Evaluating the Efficacy of a Multistrain Probiotic Supplementation for Prevention of Neonatal Sepsis in 0-2 Months Old Low Birth Weight Infants in India – The 'ProSPoNS' Study Protocol for a Phase III, Multicentric, Randomized, Double-Blind, Placebo-Controlled Trial.

Anju Pradhan Sinha (apradhandr@gmail.com)
Indian Council of Medical Research New Delhi https://orcid.org/0000-0002-0830-7723
Subodh S Gupta
Mahatma Gandhi Institute of Medical Sciences, Sewagram , Wardha
Ramesh Poluru
The International Clinical epidemiology Network (INCLEN) Trust International
Abhishek V Raut
Indian Institute of Technology Roorkee
Narendra K Arora
The International Clinical epidemiology Network (INCLEN) Trust international
Ravindra Mohan Pandey
all India Institute of Medical sciences, New Delhi
Aditya Ranjan Sahu
Next Gen Pharma Pvt. Ltd
Adhisivam Bethou
Jawaharlal Institute od Postgraduate Medical Education and Research (JIPMER)
Sunil Sazawal
Centre for public health Kinetics (CPHK)
Sailajanandan Parida
Asian Institute of Public Health
Ashish Bavdekar
King Edward Memorial hospital research centre
Arvind Saili
Lady Hardinge Medical college and associated kalawati saran Children's hospital
Rajani Gaind
Vardhaman Mahavir Medical college
Arti Kapil

All India Institute of Medical Sciences, New Delhi
Bishan S Garg
Mahatma Gandhi Institute of Medical sciences, sevagram, Wardha
Chetna Maliye
Mahatma Gandhi Institute of medical Sciences, Sevagram, Wardha
Manish Jain
Mahatma Gandhi Institute of Medical Sciences, sevagram, Wardha
Kamlesh Mahajan
Mahatma Gandhi Institute of medical sciences, sevagram, wardha
Pratibha Dhingra
Centre for Public Health kinetics
Keshab c Pradhan
Asian Institute of public Health
Anand S Kawade
King Edward Memorial hospital Research centre
Sushma Nangia
Lady Hardinge Medical college and associated kalawati saran children's hospital
Ajit Mukherjee
Indian Council of Medical research new Delhi
Reeta Rasaily
Indian Council of medical research New Delhi
Radhey Shyam Sharma
Indian Council of Medical Research New Delhi

Study protocol

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Abstract

Background: Progress has been made in reduction of under five mortality in India, however, neonatal mortality is reducing at a slower rate. Efforts are required to bring down neonatal mortality in order to attain the SDG-3. Prevention of sepsis among the high risk, vulnerable low birth weight neonates by a newer intervention with probiotic supplementation is promising.

Methods/design: A phase III, multicentre, randomized, double blind, placebo-controlled is being conducted at six sites in India. A total of 6144 Healthy LBW infants fulfilling the eligibility criteria would be enrolled within first week of life, after obtaining written informed consent from the parents of the infant. Randomization in 1:1 ratio, stratified by site, sex and birth weight would be done through an interactive web response system (IWRS) using a standard web browser and email service Vivomixx R a probiotic containing a mix of 8 strains of bacteria, in a suspension form standardized to deliver 10 billion CFU/ml, or an organoleptically similar placebo would be fed to enrolled infants in a 1ml/day dose for 30 days. The follow-up of enrolled infants would take place as per a pre-specified schedule for recording morbidities and outcome assessments at the six participating sites. Screening for morbidities would be conducted by trained field workers in the community, and sick infants would be referred to designated clinics/hospitals. A physician would examine the referred infants presenting with complaints and clinical signs, blood samples would be collected from sick infants for diagnosis of neonatal sepsis by performingsepsis screen and blood culture. Appropriate treatment would be provided as per hospital protocol. Study would be implemented as per the MRC guideline for management of Global Health Trials in accordance with ICH-GCP and Indian Regulatory guidelines. A Contract Research Organization would be enaged for comprehensive monitoring and quality assurance. . The final analysis would be conducted in a blinded manner as per the statistical analysis plan (SAP) to estimate the primary outcomes sepsis, possible serious Bacterial Infection (PSBI) & secondary outcomes. The codes will be broken after DMEC permission. The protocol has been reviewed by the Research Ethics Committee of the Liverpool School of Tropical Medicine (REC-LSTM), from Research Ethics Committees of the six subject recruitment participating sites

Discussion: This adequately powered and well-designed trial would conclusively answer the question whether probiotics can prevent neonatal sepsis in the high risk group of Low Birth Weight infants as indicated by a pilot study in 1340 LBW infants, evidence from systematic reviews of hospital based studies and a primary study on healthy newborns in Orissa. Results of the study would be generalizable to India and other Low–middle income countries.

Trial registration: The study is registered at the Clinical Trial Registry of India (CTRI; 1 http://ctri.nic.in); Number CTRI/2019/05/019197, date 16 May 2019).

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the latest manuscript can be downloaded and accessed as a PDF.

