Oct 20, 2020

The impact of delayed treatment on progression of uncomplicated *P. falciparum* malaria to severe malaria: a pooled multicentre individual-patient meta-analysis.

PLOS Medicine

Andria Mousa[1], Dr Joseph Challenger[1], Dr Lucy Okell[1]

[1]MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, Imperial College London, London, UK

1 Works for me dx.doi.org/10.17504/protocols.io.bgzfjx3n

Andria Mousa

EXTERNAL LINK

https://doi.org/10.1371/journal.pmed.1003359

THIS PROTOCOL ACCOMPANIES THE FOLLOWING PUBLICATION

Mousa A, Al-Taiar A, Anstey NM, Badaut C, Barber BE, Bassat Q, Challenger JD, Cunnington AJ, Datta D, Drakeley C, Ghani AC, Gordeuk VR, Grigg MJ, Hugo P, John CC, Mayor A, Migot-Nabias F, Opoka RO, Pasvol G, Rees C, Reyburn H, Riley EM, Shah BN, Sitoe A, Sutherland CJ, Thuma PE, Unger SA, Viwami F, Walther M, Whitty CJM, William T, Okell LC (2020) The impact of delayed treatment of uncomplicated *P. falciparum* malaria on progression to severe malaria: A systematic review and a pooled multicentre individual-patient meta-analysis. PLoS Med 17(10): e1003359. doi: 10.1371/journal.pmed.1003359

DOI

dx.doi.org/10.17504/protocols.io.bgzfjx3n

EXTERNAL LINK

https://doi.org/10.1371/journal.pmed.1003359

PROTOCOL CITATION

Andria Mousa, Dr Joseph Challenger, Dr Lucy Okell 2020. The impact of delayed treatment on progression of uncomplicated P. falciparum malaria to severe malaria: a pooled multicentre individual-patient meta-analysis.. **protocols.io**
https://dx.doi.org/10.17504/protocols.io.bgzfjx3n

MANUSCRIPT CITATION please remember to cite the following publication along with this protocol

Mousa A, Al-Taiar A, Anstey NM, Badaut C, Barber BE, Bassat Q, Challenger JD, Cunnington AJ, Datta D, Drakeley C, Ghani AC, Gordeuk VR, Grigg MJ, Hugo P, John CC, Mayor A, Migot-Nabias F, Opoka RO, Pasvol G, Rees C, Reyburn H, Riley EM, Shah BN, Sitoe A, Sutherland CJ, Thuma PE, Unger SA, Viwami F, Walther M, Whitty CJM, William T, Okell LC (2020) The impact of delayed treatment of uncomplicated *P. falciparum* malaria on progression to severe malaria: A systematic review and a pooled multicentre individual-patient meta-analysis. PLoS Med 17(10): e1003359. doi: 10.1371/journal.pmed.1003359

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CREATED

May 31, 2020

LAST MODIFIED

Oct 20, 2020

PROTOCOL INTEGER ID

37639

Research Question, study design and conditions being studied

1 ***Research Question:***
What is the impact of improved access to treatment in reducing progression from uncomplicated *P. falciparum* malaria to severe disease?

Study design:
An individual-participant meta-analysis of observational studies of hospital admission of severe and uncomplicated *Plasmodium falciparum* malaria cases.

***Conditions or domains being studied*:**
Severe malaria (TMIH WHO 2014 criteria[1]): Diagnosis of *Plasmodium falciparum* infection and at least one of the following symptoms or severe disease types diagnosed, in the absence of an alternative cause:
-Cerebral malaria
-Severe malarial anaemia
-Hyperlactatemia
-Acidosis
-Respiratory distress
-Hypoglycaemia
-Renal failure
-Hyperparasitaemia
-Jaundice

Uncomplicated malaria (comparator group): presence of Plasmodium falciparum infection at the time of admission, diagnosed by either RDT, microscopy or PCR and absence of severe symptoms.

Delay to treatment from symptom onset (measure of exposure) will be compared between uncomplicated cases and severe malaria cases, as well as between different types of severe malaria.

