Study Protocol

Optimizing place of treatment and antibiotic regimens for young infants presenting with signs of possible serious bacterial infection

Site Protocol for Uttar Pradesh, India

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(Based on WHO Generic Protocol, Version 2.3 - 2 June 2020, Universal Trial Number (UTN): U1111-1251-1576, ERC0003289)

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EXECUTIVE SUMMARY

The WHO IMCI algorithm classifies neonates and young infants up to 2 months old with clinically suspected sepsis as "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 hospital is not feasible, the guidelines recommend further classification of these young infants into those who are critically ill[1] and those who have clinical severe infection[2]. Those with clinical severe infection (CSI), if referral is not feasible, can be managed on an outpatient basis with injectable gentamicin for 2 or 7 days and oral amoxicillin for 7 days.

Implementation 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 inherent risks, particularly that of nosocomial infection with multi-drug resistant pathogens. Therefore, only those young infants with signs of PSBI who have a favourable benefit-risk ratio should be hospitalized. Secondary analysis of data from AFRINEST study and PSBI implementation research studies showed that infants with any sign of CSI had a higher mortality rate when they were hospitalized, compared to when they received outpatient treatment. In contrast, mortality rate was lower among those with any sign of critical illness who received inpatient 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. We therefore hypothesize that majority of infants with CSI do not benefit from hospitalization. We also hypothesize that majority of infants who need hospitalization can be discharged early. We propose to test these hypotheses in the planned trials.

Overall goal

To generate knowledge that will allow us to rationalize hospitalization for young infants with PSBI in order to minimize the risk of nosocomial infections and improve clinical outcomes, by:

(1) hospitalizing only those young infants with PSBI who need hospitalized care and treating the others on outpatient basis (Study 1), and

(2) minimizing the hospital stay of those young infants who need hospitalization but improve early through early discharge and continuation of their treatment at home (Study 2).

Study 1

Background and rationale

Secondary analysis of AFRINEST data showed that the overall case fatality rate (CFR) for young infants with CSI treated at hospital was higher compared to those treated on an outpatient basis. Higher inpatient mortality could be due to any or a combination of possible scenarios: i) despite presentation with the same clinical signs, possibly infants taken to the hospital were sicker than those who were not, ii) infants who were taken to the hospital may have received unstandardized or delayed treatment

[1] Convulsions, or not able to feed at all, or no movement at all

[2] 6 signs of CSI – high body temperature ≥38°C, low body temperature <35.5°C, severe chest indrawing, fast breathing of ≥ 60 breaths per minutes in 0-6 days old infants, movement only when stimulated, not feeding well/stopped feeding well

while those who were not taken to a hospital received standardized treatment immediately, iii) hospitalized infants may have suffered from nosocomial infections with resistant pathogens.

Therefore, in order to confirm this observational finding (i.e., whether standardized outpatient care is indeed safer than standardized inpatient treatment for infants with CSI), we propose to randomise infants with CSI to either hospital or outpatient treatment and compare the outcomes.

Research question and Hypothesis

Among young infants (<2 months old) with only one low-mortality risk PSBI sign[3] presenting to outpatient/emergency department of a hospital (**Population**), does outpatient treatment with injectable gentamicin for 2 days or 7 days (as per WHO/national guidelines) and oral amoxicillin for 7 days **(Intervention)**, compared to the currently recommended inpatient hospital treatment initiated with injectable ampicillin and gentamicin and supportive care (**Control**), result in lower rates of poor clinical outcome (death within 2 weeks of initiation of treatment, deterioration during the 7-day treatment period, or persistence of the presenting sign of CSI at the end of the 7-day treatment period) (**Outcome**)?

Study 1 Simplified hypothesis: young infants with only one low-mortality risk sign of CSI 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.

Study design

This will be an open-label, two-arm, individually-randomized controlled trial.

Study population

All young infants < 2 months old, living in a geographic area where follow-up for 14 days can be accomplished presenting to outpatient clinics or emergency rooms of participating hospitals will considered for inclusion in this study if they have ONLY one of the following low-mortality-risk signs of PSBI - body temperature ≥ 38°C, or severe chest indrawing, or fast breathing (<7 days old infants).

Intervention

Outpatient treatment with injectable gentamicin (once daily) for 2 days plus oral amoxicillin (twice daily) for 7 days.

Control

Inpatient antibiotic treatment for at least 7 days initiated with WHO recommended antibiotic regimen of injectable ampicillin (four time daily) plus injectable gentamicin (once daily) along with other supportive care.[4]

Outcomes and their assessment

Poor clinical outcome defined as –

[3] Low risk of mortality signs – high body temperature ≥38°C, severe chest indrawing, fast breathing of ≥ 60 breaths per minutes in 0-6 days old infants

[4] Any change of antibiotic per se by the treating physician will not be considered as a treatment failure

- Death any time from randomization up to day 15 of initiation of therapy, or.
- 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, e.g. meningitis, bone or joint infection, on day 2, 4 or day 8 of initiation of therapy, or
- Presence of any new sign of CSI on day 4 or day 8 of initiation of therapy, or
- Persistence of the presenting sign on day 8 of initiation of therapy.

Outcome assessment will be carried out by independent outcome assessors (IOAs), who will visit all enrolled young infants on day 2, 4, 8 and 15 after enrolment. Outcome assessment will be conducted at the hospital or at home after discharge in the control arm and at home in the intervention arms. Outcomes will only be ascertained by the IOAs in accordance with the criteria mentioned above under outcomes.

Sample size

We plan to enrol 500 eligible infants in each of the two study arms (total 1000 eligible young infants) in our study site.

