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Randomised controlled trial of probiotics for preterm and small for gestational age infants

Submission date
22/03/2025

Recruitment status
Recruiting

Registration date
08/04/2025

Overall study status
Ongoing

Last Edited
03/06/2026

Condition category
Other

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

Plain English summary of protocol

Background and study aims
This study has been designed to find out how well probiotics work in the first 6 months of life in babies who are born early (also called preterm) or small in size (also called small for gestational age [SGA]). Probiotics are defined as live bacteria given as food supplements which improve health in the persons who receive them. This study is coordinated by the World Health Organization (WHO) in Geneva.
The overall aim of the study is to determine if probiotics can reduce mortality, blood stream and bowel infections, and improve growth in preterm and SGA babies. The researchers will also assess if probiotic bacteria can be found in the stool specimens of babies and mothers after birth.
Two probiotic bacteria (B. infantis and L. rhamnosus) have been widely used in preterm and term infants. Some studies have suggested that these two strains might be able to improve infections, bowel problems and growth problems in preterm and SGA infants but the studies so far have been too small to be sure. The researchers will be doing this study in five countries (Bangladesh, Ethiopia, Kenya, Nigeria and Pakistan) and they intend to show what effects these probiotics have, if any, on rates of death, infections, bowel problems and growth in preterm and SGA infants. Infections, bowel problems and growth problems are very common in preterm and SGA infants. So if probiotics are shown to have important effects the researchers will be able to update WHO guidelines to include these probiotics in healthcare programs to benefit preterm and SGA infants in the participating countries and also across the world.
The supplements used in the study have been specially made for WHO in Denmark for preterm and SGA infants under strict conditions. They will be provided as two small packets (sachets) and will contain a starch (also called maltodextrin) powder. Half of the sachets will have only maltodextrin powder. The other half of the sachets will have maltodextrin powder plus the probiotic bacteria B.infantis or L. rhamnosus. Our research staff will mix the sachets in a small amount of sterile water in a syringe and then offer the syringe to the mother to feed the baby, or the research staff will feed the baby themselves if the mother would prefer. The supplements will be given daily for 28 days.

Who can participate?
The researchers are inviting all mothers of babies in the study sites who are preterm or SGA and less than 2 days old to be part of this study. Participation in this research is entirely voluntary. It

is the choice of the mother whether to participate or not. A total of 14,000 infants will be recruited across the five countries, 9,500 preterm infants and 4,500 SGA infants.

What does the study involve?
The baby will be in the study for 6 months. During that time, the mother will be visited at home and in health facilities. Each visit should not take more than 30 minutes. The baby will be placed in one of two groups as if by lottery which is similar to tossing a coin. Depending on which group the baby is in, the baby will receive either the 'intervention' ie the two sachets with probiotics or the 'placebo' ie two identical sachets without the probiotics. The researchers will measure the baby's weight, length, and head circumference. They will ask some questions about the baby's health and health care, the pregnancy, delivery and after delivery. The researchers will access the mother's medical records to record health and health care during pregnancy, delivery and after delivery. They will give the mother two syringes to feed the supplement to the baby in the usual way that the mother feeds the baby, i.e. by mouth or by gastric tube. The syringes are a way of carefully putting the liquid into the baby's mouth, no needle will be used. Anyone the mother wishes can give the supplements to the baby. If the mother would like the research staff to give the baby the supplements, they would be happy to do so. If the baby vomits or spits out the dose within 15 minutes the researchers will repeat the dose. The researchers will visit the baby every day for 28 days at home or in the health facility to give the baby the supplement doses. They will review the baby every day until 7 days after the final dose in person or by telephone. The researchers will ask if the baby is well and if the baby has any problems with infections and diarrhoea. If the baby has any serious illnesses, the researchers will help the mother seek care from a hospital. They will collect information from the hospital records on all illnesses until the baby reaches 6 months of age. If it is possible the baby has a bloodstream infection, the researchers will help the hospital to look after the baby according to best practice standards and take a small amount of blood (2 ml) to get it analysed in their laboratory. When the results are ready the researchers will help the mother and the doctors to get the results. The researchers will also record the results of the blood specimen in their database. Some babies will be randomly selected to provide a small stool sample at enrollment, and then when they are aged 7 days, 28 days and 6 months. The mother of these babies will also be asked to collect a small stool sample from herself within 48 hours of birth. The researchers will visit enrolled babies every month for 6 months at home to ask about illnesses and health care in the baby. At 6 months the research staff will take the baby's growth measurements again (the baby's weight, length, and head circumference).

