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A trial to assess risk of dengue and evaluate a mosquito control intervention in northeastern Thailand

Submission date
29/05/2017

Recruitment status
No longer recruiting

Registration date
23/06/2017

Overall study status
Completed

Last Edited
11/07/2023

Condition category
Infections and Infestations

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

Plain English summary of protocol

Current plain English summary as of 11/12/2018:
Background and study aims
Dengue fever is globally the most common and widespread viral disease spread by mosquitoes. Mosquito control is important in order to control dengue. There is an urgent need to develop early warning of outbreaks and effective control interventions. Most current mosquito control interventions are not effective. Therefore, it is important to study new mosquito control tools in real life situations. Research is needed to determine the efficacy of the pesticide (chemical used to kill pests) pyriproxyfen in water storage containers to reduce dengue incidence by controlling the emergence of adult dengue mosquitoes from breeding sites. This important to try to create an index that predicts the rates of dengue in certain areas. The aim of this study is to assess a mosquito control intervention using pyriproxyfen and to contribute to the development of practical early warning systems to forecast changes in dengue transmission and outbreaks.

Who can participate?
Any over the age of one years who live in households in the study villages

What does the study involve?
Households are randomly allocated to one of two groups. Households in the first group have their containers treated with pyriproxyfen. This is applied every 3 months for 12 months. Participants in households are selected randomly to be followed weekly. All participating households may receive the standard dengue interventions provided by the public health authorities. Participants with a fever are tested by taking a blood sample to test whether the fever is because of dengue or for some other reason. Zika and Chikungunya infections are also be monitored. Tests are done on the blood samples to see if there are antibodies against mosquito saliva, which indicate exposure to dengue mosquitoes. Containers, which might be suitable for dengue mosquitoes to breed in, are counted and immature mosquitoes are collected if present. Adult dengue mosquitoes are also be collected, both indoors and outdoors. Those in the second group do not receive any specific treatment other than the current government programmes.

What are the possible benefits and risks of participating?
Participants may benefit from confirming fevers as dengue or not which can direct them to the proper care. Participants will also find out whether they have been bitten by dengue mosquitoes or if there is evidence of previous or active infection with other viruses transmitted by mosquitoes, in particular Chikungunya and Zika virus. Participants providing blood spots will receive a small monetary compensation. There are no notable risks, however participants may experience discomfort when providing blood samples and blood finger prick samples. As well, answering questionnaires and examination of the house will take some of participants' time.

Where is the study run from?
This study is being run by the Norwegian University of Life Sciences (Norway) and takes place in Khon Kaen and Roi Et urban municipalities in north-eastern Thailand.

When is the study starting and how long is it expected to run for?
March 2017 to September 2019 (updated 04/09/2020, previously: August 2019)

Who is funding the study?
Research Council of Norway (Norway)

Who is the main contact?
Dr Hans Overgaard
hans.overgaard@nmbu.no

Previous plain English summary:
Background and study aims
Dengue fever is globally the most common and widespread viral disease spread by mosquitoes. Mosquito control is important in order to control dengue. There is an urgent need to develop early warning of outbreaks and effective control interventions. Most current mosquito control interventions are not effective. Therefore, it is important to study new mosquito control tools in real life situations. Research is needed to determine the efficacy of a combination of pesticides (chemicals used to kill pests) called pyriproxyfen and spinosad in water storage containers to reduce dengue incidence by controlling the emergence of adult dengue mosquitoes from breeding sites. This important to try to create an index that predicts the rates of dengue in certain areas. The aim of this study is to assess a mosquito control intervention using an insecticide combination consisting of a natural product and an insect growth regulator and to contribute to the development of practical early warning systems to forecast changes in dengue transmission and outbreaks.

Who can participate?
Any over the age of one years who live in households in the study villages

What does the study involve?
Households are randomly allocated to one of two groups. Households in the first group have their containers treated with a combination of pyriproxyfen and spinosad. This is applied every three months for 12 months. Participants in households are selected randomly to be followed weekly. All participating households may receive the standard dengue interventions provided by the public health authorities. Participants with a fever are tested by taking a blood sample to test whether the fever is because of dengue or for some other reason. Zika and chikungunya infections are also be monitored. Tests are done on the blood samples to see if there are antibodies against mosquito saliva, which indicate exposure to dengue mosquitoes. Containers, which might be suitable for dengue mosquitoes to breed in, are counted and immature mosquitoes are collected if present. Adult dengue mosquitoes are also be collected, both