Study 2

Background and rationale

In the AFRINEST study, among young infants who were enrolled and received outpatient treatment, we found that three quarter of infants with signs of clinical severe infection (CSI) assessed at 48 hours after initiation of treatment (73.9%) no longer displayed any signs of illness. A total of 1.3% infants with CSI died by day 15 of initiation of treatment, and two-fifth of these deaths (39.7%) occurred within the first 48 hours of treatment. Of the infants who were clinically well (no sign of illness) at 48 hours, 0.4% died between day 3 and 15 after the initiation of the outpatient treatment. In contrast, mortality between day 3 and 15 was higher among those with persistence of the presenting sign at 48 hours (0.7%) and those who deteriorated (presence of new CSI sign or critical illness sign) at 48 hours (8.0%).

We would like to take the opportunity of conducting a concurrent study with the main study to address the issue of safe and early discharge from the hospital of infants admitted with clinical severe infection.

Hypothesis and Research question

Among hospital-admitted young infants with a high-mortality risk sign[5] or two or more signs of CSI who clinically improve 48 hours after initiation of treatment and have a negative C-reactive protein (CRP) laboratory test (**Population**), does discharge from hospital on oral amoxicillin at home for the next five days (**Intervention**), compared with continued hospital management for next five days (**Control**), non-inferior in terms of poor clinical outcome (death between randomization and day 15 of initiation of therapy, presence of any sign of CSI or CI on day 8 of initiation of therapy) (**Outcome**)?

[5] High-mortality-risk signs of CSI – movement only when stimulated or not feeding well/stopped feeding well or low body temperature (<35.5°C) or two or more signs of CSI, including low risk signs - high body temperature (≥38°C), severe chest indrawing, fast breathing (≥60 breaths per minute) in 0-6 days old infants.

Study design

This will be an open-label, two-arm, individually-randomized controlled trial.

Study population

All patients admitted to the study hospitals with relatively higher-mortality risk signs of CSI at presentation (not feeding well, movement only on stimulation, or low body temperature < 35.5^{o}C, or two or more of the six signs of CSI) will be assessed for eligibility for this study 48 hours after initiation of treatment and considered for inclusion in the study if: i) clinically well on day 3 defined as absence of all signs of critical illness or CSI, and ii) Laboratory test negative, and iii) Family lives within a catchment area where a follow-up of up to 14 days can be accomplished.

Intervention

Discharge from hospital and home treatment with oral antibiotic for five days.

Control

Continued inpatient hospital injectable antibiotic treatment and supportive therapy for a total of 7 days.

Outcome assessment

- Death between randomization (day 3 of initiation of therapy) and day 15 of initiation of therapy, or
- 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, e.g. meningitis, bone or joint infection, on day 8 of initiation of therapy, or
- Presence of any sign of CSI on day 8 of initiation of therapy

Outcome assessment will be carried out by a team of independent outcome assessors. An assessor will visit all enrolled young infants in the control arm at the hospital or at home after discharge and intervention arm enrolees at home on Day 8 and 15 of initiation of treatment.

Sample size

We plan to enrol 375 eligible infants in each of the two study arms (total 750 eligible young infants).

End of Executive Summary

BACKGROUND AND RATIONALE

Neonatal mortality has substantially reduced over the last few decades, but still an estimated 2.5 million neonatal deaths occur worldwide annually accounting for 46% of under-five deaths(1). Neonatal infections account for over 35% of all neonatal deaths in South Asia and sub-Saharan Africa(2). The WHO IMCI algorithm classifies neonates and young infants with clinically suspected sepsis as "Possible Serious Bacterial Infection (PSBI)". This classification is based on the following seven clinical signs – fast breathing in 0-6d old babies, severe chest indrawing, high body temperature (≥ 38^{o}C), low body temperature (<35.5^{o}C), not able to feed at all or not feeding well/stopped feeding well, convulsions, and movement only when stimulated or no movement at all(3). Current WHO guidelines recommend that young infants with PSBI should be managed in a hospital with injectable antibiotics and supportive care(4). When referral to hospital is not feasible, the WHO guideline recommends further classification of these infants into those who are critically ill[6] and those who have clinical severe infection[7](5). Infants with clinical severe infection (CSI) can be managed on an outpatient basis with injectable gentamicin for 2 or 7 days and oral amoxicillin for 7 days(5) based on clinical trials from Africa(6, 7) and Asia(8, 9).

Implementation 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 with PSBI in different settings are taken to a hospital. However, hospitalization has inherent risks, particularly that of nosocomial infection with multi-drug resistant pathogens. Therefore, only those young infants with signs of PSBI who have a favourable benefit-risk ratio should be hospitalized. Secondary analysis of data from AFRINEST study and PSBI implementation research studies showed that infants with any sign of CSI had a higher mortality rate when they were hospitalized, compared to when they received outpatient treatment. In contrast, mortality rate was lower among those with any sign of critical illness who received inpatient 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. We therefore hypothesize that majority of infants with CSI do not benefit from hospitalization. We also hypothesize that majority of infants who need hospitalization can be discharged early. We propose to test these hypotheses in the planned trials.

India loses an estimated 670,000 newborns each year (SRS-2016) – the state of Uttar Pradesh (UP) alone accounts for about a quarter of these deaths. Our recent study based on a rigorous prospective follow-up of ~40,000 newborns found the NMR in UP to be 42 per 1000, 37% higher than government estimates. Severe neonatal infection is the most important cause of neonatal mortality in UP, accounting for 39% of all deaths. Based on an estimated PSBI rate of 8% of all births, the current SNCU capacity at 12 beds per district can only meet 5% of the total need at full capacity. Given this tremendous deficit in capacity and high rates of mortality due to infections, the proposed study is of great importance for the state and country. The PI has already been in communication with the Deputy Commissioner, Child Health, Govt. of India, who has highlighted this as a very high priority for the country, and has requested the PI to conduct this study.