What are the possible benefits and risks of participating?
There is a small risk that the organisms in the probiotic could enter the bloodstream (this is called probiotic sepsis). The researchers will monitor the baby carefully for signs of bloodstream infection for 7 days after the supplement administration. They will also help with referral to hospitals to treat with appropriate antibiotics if there is any concern that any infection may have occurred.
Preparing the supplement in an unhygienic way can cause contamination and result in diarrhoeal illness in the baby. This is why the researchers are going to use sterile water and prepare the supplements themselves for the mother to give to the baby, so this should not occur. They will also monitor the baby daily for diarrhoea and other illnesses for 7 days after giving the supplement dose.
Studies have shown that probiotic organisms in supplements can also spread to other family members and across hospital wards. This will be reduced by careful preparation of the supplements and handwashing before and after the supplement is administered to the baby. However, the possibility of spread cannot be completely removed. Some probiotics can reduce the effect of antibiotics (this is called antibiotic resistance). However, the probiotics used in this study have been tested and do not have this problem. The mother may become tired of the

research staff visiting at home. If at any time during the study, the mother is not comfortable about anything the researchers will make sure that they will listen to the mother's concerns and will stop visiting if the mother wishes it.
The mother and baby will not receive any direct benefit from taking part in this study. However, the mother and baby will receive examinations and advice for the treatment of illnesses. Also, if the mother has any questions about her or her baby's health the researchers will be happy to answer them. The researchers will pay for any test that they perform and the blood culture and stool tests but they won't be able to pay for any extra tests. They will not be able to pay for additional hospital investigations or treatment.
They will give the mother a small token of appreciation for her time. The results of the study will help answer important research questions about probiotics in preterm and SGA babies.

Where is the study run from?
The study is sponsored by WHO Department of Department of Sexual, Reproductive, Maternal, Child, Adolescent Health and Ageing (LHR) and coordinated by Johns Hopkins University (JHU) (USA)

When is the study starting and how long is it expected to run for?
July 2024 to August 2027

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

Who is the main contact?
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Contact information

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Public, Scientific, Principal investigator

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Additional identifiers

Protocol serial number
Funder Investment Number INV070288

Study information

Scientific Title
Efficacy of probiotic supplementation in preterm and small for gestational age infants: a multi-centre, placebo-controlled, individually-randomised trial

Acronym
PROPS

Study objectives
This study investigates the hypothesis that probiotic supplements improve health outcomes in preterm and term small for gestational age infants more than placebo supplements

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 16/04/2025, World Health Organization Research Ethics Review Committee (Avenue Appia, Geneva, 1202, Switzerland; +41 (0)227912111; ercsec@who.int), ref: 4223

Primary study design
Interventional

Study design
Double-blind individually randomized placebo-controlled parallel-group multi-centre clinical trial

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Improvement in health outcomes (survival, necrotising enterocolitis, infections and growth)

Interventions
1. Screening, assessment of eligibility, enrolment:
1.1. Screening:
Hospital staff (i.e. the doctors and nurses in the hospital who are routinely caring for mothers during labour and babies after birth) are part of the study team and have approval from the

hospital administration units to notify live births to the site research team. Notification will occur as soon as possible after birth and within 48 hours.
The hospital staff will ask all mothers of all live-born babies for authorisation to be approached by the research team as soon as feasible after birth and within 48 hours. The mothers will be given a copy of the screening information sheet by the hospital staff or the hospital staff will read the information sheet to the mother. If the mother gives authorisation, the research team will then visit the family while the baby is still in hospital, inform the family about the study and ask the mother of the infant for their informed written consent to conduct the screening procedures (as listed in the table below).
Mothers will be given as much time as possible to reflect on participation. The research team will explain that consent is needed before the baby is 48 hours old because probiotics may have maximum benefit in very young babies under 2 days of age. The research team will explain that if the mother is unable to decide it will not influence any care she receives from the study hospital.

1.3. Consent for the main trial:
The mothers of eligible infants will be asked for informed written consent for the infant to be randomised and included in the trial. This consent will be done by senior experienced research staff who are not hospital staff. At the time of screening the mother will be asked if she would like to hear about the main trial as well or if she would like the team to return at a more convenient time. A standardised informed consent form will be used and the procedures below will be followed. The mother of the infant is required to give consent in this trial because biological specimens will be taken from the mother and her health care record will be accessed. Sometimes the mother will need to discuss with the father of the baby before consent is given. Only mothers above the legal age of consent can give consent in this trial.

