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THE EFFECT OF DELAYED TREATMENT ON PROGRESSION TO SEVERE *PLASMODIUM FALCIPARUM* MALARIA: A POOLED MULTICENTRE INDIVIDUAL-PATIENT ANALYSIS

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Delay in receiving treatment for uncomplicated malaria (UM) is often reported to increase the risk of developing severe disease, but findings are not consistent across all studies. Understanding which factors underpin progression to severe disease is important in quantifying the potential impact of improving access to treatment and identifying high-risk groups. We searched Ovid MEDLINE and Embase to identify studies on severe P.falciparum malaria with any information on treatment delay, such as duration of symptoms or fever, and contacted authors to obtain individual-patient data. To date, we have pooled data from seven studies in Uganda, The Gambia, Benin, Yemen and Malaysia of 1,377 patients with severe malaria and 2,273 UM controls. Definitions of severity phenotypes were standardised across the studies to compare treatment delay in UM patients with different severe disease manifestations using mixed-effects logistic regressions adjusted for age. An illness duration of ≥ 24 hours prior to arriving at the health facility in children was associated with increased odds of severe malarial anaemia (SMA) compared to UM controls; OR=4.50 (2.06-9.84). Arriving at the facility within 4 days of symptom onset is estimated to prevent 49% of SMa cases, whilst treatment within 24 hours could prevent 76% of SMa cases. Duration of illness was significantly shorter in those with cerebral malaria (CM), hyperlactatemia and hyperparasitaemia compared to controls, whilst no difference was observed for respiratory distress syndrome (p=0.23) or hypoglycaemia (p=0.12). Our results suggest improving rapid access to treatment would probably be highly effective at preventing SMA. CM, hyperlactatemia and hyperparasitaemia have a faster onset and trigger treatment seeking earlier, thus access to treatment would be required within a shorter time-frame to prevent these faster-developing phenotypes. We are continuing to gather additional datasets and explore the pathway to severe disease as well as the effects of accessibility, failure and source of initial treatment prior to the study, transmission intensity, seasonality and socioeconomic determinants.

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MALARIA ATTRIBUTABLE FEVER IN LOW AND HIGH TRANSMISSION SETTINGS OF ZAMBIA: DIFFERENCES BETWEEN ACTIVE AND PASSIVE CASE DETECTION

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Fever is a common symptom of malaria. It is also one of the main symptoms of many other illnesses such as diarrhea and pneumonia. For these diseases, diagnosis with a fever is usually the first point of entry into the health surveillance system. The Zambian government uses active and passive sampling strategies like the malaria indicator survey and rapid surveillance reporting systems for monitoring febrile illnesses and assessing their burden in the community. Understanding the characteristics of febrile illness obtained through these methods can help in adapting treatment guidelines suited to various malaria transmission settings, thereby helping to mitigate threats due to changes in the epidemiological profile as countries strive for malaria elimination. Towards this goal, we examined the correlation of fever and malaria between a cross-sectional analysis of 7,875 actively detected individuals and 513, 307 passively detected health seeking individuals from a health center rapid reporting surveillance system over the period of 2012 to 2015. The participants were drawn from low and high transmission areas in Choma and Nchelenge Districts in Southern and Luapula Provinces of Zambia. Choma and Nchelenge Districts have a malaria prevalence of 1% and 30% respectively. Fever was classified as having a body temperature above 37.5 ^{0} C, while malaria was assessed by a point-of-care rapid diagnostic test (RDT) for *Plasmodium falciparum.* From Choma District and the actively detected data, none of the febrile individuals yielded a positive RDT while 0.5% were RDT positive but afebrile. In Nchelenge District, 80% of the actively detected fevers were attributable to malaria. Among the passively sampled individuals, only 5% of those febrile were RDT positive in Choma District while 56% of fevers were attributable to malaria in Nchelenge. All fever cases were once considered as malaria but as transmission declines, there is need for more information on what is causing fever and how to address it. Our results suggest the need for rigorous integrated management of febrile illness and introduction of point of care diagnostics for non-malaria fever.

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EPIDEMIOLOGY OF SUBPATENT *PLASMODIUM FALCIPARUM* INFECTIONS IDENTIFIED BY HIGH-SENSITIVITY REAL-TIME PCR DETECTION DURING COMMUNITY-BASED PROACTIVE AND REACTIVE CASE DETECTION IN WESTERN KENYA

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Low-level, asymptomatic *Plasmodium falciparum* infections are common in high-transmission settings, and the availability of conventional malaria

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