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Optimal place of treatment for young infants aged less than 2 months with any one low-mortality-risk sign of possible serious bacterial infection

Submission date
24/11/2020

Recruitment status
No longer recruiting

Registration date
20/01/2021

Overall study status
Completed

Last Edited
05/06/2024

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Young infants up to 2 months old with clinically suspected sepsis are classified by the WHO algorithm as having Possible Serious Bacterial Infection (PSBI). WHO guidelines recommend that young infants with PSBI should be managed in a hospital with injectable antibiotics and supportive care. When referral to a hospital is not feasible, the guidelines recommend further classification of these young infants into those who are critically ill and those who have clinical severe infection (CSI). If a hospital referral is not feasible, infants with CSI can be managed on an outpatient basis with injectable gentamicin for 2 or 7 days and oral amoxicillin for 7 days. Previous research on the above guidelines has demonstrated that outpatient treatment is safe and effective when hospitalization is not feasible.

Overall a quarter to half of newborns in different settings are taken to a hospital. However, hospitalization has associated risks, so only those young infants with signs of PSBI who have a favourable benefit-risk ratio should be hospitalized.

Previous observational studies have shown that the fatality rate for young infants with clinical severe infection (CSI) treated at the hospital was higher compared to those treated on an outpatient basis. This could be due to: the infants who were taken to the hospital being sicker than those who were not, despite presentation with the same clinical signs; unstandardized or delayed treatment in hospitals and infants who were not taken to a hospital receiving standardized treatment immediately; or hospitalized infants might have suffered from an infection that was acquired in the hospital from a treatment-resistant pathogen which therefore has worse outcomes.

In contrast, the mortality rate was lower among those with any sign of critical illness who received in-hospital treatment, compared to those who received outpatient treatment. This seems logical because critically ill young infants need supportive care in addition to antibiotics, whereas infants with CSI primarily need antibiotic treatment.

This study will compare the outcomes of the treatment of infants with low-mortality-risk symptoms of a possible severe bacterial infection in either hospital or outpatient treatment settings. The overall aim is to generate knowledge that will allow for only young infants with PSBI who need inpatient treatment to be admitted to hospital and to treat others on an outpatient basis.

Who can participate?
Infants will be eligible if they are aged less than 2 months old and present at one of the participating hospitals with only one of the following three symptoms that suggest a low mortality risk of CSI: body temperature ≥38°C; severe chest indrawing; or fast breathing (in those aged <7 days old).

What does the study involve?
7000 eligible young infants will be randomly allocated to receive one of the following antibiotic treatments:
1. Injectable gentamicin (once daily) at the hospital for 2 days, and oral amoxicillin (twice daily) at home for 7 days
2. The WHO recommended antibiotic treatment with injectable ampicillin (twice daily), injectable gentamicin (once daily), and other supportive care, at the hospital for at least 7 days
The outcomes of these treatments will be compared by an independent assessor who will visit all enrolled young infants at 2, 4, 8, and 15 days after enrolment in the study.

What are the possible benefits and risks of participating?
Your infant will get treatment in hospital or as outpatient. There may not be a direct benefit for your infant and the society at this stage, but his/her participation will bring benefit for future generations. If the finding of this study shows benefits of Treatment B (outpatient treatment), you will have contributed to change global recommendation on care for young infants with a mild sign of infection. If the finding of this study shows benefits of Treatment A (standard hospital treatment), it will be recommended for all other young infants presenting with a mild sign of infection in your community.

Although the medicines being used in this study are used in young infants throughout the world and are generally known to be safe, they can rarely cause diarrhea, stomach ache or a skin rash. Since medicine is given in the home, there is a risk that response to medical problems will be slower there than in a hospital. Infants are monitored more closely in the hospital. This risk will be lowered if you contact the treating physician/nurse immediately if you see your infant has skin rash, diarrhea, or breathing problems. There is a very low risk of a serious allergic reaction. There is a very low risk of hearing problems or kidney damage. These reactions are almost never life-threatening. If the treating physician/nurse thinks it is necessary, we will treat these side effects by stopping the medicine earlier than planned. If this occurs, a different type of medicine will be used instead. Contact the study health worker or the person listed below if you have any questions about the drugs.

Where is the study run from?
The WHO is coordinating this study. While in each country, implementing partners are responsible for running the study. There will be seven study sites (four in Asia and three in Africa). In Asia, research teams from Bangladesh, India (two sites), and Pakistan will implement these studies, while in Africa, research teams from Ethiopia, Nigeria, and Tanzania will conduct this study.

When is the study starting and how long is it expected to run for?
From January 2021 to May 2024

Who is funding the study?
The Bill and Melinda Gates Foundation (BMGF) (USA)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
U1111-1251-1576

Study information

Scientific Title
Optimizing place of treatment for young infants presenting with any low-mortality-risk sign of possible serious bacterial infection.