[6] Signs of critical illness: Convulsions, or not able to feed at all, or no movement at all

[7] 6 signs of CSI – high body temperature ≥38^{o}C, low body temperature <35.5^{o}C, severe chest indrawing, fast breathing of ≥ 60 breaths per minutes in 0-6 days old infants, movement only when stimulated, not feeding well/stopped feeding well

Overall goal

To generate knowledge that will allow us to rationalize hospitalization for young infants with PSBI in order to minimize the risk of nosocomial infections and improve clinical outcomes, by:

(1) hospitalizing only those young infants with PSBI who need hospitalized care and treating the others on outpatient basis (Study 1), and

(2) minimizing the hospital stay of those young infants who need hospitalization but improve early through early discharge and continuation of their treatment at home (Study 2).

STUDY 1: Optimizing place of treatment and antibiotic regimens for young infants presenting with signs of possible serious bacterial infection

The WHO PSBI guideline, developed based on available evidence, has now been adopted by several countries. Implementation research has shown that this guideline can be safely scaled up in diverse settings. In randomized controlled trials that led of the above guideline, and the subsequent implementation research studies in 11 sites in six countries, 8-12% of all young infants had at least one episode of PSBI within the first two months of life. However, it is not yet clear if all infants with signs of PSBI benefit from hospitalization and inpatient treatment. We have therefore reviewed and analysed the data from PSBI implementation research sites[8] and AFRINEST study(6, 7) to gain further insights into PSBI management and its outcomes. These new data provide us a potential opportunity to further simplify management of PSBI, while improving clinical outcomes. The key findings are summarized below:

Some clinical signs have relatively low case fatality when they occur as single signs

Secondary observational analysis of AFRINEST data (under publication) showed that some of the more common clinical signs of PSBI are associated with relatively low mortality. Specifically, having only fever (temperature $\geq$ 38^{o}C) in infants 0-59 days of age, only severe chest indrawing in infants 0-59 days of age, or only fast breathing in infants 0-6 days of age had relatively low case fatality rates (CFR) of 0.8%, 0.9% and 2.0%, respectively.

Those with movement only on stimulation (3.2%) or not feeding well (4%) or low body temperature (11.0%) had much higher mortality. Infants presenting with multiple signs of CSI (two or more) also had a relatively higher risk of mortality (5.7%).

As expected, signs of critical illness (CI) were associated with a very high risk of death (convulsions 11.3%, unable to feed at all 22.9% and no movements at all 25.0%) (Table 1).

An important implication of these findings is that young infants with signs associated with a relatively lower risk of mortality (fast breathing in 0-6 days of age, or temperature $\geq$ 38^{o}C or severe chest indrawing in 0-59 days of age) may not need referral for inpatient treatment in a hospital. If these signs of PSBI could be managed at outpatient level, it could reduce the need for hospitalization by over 70%.

[8] Implementation of an innovative approach to jump start simplified management of sick young infants with possible serious bacterial infection (PSBI) where referral is not feasible for potential scale-up. Available at https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373300

On the other hand, infants who have the other signs of CSI (stop feeding well, movements only on stimulation, low body temperature), with multiple signs of CSI, as well as those who have critical illness are at a high risk of mortality and might benefit more from hospitalization.

Table 1 Case fatality rate by clinical signs of clinical severe infection and of critical illness

Classification/clinical signs	Number of young infants	Mortality, n (%)
Clinical Severe Infection (CSI)	**5037**	**111 (2.2%)**
Fever	1409 (28.0%)	11 (0.8%)
Severe chest indrawing	1329 (26.4%)	12 (0.9%)
Fast breathing 0-6d	1291 (25.6%)	26 (2.0%)
Movement only on stimulation	31 (0.6%)	1 (3.2%)
Feeding poorly	251 (5.0%)	10 (4.0%)
Low body temperature	182 (3.6%)	20 (11.0%)
≥2/6 signs of CSI	544 (10.8%)	31 (5.7%)
Critical illness (CI)	**166**	**28 (16.9%)**
Convulsions	97 (58.4%)	11 (11.3%)
Not feeding at all	35 (21.1%)	8 (22.9%)
No movement at all	12 (7.2%)	3 (25.0%)
≥2/3 signs of CI	*22 (13.3%)*	*6 (27.3%)*

Observed case fatality of infants with CSI was higher with inpatient than with outpatient treatment

We analysed mortality by place of treatment for all infants classified as PSBI in AFRINEST and implementation research studies. It is surprising that CFR was higher in hospitalized young infants compared to those treated on an outpatient basis when they refused referral for the same signs of CSI (Table 2).

The overall CFR for young infants with CSI treated at hospital was three times higher (6.5%) compared to those treated on an outpatient basis (1.9%). When we examined mortality associated with each clinical sign by place of treatment, for most signs the CFR was lower for infants treated as outpatients. When we combine the CFR for the three low-mortality risk signs (temperature of $\geq$ 38^{o}C or severe chest indrawing in infants 0-59 days of age, or fast breathing in 0-6 days of age), it was 4% for those treated as inpatients in a hospital versus 1% for those treated as outpatients. (Table 2)

A similar picture emerges from preliminary unpublished data from the PSBI implementation research studies in several countries (Table 2). CFR among infants with CSI was 1.0% in those treated as outpatients and 2.6% for those treated as inpatients in a hospital.

