# Once, Twice, is Three times always necessary? A UK single-centre retrospective analysis of malaria diagnostics


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## Introduction

Malaria is a treatable, but potentially fatal, protozoal infection. 1300-1800 cases imported into UK each year → 2-8 deaths.

Must consider malaria in any febrile individual with travel history to endemic area. With no reliable clinical signs/symptoms of disease, guidelines advise patients to have 3 blood films over 48-hour period to exclude diagnosis, should initial tests prove negative.

This study reviews malaria diagnostics at a tropical medicine tertiary referral centre across 7-year period. It reviews guideline adherence across primary/ secondary care, and questions if serial blood films are truly necessary. Because **how often do we actually miss malaria on the first or second blood film?**

## Methods

All samples sent to Newcastle upon Tyne NHS Hospitals Foundation Trust between 2011-17 included. Each sample had thick + thin films prepared; these were reviewed independently by ≥2 microscopists in the lab (NEQAS assessed). Initial sample additionally had rapid diagnostic test (CareStart™) performed to detect malarial antigens (pLDH/HRP-2).

Data collected included:
- Sample draw time
- Presence/ absence + subspecies malarial parasite
- RDT result.

Patient samples separated into 'episodes' consisting of one/two/three or more blood samples. If samples (from same patient) taken >30 days apart, or following new exposure risk, defined as new episode.

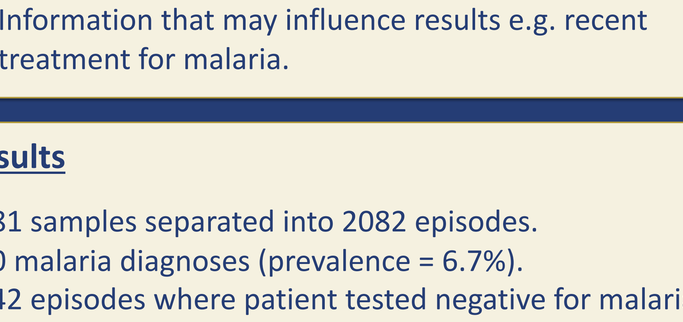
Electronic patient records accessed for:
- Travel history (available for 52% episodes)
- Location sample taken (1°/2° care)
- Information that may influence results e.g. recent treatment for malaria.

## Results

3381 samples separated into 2082 episodes.
140 malaria diagnoses (prevalence = 6.7%).
1942 episodes where patient tested negative for malarial parasites, of these:
- 1338 episodes with one blood sample
- 307 two samples
- 297 three or more samples.

611 (31.5%) episodes from patients who had all samples sent in primary care, 1292 episodes (66.5%) all from secondary care, and remainder from patients referred from primary to secondary care to complete work-up (2.0%).
Of the patients with three or more samples taken for an episode, 69.7% had this completed within recommended 48-hour timeframe (summarised in fig 1).

**Figure 1:** Samples, episodes and location of sample draw




*P. falciparum* made up majority of cases of malaria (97, 69.3%), followed by *p. vivax* (18, 12.9%). There were 5 mixed infections (*p.falciparum* + non-falciparum species). Data on subspecies unavailable for 2 cases (figure 2).

**Figure 2:** Malaria subspecies

| Subspecies | No. | Percentage |
|---|---|---|
| Falciparum | 97 | 69.3% |
| Malariae | 3 | 2.1% |
| Ovale | 15 | 10.7% |
| Vivax | 18 | 12.9% |
| Mixed | 5 | 3.6% |
| Unknown | 2 | 1.4% |
| Total | 140 | |

Most diagnoses made in patients with travel history to Central or West Africa (62.9% cases) (figure 3).
Patients who gave a history of travel to the Central or West Africa world region also had the greatest risk of having falciparum malaria (13.1% patients with travel history to this area).
Patients with a travel history to South America had the greatest risk of having non-falciparum malaria (6.2%) (figure 4).