1.4. Co-enrolment guidelines:
Infants who are enrolled in other intervention studies will not be included in the PROPS trial.

2. Assignment of interventions:
2.1. Allocation and sequence generation:
Each site will have their own randomisation lists and randomisation will be done separately for the preterm and term SGA infants. i.e. There will be two randomisation coding ‘lists’: one for preterm infants and one for SGA infants. The randomisation coding lists will be prepared and held by an external statistician who is not part of the study. Allocation to intervention and control groups will be done through a computerised server-based system with computer-generated random numbers. A backup paper-based randomisation system will also be available if internet connectivity is disrupted. Random permuted blocks of variable sizes (6, 8, 10 or 12) will be used during randomisation. This ‘blocking’ will also be prepared by the external statistician and will be accessible only to that statistician.

2.2. Allocation concealment and blinding:
The participants (i.e., participants, care providers), hospital staff and all investigators (i.e. the site teams including the intervention, data collection, data management and data analysis teams, the WHO TCU (including the project managers and internal statistics team) will be blinded to the group allocation, i.e. they will not know if the infant receives intervention or placebo sachets.

The intervention powder will be identical in appearance, consistency, taste and smell to the placebo powder. The intervention and placebo will be placed in foil sachets that are also identical in appearance and packaging. The sachets will be labelled and assembled into boxes and packs by an experienced packing team. The packing team will ensure that all labelling does not distinguish between placebo and intervention groups.

Each infant who is randomised will be allocated a randomisation number which will become their participant ID number. The randomization sequence will be generated by the external statistician who is independent to the PROPS trial. A designated WHO project coordinator will ensure that this code is sent to the packing team only and not to any other staff.

3. Intervention and placebo supplementation:
3.1. Intervention and placebo formulation, sachets, dose and duration:
The intervention will be a high-quality, pharmaceutical-grade product with known safety containing Lactobacillus rhamnosus GG DSM33156 and Bifidobacterium longum subsp. Infantis DSM33361. The doses will be 1 billion CFU of L rhamnosus GG and 0.35 billion CFU B. Infantis at 'end of shelf' i.e. on administration to the infant. Each strain will be mixed with 0.5 grams of maltodextrin lyophilized powder and provided separately in its own foil sachet.
The placebo will contain identical maltodextrin lyophilized powder but will be provided alone (i. e. without the probiotic strains) and will be packaged in its own identical foil sachets. It will be identical in appearance, taste, consistency and packaging to the intervention.
Each infant will receive two sachets. In the intervention group the infant will receive one L rhamnosus GG sachet and one B. Infantis sachet. In the comparator group the infant will receive two placebo sachets.
The researchers have allowed 50% overage to account for accidental spillage, and vomiting or spitting of the dose by the infant. i.e. they have allocated 84 sachets for each infant, two for each day for 28 days (56 sachets) and 28 backup doses.
The intervention and placebo supplements will be provided daily for 28 days from enrolment.

3.2. Manufacturing:
A reputable manufacturer with a demonstrated record of high-quality production of these strains for preterm infants has been engaged to produce the trial intervention and placebo. The manufacturer will produce the supplements according to their high-quality specifications and standards for preterm infants (called 'pre-inf' standards) and will pack them into identical intervention and placebo foil sachets. The sachets will be maintained at 2 to 8 deg C throughout the manufacturing process. After production of the sachets, the manufacturer will 'handover' to a specialised packing team who will organise the labelling, packing and shipping to the sites. The manufacturer will provide documentation about which batches are intervention and placebo only to the specialised packing team.

The manufacturer will also provide certificates of compliance and analysis to be able to address: dose, potency, formulation, and testing for purity, quality, contamination, species and strain identity, storage conditions, stability and viability at the end of shelf life.

3.3. Labelling, packing and shipping to sites:
The packing team will carefully label all sachets and boxes with the randomisation code provided by the study's external statistician, ensuring that the intervention and placebo sachets are kept separate. The team will assemble the sachets into packs, cartons and pallets for each site, label the cartons and pallets with the secondary and tertiary labelling and packaging according to country regulations, ship the cartons to each study site, provide the necessary regulatory and customs clearance documents, ensure adequate storage conditions (refrigeration at 2 to 8 deg C) are in place on arrival in the country, and ensure a smooth transition to customs officials and the onsite investigators in the country. The packing team will ensure the cold chain of 2 to 8 deg C throughout.