There could be at least three explanations – alone or in combination – for the higher case fatality with hospital treatment than outpatient treatment. First, despite the same clinical signs of illness it is possible that the infants taken to the hospital by their parents were sicker than those who were not. Second, infants who were taken to the hospital may have received unstandardized treatment perhaps after a time delay while those who were not taken to a hospital received standardized and immediate

treatment. Third, hospitalized infants may have suffered from nosocomial infections with resistant organisms.

A well-designed randomised controlled trial to compare the outcome of infants with CSI who receive inpatient treatment versus those who receive outpatient treatment can minimize potential bias due to differential care-seeking based on case severity or non-standardized treatment, and confirm whether hospitalization truly increases the risk of adverse clinical outcomes.

Table 2 Case fatality rate by clinical signs of clinical severe infection and critical illness by place of treatment

Classification/clinical signs	Received outpatient treatment		Received inpatient treatment	
	No. of infants with the sign	Deaths (CFR)	No. of infants with the sign	Deaths (CFR)
AFRINEST				
Clinical Severe Infection (CSI)	4685	88 (1.9%)	352	23 (6.5%)
Fever	1383	11 (0.8%)	26	0 (0.0%)
Severe chest indrawing	1310	10 (0.8%)	19	2 (10.5%)
Fast breathing 0-6d	1033	16 (1.5%)	258	10 (3.9%)
Movement only on stimulation	29	1 (3.3%)	1	0 (0.0%)
Feeding poorly	243	9 (3.7%)	8	1 (12.5%)
Low body temperature	161	15 (9.3%)	21	5 (23.8%)
≥2/6 signs of CSI	525	26 (5.0%)	19	5 (26.3%)
Implementation research[9]				
Clinical Severe Infection (CSI)	2548	26 (1.0%)	498	13 (2.6%)

Research question for Study 1

Does outpatient treatment for young infants with low-mortality risk clinical severe infection signs result in better outcomes than hospital treatment?

Among young infants <2 months old with only one low-mortality risk PSBI *sign*[10] presenting to outpatient/emergency department of a hospital (**Population**), does outpatient treatment with injectable gentamicin for 2 days (or 7 days, as per WHO/national guidelines) and oral amoxicillin for 7

[9] The data from the ongoing PSBI implementation research is preliminary and better data will be available after completion of data collection by end-2019. PSBI IR Data from Nigeria (2 sites), Malawi, Pakistan and India (4 sites) was included in this analysis.

[10] Low-mortality-risk signs of CSI – high body temperature >=38°C, severe chest indrawing, fast breathing of >= 60 breaths per minutes in 0-6 days old infants

days **(Intervention)**, compared to the currently recommended inpatient hospital treatment initiated with injectable ampicillin and gentamicin and supportive care (**Control**), result in lower rates of poor clinical outcome (death within 2 weeks of initiation of treatment, deterioration during the 7-day treatment period, or persistence of the presenting sign of CSI at the end of the 7-day treatment period) (**Outcome**)?

Note: As can be seen from Table 2, case fatality among young infants with CSI was lower in outpatient settings, regardless of whether they presented with low- or high-mortality risk signs. So, a question may arise as to why are we distinguishing between low- and high-mortality risk signs for randomizing place of treatment in this study. This choice is based on a conscious decision to follow a conservative approach in rationalizing place of treatment. Since the comparative data from these existing studies is observational, we cannot yet attribute this observed difference between case fatality in in-patient vs out-patient settings, to increased risk due to hospitalisation alone. We have therefore chosen to move cautiously, by randomizing infants who have a lower risk of dying in both settings in this study.

Expected policy change after proposed research

If the outpatient treatment arm is better than the inpatient treatment for young infants with one low mortality risk sign, such infants will not require hospital referral in the future. Only the remaining young infants with clinical severe infection signs associated with higher risk of mortality[11] or those with critical illness would need to be treated at a hospital. This may reduce the need for hospitalization by 70%-80%, which would not only reduce treatment costs for both the health system and the families, but also increase treatment coverage, avoid nosocomial infections and thus result in lower mortality due to neonatal infections.

Scope

The scope of this trial is to evaluate the effect of outpatient treatment on study outcomes for young infants < 2 months old with only one low-mortality risk sign of CSI presenting to outpatient/emergency department of a hospital, to generate the evidence required for WHO guidelines on this intervention. Our approach is to conduct a multi-country, multi-centre individually randomized controlled trial to determine the efficacy and safety of outpatient treatment with injectable gentamicin for 2 days (or 7 days, as per WHO/national guidelines) and oral amoxicillin for 7 days, compared to inpatient treatment with injectable ampicillin and gentamicin and supportive care.

Hypothesis and objectives

The main hypothesis is that young infants with only one low-mortality risk sign of CSI 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.

The primary objective is to measure the effect of outpatient treatment on clinical outcome (death within 2 weeks of initiation of treatment, deterioration during the 7-day treatment period or persistence of the presenting CSI sign after the 7-day treatment period), compared with inpatient treatment in young infants < 2 months old with only one low-mortality risk sign of CSI.

[11] High-mortality-risk signs of CSI – movement only when stimulated or not feeding well/stopped feeding well or low body temperature or two or more signs of CSI, including low risk signs - high body temperature (≥38°C), severe chest indrawing, fast breathing (≥60 breaths per minute) in 0-6 days old infants

Study design

This will be an open-label, two-arm, individually-randomized controlled trial.

