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Can giving adolescents preventive treatment for malaria, before vaccination, improve immune responses to these vaccines?

Submission date
11/07/2019

Recruitment status
No longer recruiting

Registration date
23/08/2019

Overall study status
Completed

Last Edited
21/10/2024

Condition category
Other

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Infectious diseases remain very common in low-income countries (LICs). Vaccines protect people against infectious diseases, but several important vaccines do not work as well in LICs compared to high-income countries (HICs) and in rural, compared to urban, settings. One possible reason for this might be that people living in these settings are more likely to have malaria infections. Malaria infections impact on the immune system and may change an infected person's response to a vaccine. This study aims to investigate whether giving adolescents presumptive treatment for malaria, before vaccination, will lead to a better immune response to these vaccines.

Who can participate?
Healthy volunteer children (aged 9-17 years, with no gender restriction) from selected schools located in Jinja district, Uganda. Malaria is very common in this area.

What does the study involve?
Children are randomly allocated to receive either monthly dihydroartemisinin-piperaquine (DP), a drug that has been shown to reduce the risk of getting malaria, or a monthly (inactive) placebo. They are then vaccinated against tuberculosis, yellow fever, human papilloma virus (which can cause cancer of the cervix [or opening] of the womb, and other cancers), typhoid and tetanus. Four weeks after vaccination, their immune responses to each vaccine are measured.

What are the possible benefits and risks of participating?
Participants will benefit from receiving the vaccines and treatments as they are expected to provide protection against infectious diseases. Participants and their families, schools and communities will benefit from improved understanding of malaria and vaccines. No major risks to the participants are anticipated since all the treatments and vaccines to be given are licensed and known to be safe. The main risk to participants will be time lost from school work, and the researchers will work with teachers and parents to minimise this. Very rarely, a vaccine may cause a severe allergic reaction, so individuals who have previously suffered a possible allergic reaction to drugs or vaccines or their components will not be included in the study.

Where is the study run from?
The host institution for the study will be the Medical Research Council/Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit (MRC/UVRI & LSHTM), Entebbe, Uganda.

When is the study starting and how long is it expected to run for?
May 2018 to April 2022

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Prof. Alison Elliott
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Contact information

Type(s)
Public

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
1.0

Study information

Scientific Title
The effect of intermittent preventive treatment for malaria with dihydroartemisinin-piperaquine on response to vaccines among rural Ugandan adolescents

Acronym
POPVAC B

Study objectives
Malaria infection suppresses responses to unrelated vaccines, and this effect can be reversed, at least in part, by monthly preventive treatment of malaria in schools in high transmission settings

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 05/06/2019, London School of Hygiene and Tropical Medicine Ethics Committee (LSHTM, Keppel St, London WC1E 7HT; ethics@lshtm.ac.uk; +44 (0)207 6368636), ref: 16033.
2. Approved 06/09/2018, Uganda Virus Research Institute Research Ethics Committee (The REC secretariat, Uganda Virus Research Institute, P.O Box 49, Entebbe, Uganda; +245 (0)414321962; fayebazibwe@uvri.go.ug or directoruvri@uvri.go.ug), ref: GC/127/18/09/681.
3. Approved 07/05/2019, Uganda National Council for Science and Technology (Plot 6, Kimera Road, Ntinda, P.O. Box 6884, Kampala, Uganda; +256 (0)414 705500; info@uncst.go.ug), ref: HS 2487.
4. Uganda National Drug Authority (Secretariat office Kampala, Plot 19 Lumumba Avenue, P.O. Box 23096, Kampala, Uganda; +245 (0) 417 788 100; ndaug@nda.or.ug), ref: CTC0117/2020

Study design
Single-centre individually randomized double-blind placebo-controlled two parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
School

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Vaccine responses

Interventions
A randomisation code will be generated by the trial statistician using a randomly permuted block size. Participants will be allocated in a 1:1 ratio to receive either (DP) or placebo. Participants in the DP arm will receive two DP doses, one month apart, prior to immunisation followed by monthly DP doses for one year thereafter. Each dose will comprise treatment once a day for three consecutive days. DP will be dosed using weight-based guidelines targeting a total dose of 6.4 mg/kg dihydroartemisinin and 51.2 mg/kg piperaquine. Participants in the placebo arm will receive doses of placebo at the same time points as the DP arm receive DP, i.e. two doses of placebo, 1 month apart prior to immunisation followed by monthly placebo for one year thereafter. Both DP and placebo will be taken orally. As yet, routine preventive malaria treatment in schools is not Uganda Ministry of Health policy.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Dihydroartemisinin-piperaquine

Primary outcome measure
1. BCG: BCG-specific IFN-gamma ELIspot response 8 weeks post BCG immunisation
2. YF-17D: neutralising antibody titres (plaque-reduction neutralisation test) at 4 weeks post YF immunisation
3. Ty21a: Salmonella typhi lipopolysaccharide (LPS)-specific immunoglobulin(Ig)G concentration at 4 weeks post Ty21a immunisation
4. HPV: IgG specific for L1-proteins of HPV-16/18 at 4 weeks post HPV priming immunisation
5. Td: tetanus and diphtheria toxoid-specific IgG concentration at 4 weeks post Td immunisation

Secondary outcome measures
1. Protective immunity is measured using proportions with protective neutralising antibody (YF); protective IgG levels (TT); seroconversion rates (Ty21a) at 4 weeks post the corresponding immunisation

2. Response waning is measured using primary outcome measures (all vaccines) repeated at week 52, and area-under-the curve (AUC) analyses
3. Priming versus boosting is measured using effects on priming versus boosting will be examined for HPV only, comparing outcomes 4 weeks after the first, and 4 weeks after the second vaccine dose
4. Current malaria infection status and intensity is assessed retrospectively by PCR on stored samples collected on immunisation days and at week 52.

