Increased imported severe *Plasmodium falciparum* malaria involving hyperparasitaemia (>10%) in a UK hospital following relaxation of COVID-19 restrictions compared to the pre-pandemic period

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Highlight:

We identified and compared patients diagnosed with *Plasmodium falciparum* malaria at a large hospital in London, UK prior to the COVID-19 pandemic versus following relaxation of COVID-19-associated restrictions. We found that parasitaemias, rates of hyperpasitaemia and severe malaria were significantly higher in the period post-relaxation of COVID-19 restrictions.

Main manuscript:

Malaria remains a major cause of morbidity and mortality with an estimated 241 million cases and 627,000 deaths (96% of which occurred in Africa) in 2020; a significant proportion (estimated at over two-thirds) of these deaths have been attributed to (coronavirus disease 2019) COVID-19 pandemic associated disruptions.[1] In view of COVID-19 public health measures including travel restrictions, major declines in travel-related malaria cases have occurred over the course of the COVID-19 pandemic.[2–4] The impact of the more recent relaxation of COVID-19 restrictions on travel-associated malaria remains to be fully elucidated. A significant increase in cases of severe imported malaria cases was observed in Spain in 2021 following partial relaxation of COVID-19 restrictions (trends or differences in parasitaemias/hyperparasitaemia rates over the course of the study period were not reported).[5] The UK completely removed all COVID-19 associated restrictions on international travel in March 2022 (one of the first countries to do so). We sought to investigate whether following the removal of these travel restrictions the rate of severe imported *Plasmodium falciparum* malaria and/or the rate of hyperparasitaemia, defined by the World Health Organisation

(WHO) as *P. falciparum* parasitaemia >10% and which indicates severe malaria in all settings, differed significantly when compared to the pre-pandemic period.[6]

We identified all adult patients (≥18 years) diagnosed with *P. falciparum* malaria (mono-infection) at King's College Hospital, a large teaching hospital in London, UK, over a 4-month period (01 March 2022 - 30 June 2022) and compared this to the corresponding 4-month period in 2019 (March 2019 - June 2019) prior to the COVID-19 pandemic. We included both admitted patients and those discharged directly from our emergency department with outpatient follow up. We collected and compared data on age, gender, malaria prophylaxis, time from symptom onset to diagnosis, rates of severe malaria (as per the WHO criteria[6]), peak parasitaemias, hyperparasitaemia rates, intensive care unit (ICU) admissions and mortality. To investigate whether any significant differences between 2019 and 2022 were likely attributable to the COVID-19 pandemic rather than simply being a time-related phenomenon, we also collected data for the corresponding 4-month period in 2016 (March 2016 - June 2016) and compared this to 2019. No ethical approval was required as this study used data collected as part of routine patient care.

The proportion of patients with severe malaria was significantly higher following the relaxation of COVID-19 travel restrictions in 2022 (10/24, 42%), compared to before the pandemic in 2019 (0/21), $P = 0.0007$ (Table 1). We also found that rates of hyperperasitaemia were significantly higher in 2022 (6/24, 25%) compared to 2019 (0/21), $P = 0.023$**.** Additionally, peak parasitaemias were significantly higher in the 2022 group vs. the 2019 group ($P = 0.043$). There were no significant differences between the 2022 and 2019 groups with regards to age, gender, rates of malaria prophylaxis, time from symptom onset to diagnosis, ICU admissions

or mortality. In terms of ICU admissions, 4 of 24 patients (17%) were admitted in 2022 compared to zero patients in 2019 but this did not reach statistical significance (P = 0.112) likely due to the relatively small study group sizes. ICU admissions were however significantly higher in the 2022 group when compared with the 2016 and 2019 pre-pandemic groups combined (P = 0.023). When comparing the 2019 and 2016 groups, there were no statistically significant differences in age, gender, malaria prophylaxis, time from symptom onset to diagnosis, severe malaria rates, hyperparasitaemia rates, peak parasitaemias, ICU admissions or mortality. There were no severe malaria cases or cases of hyperparasitaemia in any of the study groups caused by mixed infections or non-*P. falciparum* species.

Sub-Saharan Africa was the region of *P. falciparum* acquisition for all patients in all study groups. The low rates of malaria prophylaxis across all 3 study groups, possibly attributable at least in part to patient beliefs of pre-existing malaria immunity, highlights the need to reinforce the potential severity of the condition and hence paramount importance of prophylaxis for all travellers to malaria endemic settings. A recent study of returned travellers in Canada during the peri-COVID-19 pandemic period found a decrease in individuals seeking pre-travel advice and a trend towards decreasing malaria prophylaxis possibly due to factors including fear of acquisition of COVID-19 in healthcare settings and possible stigma associated with travel during the pandemic.[4] Enhanced efforts are required to ensure that these trends (where present) do not continue in the current period post-relaxation of COVID-19 restrictions.

