co-morbidities and potential immuno-compromise may also contribute. This may be correlated with higher mortality rates in these two age groups as shown by [18].

Many patients at presentation have relatively low parasitaemia levels mostly in the 0.1-0.5% range. This may reflect the effectiveness of the message from the UK malaria report 2015 [2], urging travellers to “take fever seriously” and visit a doctor, after visiting a malarious region and is probably reflected in the low mortality rate seen. The mortality rate at CUHFT was higher than the national average. This may reflect CUHFT being a tertiary centre with a wide catchment area and a low incidence of disease. Some delay in diagnosis of some cases may have occurred and this may explain the higher fatality rate.

Acknowledgements
We would like to acknowledge and thank the UK office of National Statistics and The Malaria Research Laboratory for providing statistical data.

**Study Limitations**

As a retrospective study of patient records this was limited by lack of complete patient data in parts, in some cases it wasn’t recorded and in some cases unavailable as it was classified in the case of armed forces.

**Potential conflicts of interest**

No conflicts of interest.
References


Figure Legends

**Figure 1a:** Malaria cases in CUHFT by year over a 15-year period. Infections over the 15 years, *P. falciparum* 66.7% (150/225), *P. vivax* 15.1% (34/225), *P. malariae* 4% (9/225) and *P. ovale* 6.7% (15/225). For 17 patients the causative organism was not recorded.

**Figure 1b:** UK malaria cases by year, 1996 to 2016. Data source: Public Health England (PHE) Malaria Reference Laboratory, London School of Hygiene and Tropical Medicine, London, supplied by the Travel and Migrant Health Section, PHE National Infections Service, Colindale, London.

**Figure 2:** Malaria cases in CUHFT by age group and sex, there were 158 male patients and 61 female patients over the 15-year period.

**Figure 3a:** Malaria cases in CUHFT by country in which infection was acquired. ‘Other’ represents 17 countries, i.e. Mauritius/Nepal/Laos/Vietnam/Cambodia/Namibia/Botswana/S. America, Mali/Benin/Iraq/Gabon/Malaysia/Somalia/Algeria/Mozambique and Zimbabwe that each contributed 1 case.

**Figure 3b:** National figures for the total numbers of people travelling to malarious countries, total malaria cases in the UK and proportions of travellers being infected. Data sources: Office of National Statistics and Public Health England (PHE) Malaria Reference Laboratory, London School of Hygiene and Tropical Medicine, London supplied by the Travel and Migrant Health Section, PHE National Infections Service, Colindale, London.

2 cases seen in CUHFT that were recorded as Undefined Africa (Figure 3a) have been excluded in this table.

**Figure 4a:** Malaria cases by reason for travel between 2002 and 2016, Addenbrooke’s hospital.

**Figure 4b:** Malaria cases in CUHFT by patient’s region of birth.
**Figure 5:** Malaria cases based on prophylaxis use, CUHFT
Figure 1b
Figure 3a

Malaria Cases by Country infection acquired (2002-2016)

- Other
- Burkina Faso
- Egypt
- Niger
- Undefined Africa
- S. Africa
- Madagascar
- Congo
- Pakistan
- Afghanistan
- Ethiopia
- Malawi
- Liberia
- Sudan
- Ivory Coast
- Gambia
- India
- Sierra Leone
- Tanzania
- Cameroon
- Angola
- Guinea
- Senegal
- Kenya
- Ghana
- Nigeria
- Thailand
- Uganda
- Zambia

Number

Malaria Cases

0 5 10 15 20 25 30 35 40 45

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<td>929,027</td>
<td>5,443,669</td>
<td>6,372,695</td>
<td>3</td>
<td>20</td>
<td>0.003133839</td>
</tr>
<tr>
<td>Uganda</td>
<td>112,972</td>
<td>442,219</td>
<td>555,191</td>
<td>10</td>
<td>1043</td>
<td>1.878631101</td>
</tr>
<tr>
<td>Vietnam</td>
<td>149,084</td>
<td>726,157</td>
<td>875,241</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zambia</td>
<td>119,584</td>
<td>253,298</td>
<td>372,881</td>
<td>3</td>
<td>144</td>
<td>0.38618588</td>
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<tr>
<td>Zimbabwe</td>
<td>205,354</td>
<td>430,337</td>
<td>635,671</td>
<td>1</td>
<td>93</td>
<td>0.148302536</td>
</tr>
</tbody>
</table>

Figure 4a
Figure 4b

PERCENTAGE OF MALARIA BY REGION OF BIRTH

- Africa: 35%
- UK: 29%
- Unknown: 26%
- Other: 5%
- Europe: 2%
- Indian subcontinent: 3%
Figure 5

Malaria Prophylaxis

- No Data: 32 cases
- None: 110 cases
- Prophylaxis:
  - Unknown: 25 cases
  - Fansidar: 4 cases
  - Mefloquine: 10 cases
  - Chloroquine-Proguanil: 4 cases
  - Proguanil: 4 cases
  - Chloroquine: 3 cases
  - Malarone: 24 cases
  - Doxycycline: 4 cases

Total Malaria Cases: 32 + 110 + 25 = 167