Overall study start date
01/05/2018

Completion date
30/04/2022

Eligibility

Key inclusion criteria
1. Attending the selected school and planning to continue to attend the school for the duration of the study
2. Aged 9 to 17 years and enrolled in primary 1 to 6
3. Written informed assent by participant and consent by parent or guardian
4. Agree to avoid pregnancy for the duration of the trial (female only)
5. Willing to provide locator information and to be contacted during the course of the trial
6. Able and willing (in the investigator's opinion) to comply with all the study requirements

Participant type(s)
Healthy volunteer

Age group
Child

Lower age limit
9 Years

Upper age limit
17 Years

Sex
Both

Target number of participants
640

Total final enrolment
341

Key exclusion criteria
1. Clinically significant history of immunodeficiency (including HIV), cancer, cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illnesses.

2. Moderate or severe acute illness characterised any of the following symptoms: fever, impaired consciousness, convulsions, difficulty in breathing, vomiting; or as determined by the attending project clinician.
3. Family history of sudden death attributable to a heart condition in a first-degree relative
4. Family history of long QT syndrome
5. Know congenital prolongation of the QTc interval
6. History of known heart disease or fainting
7. Known allergy or history of adverse reaction to DP or to artemether-lumefantrine
8. History of serious psychiatric condition or disorder
9. Previous immunisation with Yellow Fever (YF), oral typhoid or Human Papillomavirus (HPV) vaccine; previous immunisation with BCG or Tetanus and diphtheria vaccine (Td) at age >5 years
10. Concurrent oral or systemic steroid medication or the concurrent use of other immunosuppressive agents within 2 months prior to enrolment
11. Current use of medications known to prolong the QT interval (Table 2)
12. History of an allergic reaction to immunisation or any allergy likely to be exacerbated by any component of the study vaccines including egg or chicken proteins
13. Tendency to develop keloid scars
14. Haemoglobin less than 80g/L
15. Positive HIV serology
16. Positive pregnancy test
17. Female currently lactating, confirmed pregnancy or intention to become pregnant during the trial period
18. Use of an investigational medicinal product or non-registered drug, live vaccine, or medical device other than the study vaccines for 30 days prior to dosing with the study vaccine, or planned use during the study period
19. Administration of immunoglobulins and/or any blood products within the three months preceding the planned trial immunisation date.

Date of first enrolment
01/04/2021

Date of final enrolment
31/05/2021

Locations

Countries of recruitment
Uganda

Study participating centre
MRC/UVRI and LSHTM Uganda Research Unit
Plot 51-59 Nakiwogo Road
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Sponsor information

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University/education

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ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Current publication and dissemination plan as of 10/06/2020:
The researchers plan to publish the study protocol on around 01/12/2019. They will also add the statistical analysis plan to the trial registration before database lock. They then plan to publish the results of the trial in a high-impact peer-reviewed journal with an intention to publish date of 30/04/2023.

Previous publication and dissemination plan:
The researchers plan to publish the study protocol on around 01/12/2019. They will also add the statistical analysis plan to the trial registration before database lock. They then plan to publish the results of the trial in a high-impact peer-reviewed journal with an intention to publish date of 30/04/2023.

Intention to publish date

01/07/2024

Individual participant data (IPD) sharing plan

The de-identified individual participant data that underlie the results reported in journal articles will be stored in a non-publically available repository (LSHTM Data Compass), together with a data dictionary. This will be done at the time of publication. Each dataset will be allocated a unique digital object identifier (DOI). Researchers who would like to access the data may submit a request through LSHTM Data Compass, detailing the data requested, the intended use for the data, and evidence of relevant experience and other information to support the request. The request will be reviewed by the Principal Investigator in consultation with the POPVAC Steering Committee, with oversight from the UVRI and LSHTM ethics committees. In line with the MRC policy on Data Sharing, there will have to be a good reason for turning down a request. Patient Information Sheets and consent forms specifically referenced making anonymised data available and this has been approved by the relevant ethics committees. Researchers given access to the data will sign data sharing agreements which will restrict the use to answering pre-specified research questions.

IPD sharing plan summary

Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	version 1.0	16/02/2021	16/08/2022	Yes	No
Statistical Analysis Plan		12/10/2022	25/10/2022	No	No
Protocol article		16/02/2021	03/05/2024	Yes	No
Results article		01/11/2024	21/10/2024	Yes	No