It is recognised that repeated exposure to *P. falciparum* in endemic regions may confer semi-immunity and thus varying degrees of protection against high parasitaemias and severe malarial disease.[7] Across the 3 study groups, the reason for travel in all instances with the exception of one patient (visiting Kenya in the 2022 study period) was to visit friends and relatives/travel to

a country of their ancestry and thus at least a proportion may have had some degree of previous malaria semi-immunity. Whether a possible decline in malarial immunity due to absence of re-exposure over the COVID-19 pandemic period contributed at all to our study findings remains unclear. This theory however is not completely supported by observational studies which have demonstrated that some degree of protection against malaria remains for at least 10 years following arrival in non-endemic countries and a study by Wipasa et al. in adults in northern Thailand which showed that there were no significant declines in antibody titres or memory B cell responses to *P. falciparum* antigens over periods of more than 5 years since the last known malaria infection.[8,9] To our knowledge, there are no reports of particularly virulent malaria strains circulating in sub-Saharan Africa at present to account for the higher rates of severe malaria and hyperparasitaemia in our 2022 study group, nor have data emerged suggesting potentially more severe forms of malaria in patients with a history of SARS-CoV-2 infection. These could however be avenues worthy of further exploration.

An important additional consideration for patient follow up given our study findings is that with higher parasitaemias (in particular with hyperparasitaemia) an increased risk of post-artemisinin delayed haemolysis (PADH) has been previously reported, rendering post-treatment checks of haematological parameters essential in this cohort.[10] Although multiple factors can contribute to anaemia in malaria, the criteria for PADH, a >10% decrease in haemoglobin occurring more than 7 days after treatment initiation in addition to a raised lactate dehydrogenase (increase >10% and/or level > 390 UI/l) or low haptoglobin (<0.1 g/l) in blood, were met by the two patients with the highest parasitaemias (50% and 70%) in our study; one of whom required blood transfusions.

Of note, we additionally investigated the number of malaria diagnoses during the COVID-19 pandemic in the corresponding 4-month (March to June) periods in 2020 and 2021. In concordance with other studies of imported malaria during the COVID-19 pandemic[2,3], there was a marked decline in malaria diagnoses. We had only 1 malaria case in the 2020 4-month period which was non-severe and with a peak parasitaemia of <0.1%. In the 2021 4-month period there were 13 cases; 2/13 (15%) were severe and 1/13 (8%) had hyperparasitaemia.

Despite our study being limited by its size and by its retrospective nature, the latter meaning that the extent of the medical/travel history recorded in patients' medical notes was variable, this is the first study to our knowledge comparing rates of severe imported *P. falciparum* malaria involving hyperparasitaemia and/or malaria parasitaemias following the removal of COVID-19 travel restrictions to before the pandemic. The findings are compelling and larger studies, possibly also incorporating investigation of host immune responses to malaria, are warranted.

	2016	2019	2022	2016 vs. 2019*	2019 vs. 2022*
Number of Patients	14	21	24	NA	NA
Age in years: mean, median and range	44, 43, 33 – 57	46, 48, 25 - 73	49, 47, 26 - 74	*P* = 0.488	*P* = 0.437
Gender - Male	4/14 (29%)	11/21 (52%)	18/24 (75%)	*P* = 0.311	*P* = 0.133
Took malaria prophylaxis†	1/12 (8%)	5/18 (28%)	2/24 (8%)	*P* = 0.358	*P* = 0.118
Proportion of patients whose reason for travel was VFR/travel to a country of their ancestry†	(10/10, 100%)	(18/18, 100%)	(21/22, 95%)	NA (100% in both groups)	*P* = 1.00
Proportion of patients who were non-VFR travellers†	0	0	(1/22, 4.5%)	NA (zero patients in both groups)	*P* = 1.00
Proportion of patients who were new entrants to the UK/new migrants†	0	0	0	NA (zero patients in both groups)	NA (zero patients in both groups)
Proportion of patients who were visitors to the UK†	0	0	0	NA (zero patients in both groups)	NA (zero patients in both groups)
Days from symptom onset to diagnosis: mean, standard deviation and range†	4.4, 2.3, 1-7	3.8, 3.1, 1-14	4.7, 2.0, 1-8	*P* = 0.519	*P* = 0.271

Proportion of patients with severe malaria	3/14 (21%)	0	10/24 (42%)	*P* = 0.056	***P* = 0.0007**
Patients with hyperparasitaemia (>10%)	0	0	6/24 (25%)	NA (zero patients in both groups)	***P* = 0.023**
Peak parasitaemia: mean, median and range	1.75, 0.55, 0.1 – 8.8	0.79, 0.50 <0.1 – 4	8.57, 2.3, <0.1 – 70	*P* = 0.288	***P* = 0.043**
ICU admissions	0	0	4/24 (17%)	NA (zero ICU admissions in both groups)	*P* = 0.112
Deaths	0	0	0	NA (zero deaths in both groups)	NA (zero deaths in both groups)

Table 1. Comparison of patients diagnosed with *Plasmodium falciparum* malaria in 2016, 2019 and 2022 at King's College Hospital, London, UK

[*] Statistical comparisons for age, days from symptom onset to diagnosis, and peak parasitaemia (peak parasitaemias were log transformed prior to statistical analysis) data were conducted with the Analysis of Variance (ANOVA) test and all other comparisons were conducted with the Fisher's Exact test. A p-value of ≤ 0.05 was considered statistically significant.

[†] Where recorded in patient notes

Abbreviations: Intensive care unit (ICU), Not applicable (NA), visiting friends and relatives, World Health Organisation (WHO)

Declaration of competing interest

None of the authors have any competing interests to declare

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