Study participants

All young infants < 2 months old, living in a geographic area where follow-up for 14 days can be accomplished presenting to outpatient clinics or emergency rooms of participating hospitals will considered for inclusion in this study if they have ONLY one of the following low-risk signs of PSBI:

- Body temperature ≥ 38°C, or
- Severe chest indrawing, or
- Fast breathing (<7 days old infants).

Infants will be excluded if they have any of the following:

- Weight <2kg at the time of presentation (if age at screening is less than 10 days) or weight for age <-3z, or
- Appearance of low-mortality risk signs in first 24 hours of life[12], or
- Signs of critical illness (no movement at all, unable to feed at all, convulsions), or
- Signs of CSI associated with a high 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), or
- Any sign suggestive of another serious illness/condition, such as major congenital malformations, severe jaundice, conditions requiring major surgery, meningitis, bone or joint infection, severe dehydration, etc., or
- Hospitalized for any illness in the previous 2 weeks, or
- Prior use of injectable antibiotics for the same illness, or
- Previously included in this study or currently included in any other study.

Intervention

Outpatient treatment with injectable gentamicin (once daily) for 2 days (or 7 days, as per WHO/national guidelines) plus oral amoxicillin (twice daily) for 7 days.

Control

Inpatient antibiotic treatment for at least 7 days initiated with WHO recommended antibiotic regimen of injectable ampicillin (four time a day) plus injectable gentamicin (once daily) along with other supportive care.

One of the possible reasons that outpatient care was observed to be better than hospital care in previous studies might be the poor quality of care in hospitals. In this study, we would like to reduce this factor as far as practically feasible. This means that the quality of care at the study hospitals will be reviewed against the WHO pocketbook for hospital care for children(4) and will be improved using quality improvement approaches to ensure a "minimum" quality of hospital care. Efforts to improve quality of care will also be made at outpatient facilities.

[12] Some signs of PSBI mimic other conditions such as perinatal asphyxia, transient tachypnoea etc. Therefore, it was decided during the investigators and Technical Advisory Group (TAG) meeting in March 2020 that newborn presenting with any sign of clinical severe infection within 24 hours of birth will not be eligible.

Outcomes

Poor clinical outcome defined as –

- Death any time from randomization up to day 15 of initiation of therapy, or.
- 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, e.g. meningitis, bone or joint infection, on day 2, 4 or day 8 of initiation of therapy, or
- Presence of any new sign of CSI on day 4 or day 8 of initiation of therapy, or
- Persistence of the presenting sign on day 8 of initiation of therapy.

Outcome assessment

Outcome assessment will be carried out by a team of independent outcome assessors (IOAs), who will visit all enrolled young infants on day 2, 4, 8 and 15 after enrolment. Outcome assessment will be conducted at the hospital or at home after discharge in the control arm and at home in the intervention arms. A separate IOA will work at the hospital and a separate one at home so there is no bias in the assessment. Outcomes will only be ascertained by the IOAs in accordance with the criteria mentioned above under outcomes.

Sample size

Sample size was calculated to be able to test both the superiority and non-inferiority hypotheses.

1. ***Intervention is superior to standard of care in reducing poor clinical outcomes:*** Assuming that 6% of infants in the standard care group will have poor clinical outcome (as defined above, based on AFRINEST study data), and 95% confidence level and 90% power, we will need 3135 infants per group for detecting 30% lower outcome in the intervention group (4.2% vs 6.0%). We will be able to detect 25% lower outcome in the intervention group (4.5% vs. 6.0%) with 80% power if we enrol 3468 infants per group.
2. ***Intervention is non-inferior to standard of care with respect to poor clinical outcomes:*** Assuming that 6% of infants in both the intervention and standard care group will have poor clinical outcome, 95% confidence level (one-sided), 90% power and a 1.8% non-inferiority margin, we will need to enrol 2983 infants per group. With 80% power and a 1.5% non-inferiority margin, we will need to enrol 3101 infants per group.

We will therefore enrol a total of 7000 infants with a single low-mortality risk sign in Study 1 across all the study sites in this multi-centre trial. The Study Data Safety Monitoring Board (DSMB) will perform the interim analyses at 25%, 50% and 75% of enrolment and if required, will recalculate the sample size to enable us to answer the research question.

Based on the above sample size calculation, for the UP site, we will be enrolling a total of 1000 infants in Study 1, over a period of 24-30 months, i.e., at a required enrolment rate of approx. 40 young infants per month. This number and duration may be updated at a later date based on interim analyses and recalculation of sample size, if needed, by the DSMB.

STUDY 2 (concurrent study to optimize the duration of stay in hospital)

Background and rationale

In high-income settings, infants with clinical suspicion of sepsis are hospitalized and treatment with parenteral antibiotics is initiated after taking samples for sepsis screening and blood culture. After 48 hours, if the infant is clinically well and laboratory tests do not indicate infection, antibiotics are stopped, and the infants are discharged from the hospital(10). However, this is almost never done in low- and middle-income countries (LMICs), where once parenteral antibiotics are started, they are continued for 7-10 days.

In the AFRINEST study, among young infants with any sign of CSI who were enrolled and received outpatient treatment, 1.3% died up to 15 days after the initiation of treatment. Two-fifth (39.7%) of these deaths occurred in first 48 hours of treatment. Among those who survived and assessed at 48 hours of treatment, we found that three quarter of infants (73.9%) did not have any signs of illness. Of these infants who recovered by 48 hours, 0.4% died between day 3 and day 15. In contrast, mortality between day 3 and day 15 was higher among infants who still had the presenting sign at 48 hours (0.7%) or those who deteriorated (presence of new CSI sign/critical illness sign) at 48 hours (8.0%) (table 3).