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Who is the main contact?
Dr Hans Overgaard
hans.overgaard@nmbu.no

Study website
http://www.dengueindex.com/

Contact information

Type(s)
Scientific

Contact name
Dr Hans Overgaard

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Research Council of Norway project no. 250443

Study information

Scientific Title
Assessing dengue transmission risk and a vector control intervention using entomological and immunological indices in northeastern Thailand: a cluster-randomized controlled trial

Acronym
DENGUE-INDEX

Study objectives
Current hypothesis as of 11/12/2018:
The study arm receiving the pyriproxyfen treatment of household water storage containers will have a lower density of adult Ae. aegypti and Ae. albopictus females per house collected both indoors and outdoors compared to the study arm not receiving this intervention.

Previous hypothesis:
The study arm receiving the pyriproxyfen/spinosad combination treatment of household water storage containers will have a lower density of adult Ae. aegypti and Ae. albopictus females per house collected both indoors and outdoors compared to the study arm not receiving this intervention.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Added 12/12/2018:
1. London School of Hygiene and Tropical Medicine Ethical Committee, 16/08/2017, ref: 14275
2. Khon Kaen University Ethics Committee, 01/09/2017, refs: 4.4.01:29/2017, HE601221
3. Regional Committee for Medical and Health Research Ethics, Section B, South East Norway (REK), 13/03/2018, ref: 2017/1826b

Study design
Stratified cluster-randomized controlled trial

Primary study design
Interventional

Secondary study design
Cluster randomised trial

Study setting(s)
Community

Study type(s)
Prevention

Participant information sheet
See trial outputs table

Health condition(s) or problem(s) studied
Dengue

Interventions
Current intervention as of 11/12/2018:
Following 12 months of baseline data collection (this includes epidemiological and entomological data), household intervention begins in the selected intervention clusters. The households in the other half – the control arm clusters – do not receive any specific intervention initiated by the project. As far as feasibly possible, abandoned households, non-permanent households, and vacant lots inside intervention clusters are also treated. During the study period, both intervention and control clusters may be subjected to governmental action as part of the existing national dengue control program response. The intervention specifically targets mosquito immature stages by applying pyriproxyfen to all permanent household containers, whether indoor or outdoor, found to contain water up to a 10 m perimeter from the house. Containers and breeding sites in other non-occupied properties are treated in the same manner. Additionally, small non-permanent containers (natural and artificial) are removed and discarded. Pyriproxyfen is applied to containers every 3 months. Pyriproxyfen is an insect growth regulator (insect juvenile hormone analogue), active against pupal stages resulting in the inhibition of adult development (prevents emergence), and altering/disrupting normal adult behavior and decreased fertility. It has low mammal toxicity and is recommended by the World Health Organization for vector control. The dose recommended by the WHO for Aedes immature mosquito control are 0.02-0.05 mg/L active ingredient (a.i.) pyriproxyfen (applied as a 0.5% granule formulation).

The 162 villages in Khon Kaen and 39 villages in Roi Et located within the respective ring roads are the sampling frames for each stratum. In each stratum, villages are randomly sampled based on probability proportional to population size, i.e., the population of occupied houses (the target denominator of the primary endpoint).

Villages are normally much larger than the target cluster size (10 houses); therefore, to select a starting point for the house selection a 50 x 50 m grid and a 100 m buffer zone around the inside of the village perimeter are superimposed over each village map. The buffer zone of approximately 100 m on the inside of each village border is applied to reduce potential 'contamination' (in-flying mosquitoes) from neighboring villages. A random grid cell is selected in each village and ten houses nearest the centroid of that cell are selected. This procedure is followed in each village Information meetings are held at the sub-district and village administrative levels to provide information about the project and benefits to the communities. Households are visited, carefully informed about the study, and informed consent obtained from the household head (see details below). A complete enumeration of all participants in the

selected clusters is completed with assistance from the local administration and village health volunteers (VHV).

The assignment of intervention and control to clusters is accomplished by two open public lottery events, one in each city. These events are carried out just before the first intervention. Representatives from each respective sub-district and village, including householders, district village heads, VHVs, and sub-district hospitals are invited to attend. Information about dengue and the purpose of the project is provided. The reasons for randomisation, its procedures and the concepts of intervention and control are explained. Attendants also have a chance to ask questions about dengue, vector control, health seeking behaviors, personal experiences of dengue and specific details about the project. The interventions are allocated at the same time as the sequence is generated, obviating the need for allocation concealment.