3.4. In-country transport and storage:
The sachets will be transported to each site and stored maintaining the cold chain with a temperature between 2 to 8 deg C in each study site (via refrigerators or cold boxes). All sachets

will be logged on arrival at the site and site logs, registers and store rooms will be maintained by designated site staff according to ICHGCP procedures.

3.5. Administration and backup doses:
The intervention delivery team will log out four sachets (two for the primary dose and two as the backup dose) for each enrolled infant each day and place the sachets in dedicated cold boxes (similar in appearance to vaccine carriers) to maintain the temperature of the sachets at 2-8 deg C throughout the day until return to the office.
To ensure the supplements are mixed 'fresh' i.e. just prior to feeding to the infant, the sachet contents will be reformulated by the dedicated intervention delivery team in designated areas in the respective site offices near the hospital wards or in the individual homes of participating infants. According to the manufacturer's instructions, to maintain cell count, the reformulated supplement must be used within 30 minutes. The manufacturer's instructions will be strictly followed to ensure hygiene and avoid environmental contamination. The research staff will use dedicated gloves throughout the process of preparation and administration and will dispose of the gloves using the standardised study SOPs. In the hospital wards, the contents of each sachet will be mixed in 1-2 ml of sterile water in the study office and placed in a syringe labelled with the infant's study details. The prefilled syringes will then be placed in separate containers within cold boxes at 2 to 8 degrees Celsius for transport to the hospital ward. At the home visits, the sachets will be transported in their packaging in the cold boxes at 2 to 8 degrees Celsius. The intervention team will bring with them a small table. They will use this table to reformulate the sachet into study syringes using exactly the same method that is used for the hospital ward sachets.
The supplements will be administered enterally (i.e. orally or by gastric tube) to the infant using syringes in health facilities or at home. The sachet contents will ideally be given to the infant by the mother who will be directly observed by the intervention delivery team (directly observed therapy [DOT]). It may take some time to administer the supplement to young preterm and SGA infants. Mothers will be advised to take as much time as is needed to administer the supplement.
If the intervention delivery team becomes aware that an infant has vomited soon after the study sachet ingestion (within approximately 15 minutes), they will give the backup dose to the infant. The dosing will repeated once only. If the supplement is spilled then the backup dose can be given. There are no other reasons for giving the backup dose.
The amount of supplement administered to the baby will be recorded on the study level eCRF.
If the infant refuses any of the primary dose the backup dose should not be given.
Spare intervention and placebo sachets labelled with spare randomisation codes will be kept onsite. If it appears that all 84 allocated doses are used (i.e. primary dose and their backup dose) we will be able to allocate these spare doses to the infant whilst remaining blinded.
An intervention delivery CRF will be completed by the intervention delivery team which will include details of the sachets provided.
If the family have been told not to enterally feed the infant i.e. the infant has been made 'nil by mouth' or 'nil orally' by the medical team, or is unable to take enteral feeds, then the supplementation will be ceased until the infant is able to take feeds again.

3.6. Unused supplements:
If infants are not able to be supplemented (e.g. the family were not at home), the unused sachets will be brought back to the study office. If the cold chain has been maintained and the sachets are not damaged then the sachets can be logged back into the study store and reused for revisits as per the study SOPs.
At the end of the study all unused sachets will be destroyed according to national guidelines and the destruction process will be documented as per national guidelines.

3.7. Quality assurance of the intervention and placebo:
Quality assurance processes will be implemented for all steps of the intervention process. For the manufacturer quality assurance will include: predelivery testing for purity, quality, contamination, species identity and purity, and testing of 'stability' and viability at the end of shelf life.

3.8. Concomitant care and interventions that are permitted or prohibited during the trial:
Infants will be able to receive all other health care from the hospitals and health facilities that they require. There are no restrictions. We will record the receipt of other probiotics, antibiotics and other medicines during the monthly data collection visits.

4. Follow up:
Infants are followed up daily in hospital and 4 weekly at home. Data on all primary and secondary endpoints are taken at those times until the infant reaches 6 months.