Table 3 Proportion of infants with CSI with clinical outcome at 48 hours after the initiation of outpatient treatment and their outcome 2 weeks after initiation of treatment

	Assessed at 48 h	Clinically well[1] at 48h		Persistence of the presenting CSI sign at 48h		Deteriorated[2] at 48h	
		N_1	Death by day 15 n_1 (%[3])	N_2	Death by day 15 n_2 (%[4])	N_3	Death by day 15 n_3 (%[5])
Clinical Severe Infection (CSI)	**4465**	**3300**	**15 (0.4%)**	**1003**	**7 (0.7%)**	**162**	**13 (8.0%)**
High body temperature	1358	1248	5 (0.4%)	67	0	43	2 (4.7%)
Severe chest indrawing	1302	787	2 (0.3%)	487	3 (0.6%)	28	3 (10.7%)
Fast breathing 0-6d	924	508	0	372	1 (0.3%)	44	2 (4.5%)
Movement only on stimulation	28	20	0	7	0	1	0
Feeding poorly	229	192	0	25	0	12	2 (16.7%)
Low body temperature	132	107	2 (1.9%)	18	2 (11.1%)	7	2 (28.6%)
≥2/6 signs of CSI	492	438	6 (1.4%)	27	1 (3.7%)	27	2 (7.4%)

[1] no sign of CSI at 48 hours after the initiation of treatment.
[2] either presence of sign of critical illness or a new sign of CSI at 48 hours after the initiation of treatment.
[3] $\%=n_1/N_1 x100$
[4] $\%=n_2/N_2 x100$
[5] $\%=n_3/N_3 x100$

We would like to take the opportunity of conducting a concurrent study with the main study to address the issue of early and safe discharge from infants admitted with clinical severe infection from the hospital.

Research question

Is it safe to discharge young infants with high-mortality risk clinical severe infection signs after 48 hours of injectable antibiotics if they are clinically well and a lab test for infection is negative?

Among hospital-admitted young infants with a high-mortality risk sign[13] or two or more signs of CSI who clinically improve 48 hours after initiation of treatment and have a negative C-reactive protein (CRP) (**Population**), does discharge from hospital on oral amoxicillin at home for the next five days (**Intervention**), compared with continued hospital management for next five days (**Control**), non-inferior in terms of poor clinical outcome (death between randomization and day 15 of initiation of therapy, presence of any sign of CSI or CI on day 8 of initiation of therapy) (**Outcome**)?

Expected policy change after proposed research

If the two study groups are found to be equivalent, a vast majority of hospitalized young infants with high-mortality risk CSI signs will need only two days hospital stay, followed by a switch to oral antibiotic for next five days at home. We believe that this strategy of clinical assessment and supported by a laboratory test is affordable in programmatic settings. If proven to be safe and effective, this strategy would improve availability of hospital beds for infants who need hospitalization, reduce overcrowding and unnecessary work pressure on limited staff thus improving quality of care, improve parents' willingness to accept hospital referral in the first place and would substantially reduce costs to the health system and as well as to the families.

Scope

The scope of this trial is to evaluate the effect of early discharge on oral amoxicillin on study outcome for young infants (0-59 days old) with a high-mortality risk signs of CSI or two or more signs of CSI who clinically improve 48 hours after initiation of treatment and have a to-be-decided[14] negative laboratory test, to generate the evidence required for WHO guidelines on this intervention. Our approach is to conduct a multi-country, multi-centre individually randomized controlled trial to determine the efficacy and safety of early discharge on oral amoxicillin, compared to inpatient treatment with injectable ampicillin and gentamicin and supportive care.

Hypothesis and objectives

The main hypothesis is that the clinical outcome (defined below in primary outcome description) in young infants with a high-mortality risk sign or two or more signs of CSI who clinically improve 48 hours after initiation of treatment and have a negative laboratory test, who are discharged and received oral amoxicillin for next 5 days will be non-inferior than in those infants who will continue inpatient hospital injectable antibiotic treatment for the next 5 days.

Study design

This will be an open-label, two-arm, individually-randomized controlled trial.

[13] High-mortality-risk signs of CSI – movement only when stimulated, or not feeding well or low body temperature (<35.5°C) or two or more signs of CSI, including low risk signs - high body temperature (≥38°C), severe chest indrawing, fast breathing (≥60 breaths per minute) in 0-6 days old infants

Study population

All patients admitted to the study hospitals with relatively higher-mortality risk signs of CSI at presentation (not feeding well, movement only on stimulation, low body temperature < 35.5°C, two or more of the six signs of CSI) will be assessed for eligibility for this study 48 hours after initiation of treatment and considered for inclusion in the study if:

- Clinically well on day 3 defined as absence of all signs of critical illness (not feeding at all, no movement at all, convulsions) or CSI (not feeding well, movement only when stimulated, low body temperature (<35.5°C), high body temperature (≥38°C), severe chest indrawing, fast breathing in <7 days old), and
- Laboratory test negative, and
- Family lives within a catchment area where a follow-up of up to day 15 can be accomplished.

Infants will be excluded from the study if they have any one of the following:

- Weight <2kg at the time of presentation (if age at screening is less than 10 days) or weight-for-age <-3z, or
- Signs of critical illness on admission (no movement at all, unable to feed at all, or convulsions), or
- Appearance of any high-mortality risk sign or multiple low-mortality risk signs in first 24 hours of life, or
- Hospitalized for any illness in the previous 2 weeks, or
- Prior use of injectable antibiotics for the same illness, or
- Previously included in this study or currently included in any other study, or
- Any other reason to stay in hospital, as decided by the treating physician.