Baseline data is collected in July 2017, November 2017, and March 2018. Allocation of interventions is done in May 2018. Interventions are carried out in July 2018, September 2018, December 2018, and May 2019. Data collections are done monthly in a subset of households per cluster and every 4 months in all households per cluster. Epidemiological and entomological data (whether baseline or follow-up) are collected continuously for 2 years with the intervention implemented after one year. The first year constitutes the baseline, the second year the follow-up period. Epidemiological data consists of blood sampling (RDT and virus detection, confirmation and serotyping using PCR methods) from participants who are recorded with a fever during weekly village health volunteer visits. Entomological data consist of immature and adult collections. There are also be annual household questionnaires administered to household heads (at the beginning, in the middle, and at the end of the trial). Additionally, there are monthly blood spot collections (for the mosquito exposure study) from two household members in three households.

Participants in households are selected randomly to be followed weekly. All participating households may receive the standard dengue interventions provided by the public health authorities. Participants with a fever are tested by taking a blood sample to test whether the fever is because of dengue or for some other reason. A 4-ml blood sample is taken from them for virus detection, confirmation and serotyping. The blood spots are taken monthly from two volunteers in three households per clusters. Zika and Chikungunya infections are also be monitored. Tests are done on the blood samples to see if there are antibodies against mosquito saliva, which indicate exposure to dengue mosquitoes. Containers, which might be suitable for dengue mosquitoes to breed in, are counted and immature mosquitoes are collected if present. Adult dengue mosquitoes are also be collected, both indoors and outdoors. Those in the second group do not receive any specific treatment other than the current government programmes.

Previous intervention:
Following 12 months of baseline data collection (this includes epidemiological and entomological data), household intervention begins in the selected intervention clusters. The households in the other half – the control arm clusters – do not receive any specific intervention initiated by the project. As far as feasibly possible, abandoned households, non-permanent households, and vacant lots inside intervention clusters are also treated. During the study period, both intervention and control clusters may be subjected to governmental action as part of the existing national dengue control program response. The intervention specifically targets mosquito immature stages by applying a mixture of pyriproxyfen and spinosad to all permanent household containers, whether indoor or outdoor, found to contain water up to a 10 m perimeter from the house. Containers and breeding sites in other non-occupied properties are treated in the same manner. Additionally, small non-permanent containers (natural and artificial) are removed and discarded. The combination larvicide is applied simultaneously to containers

every three months. Pyriproxyfen is an insect growth regulator (insect juvenile hormone analogue), active against pupal stages resulting in the inhibition of adult development (prevents emergence), and altering/disrupting normal adult behavior and decreased fertility. It has low mammal toxicity and is recommended by the World Health Organization for vector control. Spinosad is a natural insecticide produced by the soil bacterium Saccharopolyspora spinosa. It has a neurotoxic mode of action in insects with low mammal toxicity, and also recommended by WHO. The doses recommended by the WHO for Aedes immature mosquito control are 0.02-0.05 mg/L active ingredient (a.i.) pyriproxyfen (applied as a 0.5% granule formulation), and 0.1-0.5 mg /L a.i. spinosad (also a 0.5% granule formulation).

The 162 villages in Khon Kaen and 39 villages in Roi Et located within the respective ring roads are the sampling frames for each stratum. In each stratum, villages are randomly sampled based on probability proportional to population size, i.e., the population of occupied houses (the target denominator of the primary endpoint).

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Participants in households are selected randomly to be followed weekly. All participating households may receive the standard dengue interventions provided by the public health authorities. Participants with a fever are tested by taking a blood sample to test whether the fever is because of dengue or for some other reason. A 4 mL blood sample is taken from them for virus detection, confirmation and serotyping. The blood spots are taken monthly from two volunteers in three households per clusters. Zika and chikungunya infections are also be monitored. Tests are done on the blood samples to see if there are antibodies against mosquito saliva, which indicate exposure to dengue mosquitoes. Containers, which might be suitable for dengue mosquitoes to breed in, are counted and immature mosquitoes are collected if present. Adult dengue mosquitoes are also be collected, both indoors and outdoors. Those in the second group do not receive any specific treatment other than the current government programmes.

Intervention Type
Biological/Vaccine

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Pyriproxyfen

Primary outcome measure
The Adult Index (AI), is measured by collecting the number of adult female Ae. aegypti and Ae. albopictus per house (combined species) collected both indoors and outdoors for 15 minutes each location (30 minute total collection time) using a battery-driven mechanical aspirator. Collections occur once every four months in all households and once every month in three repeat sentinel households per cluster.