Intervention Type
Supplement

Primary outcome(s)
Measured from enrolment to 6 months of age:
1. Preterm infants: all-cause mortality measured using:
1.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow-up visits
1.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants
2. Term SGA infants: underweight-free survival: proportion of infants with weight for age z score (WAZ) >=-2 standard deviations (SD) who have not died, measured using:
2.1. Death:
2.1.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow-up visits
2.1.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants
2.2. Underweight: weight measurement taken by trained field workers

Key secondary outcome(s)
Mortality and morbidity measured at hospital discharge, 1 month and 6 months of age:
1. All-cause mortality (for the 6-month endpoint, this will be evaluated as a secondary outcome for term SGA infants, and as a primary outcome for preterm infants) measured using:
1.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow-up visits
1.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants
2. Cause-specific mortality due to necrotising enterocolitis, sepsis, or severe diarrhoea measured using:
2.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow-up visits
2.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants
Plus cause due to necrotising enterocolitis, sepsis, or severe diarrhoea confirmed by the trial adjudication committee
3. Incidence of suspected necrotising enterocolitis (modified Bells grade 2 or greater criteria) measured using:
3.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow-up visits

3.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants Plus cause confirmed by the trial adjudication committee
4. Episodes of suspected sepsis: incidence of suspected sepsis measured using:
4.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow-up visits
4.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants Plus cause confirmed by the trial adjudication committee
5. Episodes of confirmed sepsis: incidence of suspected sepsis with bacterial pathogens isolated from blood cultures:
5.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow up visits
5.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants Plus cause confirmed by the trial adjudication committee
6. Episodes of severe diarrhoea: incidence of severe diarrhoea measured using:
6.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow-up visits
6.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants Plus cause confirmed by the trial adjudication committee
7. Episodes of hospitalisation: incidence of hospitalisation for any cause measured using:
7.1. Mother's recall of event in the previous 4 weeks reported to trained field workers during scheduled follow-up visits
7.2. Event ascertained by trained field worker during daily hospital review of hospitalised infants Plus cause confirmed by the trial adjudication committee

Growth measured at 6 months of age:
1. Underweight in infants: proportion of infants with weight for age z score (WAZ) <-2 standard deviations (SD), measured by trained field workers
2. Wasting in infants: proportion of infants with weight for length z score (WLZ) <-2 SD, measured by trained field workers
3. Mean weight for age z score (WAZ) <-2 standard deviations (SD), measured by trained field workers
4. Mean weight for length z score (WLZ) <-2 SD, measured by trained field workers
Added 30/10/2025:
5. Stunting in infants: proportion of infants with weight for length z score (WLZ) <-2 SD, measured by trained field workers
6. Mean length for age z score (LAZ) <-2 SD, measured by trained field workers

Faecal bacteria measured at enrolment, 7 days, 28 days and 6 months of age:
1. Proportion of B. infantis, L. rhamnosus and other bacteria in infant faecal specimens measured using quantitative polymerase chain reaction (qPCR)

Faecal bacteria measured at enrolment:
1. Proportion of B. infantis, L. rhamnosus and other bacteria in maternal faecal specimens measured using quantitative polymerase chain reaction (qPCR)

Completion date
31/08/2027

Eligibility

Key inclusion criteria

1. <48 hours of age at the time of enrolment
2. Preterm (appropriate for gestational age [AGA] or small for gestational age [SGA]) or term SGA infants
3. Likely to be in the study area for the next 6 months

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Neonate

Lower age limit
0 Days

Upper age limit
2 Days

Sex
All

Total final enrolment
0

Key exclusion criteria
1. <28 weeks gestation
2. Not taking enteral feeds (e.g. due to a major congenital abnormality, mechanically ventilated, post-surgery or too unwell to be fed)
3. Confirmed sepsis at the time of enrolment
4. Indwelling central lines (including umbilical catheter/central venous line) (infants with peripheral intravenous lines will not be excluded)
5. Multiple births (e.g. twins, triplets)

Date of first enrolment
01/05/2026

Date of final enrolment
01/03/2027

Locations

Countries of recruitment
Bangladesh

Ethiopia

Kenya

Nigeria

Pakistan

Study participating centre
Projahnmo Research Foundation (PRF)
Syhlet
Bangladesh
3100

Study participating centre
Armauer Hansen Research Institute (AHRI)
Addis Ababa
Ethiopia
1165

Study participating centre
Kenya Medical Research Institute (KEMRI)
Nairobi
Kenya
00100

Study participating centre
University of Ibadan (UI)
Ibadan
Nigeria
110115

Study participating centre
Aga Khan University
Karachi
Pakistan
05444

Sponsor information

Organisation
World Health Organization

Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, Gates Learning Foundation, William H. 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

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.4	08/10/2025	03/06/2026	No	No
Statistical Analysis Plan	version 2.0	27/03/2025	16/04/2025	No	No
Statistical Analysis Plan	version 2.1	24/10/2025	30/10/2025	No	No
Study website		11/11/2025	11/11/2025	No	Yes