Enrolled young infants who develop or are diagnosed with any new non-infectious problems after initiating antibiotics, such as jaundice, cardiac problems, etc. will be managed according to the hospital guidelines. They will not be considered to have poor outcome.

Laboratory test

Based on the findings of the systematic review it was decided that a single, semi-quantitative (threshold level 10 mg/L) CRP will be performed at 48 hours after admission to decide on eligibility for enrolment into the trial.

Blood sample of 0.6-1mL will be taken by a paediatric nurse from young infants with no signs of CSI or critical illness after 48 hours of hospitalization using WHO guidelines on drawing blood(11). Consent for this sample will be taken at the time of screening for study 2. Sample will be sent to a hospital laboratory and results will be available within few hours. Young infant will be kept in hospital and same treatment will be continued until test results are available. Based on the results of the test, the treating physician will decide whether the young infant is eligible to be enrolled in the study 2. There is no major risk associated with the test. However, bruise or mild soreness around the blood test site is common and can last for a few days.

Eligible infants will be enrolled if their parents provide an informed written consent to participate in the study. They will be randomized to either continued hospitalization for up to total of seven days or discharge from hospital and home treatment with oral antibiotic for the next five days.

Intervention

Discharge from hospital and home treatment with oral antibiotic for five days.

Control

Continued inpatient hospital injectable antibiotic treatment and supportive therapy for a total of 7 days.

Outcomes

Poor clinical outcome defined as –

- Death between randomization (day 3 of initiation of therapy) and day 15 of initiation of therapy, or
- 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, e.g. meningitis, bone or joint infection, on day 8 of initiation of therapy, or
- Presence of any sign of CSI on day 8 of initiation of therapy.

Outcome assessment

Outcome assessment will be carried out by an independent outcome assessor (IOA). IOA will visit all enrolled young infants in the control arm at the hospital or at home after discharge and intervention arm enrolees at home on Day 8 and 15 of initiation of treatment. A separate IOA will work at the hospital and a separate one at home so there is no bias in the assessment.

Sample size

AFRINEST data suggests that treatment failure was about 5% in infants who were clinically well 48 hours of initiation of treatment had a poor clinical outcome by day 15. Using one-sided 95% confidence level, 90% power, 5% rate of poor clinical outcome in both intervention and control groups and a non-inferiority margin of 2.0%, the required sample size would be 2035 eligible young infants per group. With the same assumptions, except a non-inferiority margin of 1.5% and 80% power, we will require 2612 infants per group.

We will therefore enrol a total of 5250 infants in Study 2 across all study sites. The DSMB will perform the interim analyses at 25%, 50% and 75% of enrolment and if required, will recalculate the sample size to enable us to answer the research question.

We plan to enrol 750 infants in Study 2 in the UP site over a period of 24-30 months, i.e., at a required enrolment rate of approx. 30 young infants per month. This number and duration may be updated at a later date based on interim analyses by the DSMB and potential recalculation of sample size.

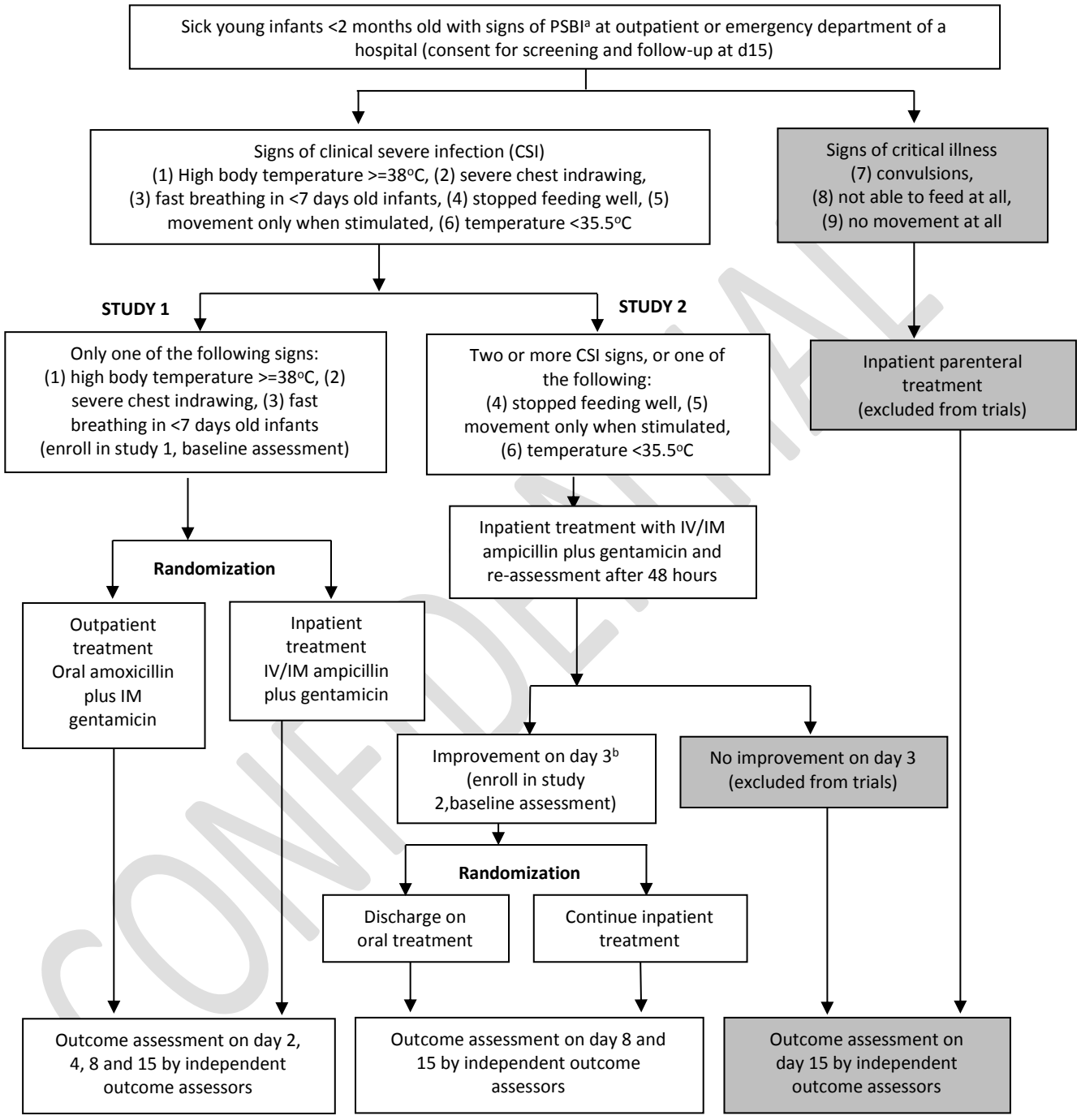
Enrolment & follow-up plan to address both research questions