Search dates, sources and strategy

2 ***Time span:***
Inceptions *to* 22/11/2017

Sources searched:
Ovid MEDLINE, Embase

***Restrictions*:**
No restrictions on language or year of publication

***Search strategy*:**
(malaria* or falciparum) AND (severe or cerebral) AND ((duration adj3 (illness or disease)) or delay* or access* or distance or travel* or case-control or risk factor or risk factors))

All terms searched in all fields.

Screening process and inclusion/ exclusion criteria

3 One reviewer will conduct study selection. Study selection decisions, and extraction will be checked by a second reviewer. EndNote X8 will be used for screening.

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Inclusion criteria:

- Studies containing data on severe disease
- Studies with available data on delay to treatment defined as duration of symptoms or fever prior to admission.
- Studies published in any language
- Studies published in any year
- Studies that contain data on patients infected with P. falciparum
- Studies of participants of any age group

Exclusion criteria:

- Studies which collected data on only uncomplicated malaria
- Case reports
- Studies with small total sample sizes (<100)
- Studies in non-endemic settings

***Types of study to be included*:**
Studies to be included are mainly case-control studies of severe vs. uncomplicated malaria. Large studies of severe disease which did not have a case-control design (e.g. cohort studies) were still considered if they were sufficiently large (n>100) and contained relevant data to allow comparisons of different types of severe malarial disease.

Exposure and outcomes

4 ***Exposure:***
The primary exposure being studied is delay to treatment, quantified as self-reported duration of illness or fever prior to being admitted to a health facility.
Secondary exposures being studied include travelling time and distance to the health facility, as well as receiving treatment prior to arriving at the health facility.

Main outcome:
The main outcome is the change in odds of severe malarial disease, overall and stratified by type of severe malarial disease. Severe malaria status is determined at the time of admission.

Additional outcomes:
Short-term mortality, need for transfusion and haemoglobin levels are secondary outcomes, provided there is available data. The odds of death and odds of increased haemoglobin will be compared between different levels of delay. Haemoglobin levels are measured at the time of admission. Mortality is defined as death during hospital stay.

Step 5: Data extraction and quality assessment

5 ***Data extraction:***
Data extracted initially will be the following: author names and contact details, country and transmission setting, ages, study design and matching, sample size, symptoms, inclusion and exclusion criteria, mean effect of delay (if measured), mortality, travel time and distance to the health facility, treatment (type) prior to admission, education of mother, definitions for severe and uncomplicated malaria.

All authors will be contacted for individual-level data as some studies may not estimate the association between delay and progression, despite having collected data on duration of illness. Missing data will also be requested.
Microsoft Excel and Stata 14 will be used for data storage and management.

Risk of bias (quality) assessment:
A quality assessment will be carried out by two reviewers using the Newcastle Ottawa risk of bias tool for non-randomised studies. Studies will also be scored separately on the number of confounders they measure, including age, travelling time/distance, and mother's education.

Strategy for data synthesis

6 Pooled analysis: Age-adjusted, mixed-effects multivariable logistic regressions will be used to account for random effects among studies and this will be done separately for children and adults aged 15 or over. ORs and 95% confidence intervals quantifying the risk of progression to severe malarial disease, specific types of severe malarial disease or mortality, will be estimated for different categories of delay prior to seeking treatment. Confounders such as age,

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travelling time, distance, mother's education and transmission intensity will be investigated in subgroup analyses to determine their impact on the association between delay to treatment and progression to severe malarial disease. Data will be analysed using Stata 14.

Analysis of subgroups or subsets

7 The main analysis (mixed-effects logistic regression of IPD) will be stratified by children (<15 years) and adults (15+ years). To explore the effects of confounders, the main analysis will be adjusted for age, distance or travelling time to the health facility, treatment prior to admission to the health facility, transmission intensity of the setting and other potential factors such mother's education. The presence of effect modification of these variables will be investigated by fitting an interaction between the effect of delay and the above factors, e.g. transmission intensity category or age.

References

8 1.World Health Organization. Severe Malaria. Tropical Medicine & International Health. 2014;19(s1):7-131. doi: doi:10.1111/tmi.12313_2.

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