Acronym
WHO PSBI

Study objectives
Young infants with only one low-mortality-risk sign of possible serious bacterial infection (PSBI) presenting to outpatient/emergency department of a hospital, who receive outpatient treatment, will experience a better, or at least non-inferior, clinical outcome than young infants that receive inpatient treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
10/06/2020, WHO Research Ethics Review Committee (20, Avenue Appia, CH-1211 Geneva 27, Switzerland; +41 227912111; ercsec@who.int), ref: ERC.0003289

Study design
International multi-center interventional open-label two-arm individually-randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Treatment of low-mortality-risk signs of possible serious bacterial infection in young infants

Interventions
Eligible participants will be randomised (1:1) to either intervention or control groups. A WHO statistician not otherwise associated with study implementation will generate a randomization scheme with random permuted bocks of variable size using a computer programme for both studies. The random allocation will be concealed in serially numbered, opaque, sealed envelopes. After obtaining consent, the research assistant will open the envelope with the next serial number, assign the young infant to one of the study groups, and record the assigned group in the case report form.

The intervention group will receive an intramuscular injection of gentamicin for 2 days, and oral amoxicillin for 7 days on an outpatient basis. The dose of gentamicin (for strength 40 mg/ml) will be: 0.2 ml for 1.5 to 2.4 kg body weight, 0.4 ml for 2.5 to 3.9 kg body weight, or 0.6 ml for 4.0 to 5.9 kg body weight, once daily. The dose of amoxicillin (dispersible tablet 250 mg) will be 1/2 tablet for 1.5 to 3.9 kg body weight, or1 tablet for 4.0 to 5.9 kg body weight, twice daily.

The control group will receive the WHO recommended antibiotic treatment with injectable ampicillin (twice daily), injectable gentamicin (once daily), and other supportive care, at the hospital for at least 7 days.

Intervention Type
Mixed

Primary outcome measure
1. Poor clinical outcome defined as any one of the following:
1.1. Death any time between baseline and 15 days
1.2. Presence of any sign of critical illness (no movement at all, unable to feed at all, or convulsions) or any sign suggestive of another serious infection (such as meningitis, or bone and joint infection) at 2, 4, and 8 days
1.3. Presence of any new sign of clinical severe infection (CSI) at 4 and 8 days
1.4. Persistence of the presenting sign at 8 days

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
01/01/2020

Completion date
15/05/2024

Eligibility

Key inclusion criteria
1. Aged <2 months
2. Living in a geographic area where follow-up for 14 days can be accomplished
3. Presenting to outpatient clinics or emergency rooms of participating hospitals with only one of the following low-risk signs of PSBI:

3.1. Body temperature ≥38°C
3.2. Severe chest indrawing
3.3. Fast breathing if aged <7 days

Participant type(s)
Patient

Age group
Neonate

Upper age limit
2 Months

Sex
Both

Target number of participants
7000

Total final enrolment
7002

Key exclusion criteria
1. Weight for age <-3 z, or weight <2 kg at the time of presentation if age at screening is less than 10 days
2. Signs of critical illness (no movement at all, unable to feed at all, or convulsions)
3. Signs of clinical severe infection (CSI) associated with a moderate risk of mortality (stopped feeding well, movement only on stimulation, low body temperature <35.5°C, or two or more of the six signs of CSI)
4. Any sign suggestive of another serious illness/condition, such as but not limited to: major congenital malformations, severe jaundice, conditions requiring major surgery, meningitis, bone or joint infection, or severe dehydration
5. Appearance of low-mortality risk signs in the first 24 h of life
6. Hospitalized for any illness in the previous 2 weeks
7. Prior use of injectable antibiotics for the same illness
8. Previously included in this study or currently included in any other study

Date of first enrolment
24/06/2021

Date of final enrolment
30/04/2024

Locations

Countries of recruitment
Bangladesh

Ethiopia

India

Nigeria

Pakistan

Switzerland

Tanzania

United States of America

Study participating centre
Projahnmo Research Foundation (PRF)
Abanti
House 37
Road 27
Block A
Dhaka
Bangladesh
1213

Study participating centre
Tikur Anbessa Hospital
Addis Ababa University
Addis Ababa
Ethiopia
1000

Study participating centre
Center for Health Research and Development, Society for Applied Studies
45, Kalu Sarai
New Delhi
India
110016

Study participating centre
Community Empowerment Lab (CEL)
26, 11, Wazir Hasan Road
Block I
Gokhale Vihar
Butler Colony

Lucknow
India
226001

Study participating centre
Ahmadu Bello University Teaching Hospital
Ahmadu Bello University (ABU)
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1044

Study participating centre
Aga Khan University Hospital
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Study participating centre
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Sponsor information

Organisation
World Health Organization

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Sponsor type
Other

Website
http://www.who.int/maternal_child_adolescent/en/

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype

Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Publication and dissemination plan
Planned publication in a high impact peer-reviewed journal. Dissemination of key findings with stakeholders will be conducted in each country after the completion of the study.

Intention to publish date
31/12/2024

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		14/07/2023	17/07/2023	Yes	No