Secondary outcome measures
1. Dengue Incidence Rate (DIR) is measured by the number of confirmed dengue cases divided by observation-days of household populations by identifying all household members with a fever at weekly VHV visits in participating households. Confirmed dengue cases are those fever patients with a positive RDT and a subsequent laboratory RT-PCR.
2. Mosquito Exposure Index (MEI) is measured using the proportion of blood samples with prescence of IgG antibodies to Ae. aegypti Nterm-34kDa salivary peptide, using immunoassays through blood samples taken from two persons per household at every four months in all households, once every month in three repeat sentinel households per cluster, and from fever cases detected during the weekly visits.
3. Infected Adult Index (IAI) is measured using the number of DENV infected adult female Ae. aegypti and Ae. albopictus per house (combined species) both indoors and outdoors for 15 minutes each using a battery-driven mechanical aspirator. DENV presence will be confirmed by real time RT-PCR.
4. Adult Sticky Trap Index (ASTI) is measured using the number of adult female Ae. aegypti and Ae. albopictus (combined species) outdoors each month using one sticky trap per house baited with an oviposition attractant hay infusion in four selected households for 7 consecutive days per month
5. Pupae/Person Index (PPI) is measured using the total number of Aedes pupae by collecting the amount of participating households divided by the number of persons in that household at

once every four months in all households and once every month in three repeat sentinel households per cluster
6. Breteau Index (BI) is measured using the number of immature Aedes positive containers per 100 houses measured at the cluster level, at once every 4 months in all households and once every month in three repeat sentinel households per cluster

Overall study start date
01/03/2017

Completion date
30/09/2019

Eligibility

Key inclusion criteria
Village:
Within ring roads of each strata (city), populated residential areas.

Cluster:
All points of the cluster are at least 100 m from the nearest point of the village border.

Household:
1. Households that are permanently inhabited
2. Households that are built or re-populated during the study period

Individuals:
1. In households where household head has signed informed consent for household to participate in project
2. A travel history outside the village during the previous 7 days
3. Chronic diseases such as HIV/AIDS or cancer
4. Apparent inability to give informed consent, e.g., due to mental disability or other incapacity, or lack of a legally authorized representative
5. Disease with similar symptoms to dengue but with evident alternative explanation
6. Age >1 year old

Participant type(s)
Other

Age group
All

Lower age limit
1 Years

Sex
Both

Target number of participants
2 strata, 18 clusters per strata, 10 households per cluster, ca 4 persons per household: 2x18x10x4=1440

Total final enrolment
539

Key exclusion criteria
Village:
1. Area <0.125 km2
2. Number of houses<100
3. Population <300
4. Coverage of residential area 70-80% (scattered housing)
5. Non-residential areas, e.g. agricultural fields, airport, industrial areas, commercial areas, (e.g. shopping malls), government offices, lakes. army camps, hospitals and schools.

Household:
1. Apartment buildings
2. Abandoned houses
3. Non-permanent households

Individual
1. Refusal to participate in the study
2. Age <1 year old

Date of first enrolment
01/07/2017

Date of final enrolment
31/07/2019

Locations

Countries of recruitment
Thailand

Study participating centre
Office of Disease Prevention and Control,no 7, Khon Kaen, Thailand.
Emergency Operations Center (EOC)
Government Road
Mueang district
Khon Kaen
Thailand
40000

Sponsor information

Organisation
Norwegian University of Life Sciences

Sponsor details
Drøbakveien 31
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Sponsor type
University/education

ROR
https://ror.org/04a1mvv97

Funder(s)

Funder type
Research council

Funder Name
Norges Forskningsråd

Alternative Name(s)
Forskningsrådet, Norwegian Research Council, Research Council of Norway

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Norway

Results and Publications

Publication and dissemination plan
The results of this trial will be published in high-impact peer reviewed journals approximately 1 year after the trial has ended.

Intention to publish date
31/12/2020

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a publically available repository: the Norwegian University of Life Sciences and the Norwegian Centre for Research Data (www.nsd.no). Data from this trial are planned to be uploaded to the journal where the main results of the trial will be published.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	20/02/2018		Yes	No
Participant information sheet			11/07/2023	No	Yes
Results article		27/05/2021	11/07/2023	Yes	No