Tables

Table 1 Schedules for study subject enrolment, intervention and assessments

TIMEPOINT	Enrolment	Allocation	Post-allocation							
			Month 1				Month 2			
	$-t_1$	0	*Week 1*	*Week 2*	*Week 3*	*Week 4, till end of month 1*	*Week 1*	*Week 2*	*Week 3*	*Week 4, till end of month 2*
ENROLMENT:										
Eligibility screen	X									
Informed consent	X									
Allocation		X								
INTERVENTIONS:										
Probiotic			←	—	—	→				
Placebo			←	—	—	→				
Infant stool collection†		X			X					X
ASSESSMENTS:										
Hospital visit		X								
Field-worker visit††			X	X	X	X	X	X	X	X
Adverse event monitoring			X	X	X	X	X	X	X	X
Data Collection and Verification			X	X	X	X	X	X	X	X

† Infant stool samples collected from one participating site (preferably in Delhi) at time of enrolment (Day 0), at end of 3rd week of supplementation (Day 21) and at end of follow up (within day 56 - 60)

†† Daily during the first week of life, thrice a week from week 2 of life till end of first month, and subsequently weekly in the second month

Figures

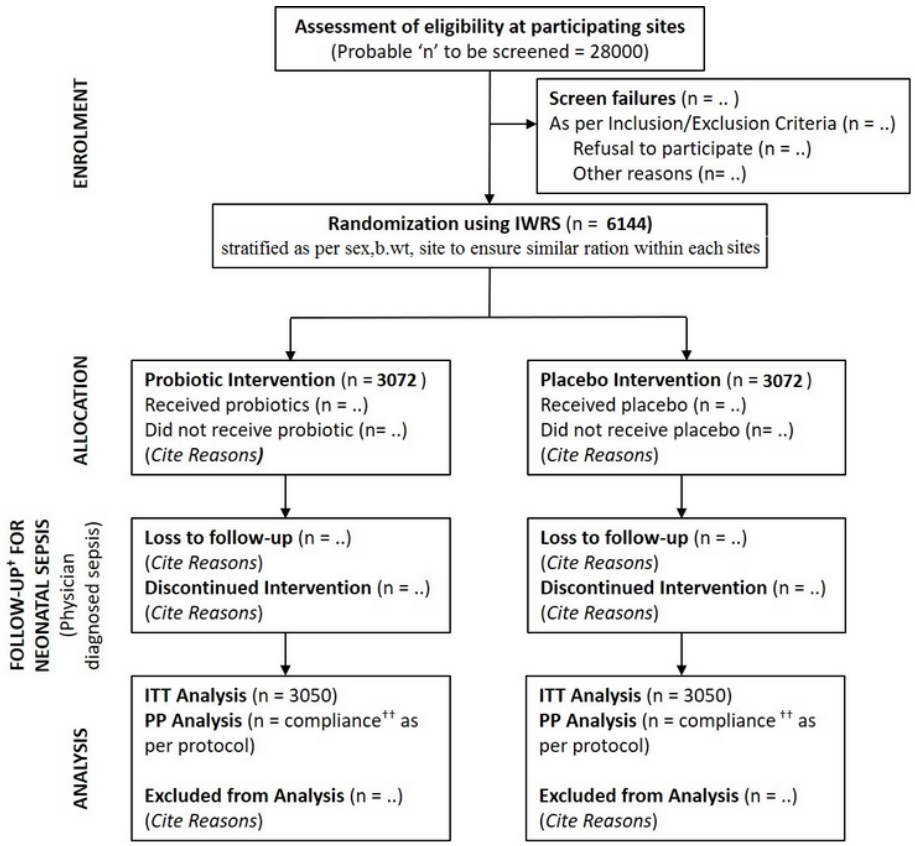

Figure 1

Study Design Randomization – Stratification by sex, birth weight and study site Footnotes to Figure 1: ITT, Intention-to-treat; PP, Per-protocol 10 † Daily during the first week of life, thrice in week 2 - 4 of life, and subsequently weekly in the second month †† Compliance defined as those enrolled infants who have ingested the study drug (for at least 25 days) and were followed up for more than 50% of scheduled visits

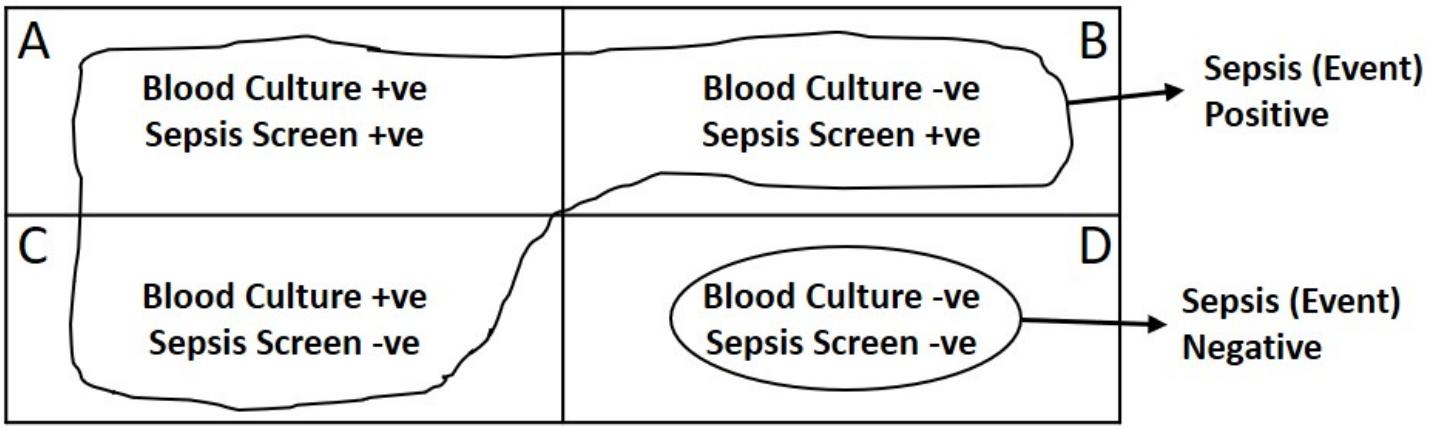

Figure 2

Possible outcomes of sepsis screen and blood culture

Supplementary Files

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- 21Sept2020SPIRITFillablechecklistV.15Aug2013.pdf