**Figure 3:** Travel history

| World Region | No. | Percentage |
|---|---|---|
| Europe and North Africa | 13 | 1.2% |
| North and Central America (including Caribbean) | 40 | 3.7% |
| South America | 34 | 3.1% |
| Central and West Africa | 304 | 27.8% |
| Southern and East Africa | 234 | 21.4% |
| Middle East and Asia | 267 | 24.5% |
| South East Asia | 195 | 17.9% |
| Oceania | 5 | 0.5% |
| Total | 1092 | |

Note: Central and West Africa world region extends to Central African Republic (CAR) in the East and Democratic Republic of Congo (DRC) in the South.

**Figure 4:** Risk of patient with a history of travel to a particular world region having a positive diagnosis of malaria made.

**Falciparum malaria**

| World Region | Cases | Risk |
|---|---|---|
| Europe and North Africa | 0 | 0.0% |
| North and Central America (including Caribbean) | 1 | 1.3% |
| South America | 1 | 1.5% |
| Central and West Africa | 76 | 13.1% |
| Southern and East Africa | 19 | 4.3% |
| Middle East and Asia | 1 | 0.2% |
| South East Asia | 0 | 0.0% |
| Oceania | 0 | 0.0% |
| Unknown | 4 | 0.2% |
| Total | 102 | |

**Non-falciparum malaria**

| World Region | Cases | Risk |
|---|---|---|
| Europe and North Africa | 0 | 0.0% |
| North and Central America (including Caribbean) | 0 | 0.0% |
| South America | 4 | 6.2% |
| Central and West Africa | 16 | 2.8% |
| Southern and East Africa | 7 | 1.6% |
| Middle East and Asia | 12 | 2.4% |
| South East Asia | 0 | 0.0% |
| Oceania | 0 | 0.0% |
| Unknown | 2 | 0.1% |
| Total | 41 | |

Note: Case number across two tables totals 143 (102 falciparum and 41 non-falciparum), as it has counted mixed infections with falciparum and other subspecies twice. It does not include the two cases where information on the subspecies was unavailable.

No patient in studied population with initial blood sample negative for malarial parasites subsequently went on to have positive film i.e. positive diagnosis, if made, always made on first sample sent for analysis. **Negative predictive value of a negative test (no malaria parasites identified) 100%** (confidence interval not calculable).

Two patients had positive RDT (for HRP-2), but no malarial parasites identified on blood film. In both cases patients had received full treatment course for falciparum malaria elsewhere in preceding 30 days.

## Discussion

Poor guideline adherence across primary/secondary care:
- Only 15.6% patients with initial negative blood film for malaria parasites went on to have second and third sample analysed.
- Only 10.7% total episodes within recommended 48-hour timeframe.
- Suggests education and retraining is required…however…all cases malaria diagnosed on first sample.

Majority of diagnoses made in patients with travel history to Central and West Africa, and the majority of these *p.falciparum*. Individuals who had a travel history to Central and West Africa also had the greatest likelihood of diagnosis of malaria being made. (Reflects situation nationally).

Previous studies have questioned necessity of serial blood films, however, found minority of cases were missed on the initial blood film, hence advice was not to change practice at the time. Both studies reviewed cohorts of patients in Australia, where there's a much greater prevalence of imported *p.vivax* infections (63%) than seen in our study (13%), or in UK as whole. Most frequently it was *p.vivax* that was not identified on the first blood film, and required a second or third film for diagnosis. Hence, with different malarial subspecies demographic to Australian populations, findings of these studies potentially less applicable to travellers returning to the UK.

Understandable for guidelines to be cautious with their advice, as it must be applicable to centres with less experience in examining for malaria parasites to reduce the likelihood of missing a diagnosis of malaria. However, at tertiary centres, with highly skilled and experienced microscopists, the practice of needing to examine three films may be unnecessary.

Study Limitations:
- Retrospective data analysis
- assumption that patients for whom travel history is available reflects study population, and that all 'episodes' involved an exposure risk
- No data on purpose of travel - individuals visiting friends and relatives are at greater risk than tourists of contracting malaria when travelling.

## Recommendations

- Prospective evaluation of situation at other centres across the UK.
- Risk stratification of patients who should be more intensively investigated to exclude malaria (e.g. based on higher probability of underlying disease.


**References**

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