The two research questions will be tested in two concurrent trials. Figure 1 lays out the participant flow and follow up approach that will allow us to answer both research questions concurrently.

Screening for PSBI will be established in outpatient clinics and emergency rooms of district or higher-level hospitals in 6 countries in South Asia and Sub-Saharan Africa. Infants with PSBI will be further classified into those having (1) a single lower mortality-risk sign of clinical severe infection, (2) a single higher mortality-risk sign or multiple signs of clinical severe infection, and (3) signs of critical illness.

The first set of infants will be included in STUDY 1 if the parents provide consent to participate in the study and randomized to outpatient or hospital treatment. The second set of infants (2) will be offered immediate hospital admission and treatment. If they accept admission, they would be considered for inclusion in STUDY 2 after two days of standard hospital care including parenteral antibiotic treatment initiated with injections gentamicin and ampicillin. The third set of infants (3) will not be enrolled in either of the studies; they will be offered immediate hospital admission and treatment.

Figure 1 Overall Patient Flow and Follow-up



[a] SIGNS OF PSBI: convulsions, not able to feed at all, stopped feeding well, severe chest indrawing, body temperature ≥38°C, body temperature <35.5°C, movement only when stimulated, no movement at all, fast breathing in 0-6 days
[b] Clinically well on day 3 defined as absence of all signs of critical illness or CSI, laboratory test negative, and family lives in a catchment area where a follow-up can be accomplished.

Study site, population and hospitals

Fig 1. Kanpur Nagar district in UP

The study will be conducted in Kanpur Nagar district of Uttar Pradesh with an estimated population of 4.8m (see map). The district comprises of Kanpur City and 10 rural blocks. The district center is located about 95kms from the state capital of Lucknow. It is amongst the most densely populated districts (1521 persons/sq km) with a two-thirds population residing in urban areas. The female literacy rate of 82% is the highest in the state, with 40% of rural women and 68% of urban women having more than 10 years of education. Figure 3 shows the administrative map of the district, with secondary-level health facilities and key population and health system indicators summarized in Table 4.

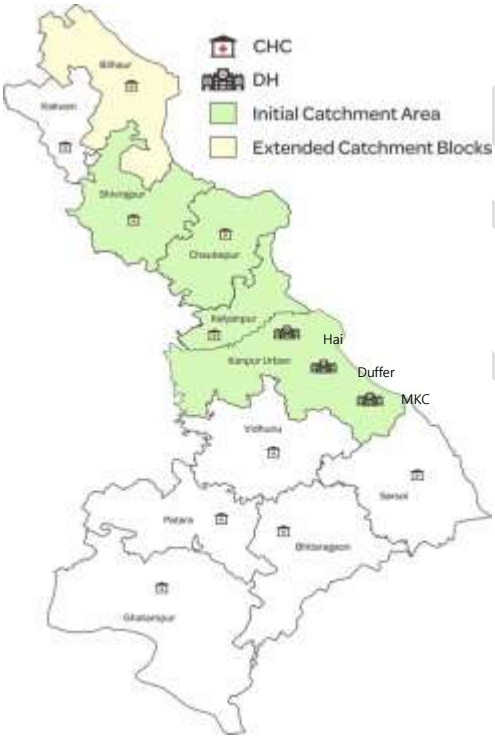


Fig 2. Map of Kanpur Nagar district

Birth cohort	100,000 live births per annum
Institutional births	76% (urban: 78%, rural: 74%)
Births in public health facilities	49% (urban: 41%, rural: 63%)
NMR (based on AMANHI study)	42 per 1000 Severe neonatal infections: 39%
Estimated PSBI prevalence	10,000 per annum (based on ANISA & SATT studies)
District-level hospitals with delivery facility & SNCU	• Hailet District Hospital (operated by GSVM Medical College) • Dufferin District Women's Hospital • MKCH District Women's Hospital
Community Health Centers	10 (of which 5 have pediatricians)
Primary health facilities	92 (urban: 50, rural: 42)
Private birthing facilities	207 (urban: 157, rural: 50)
Community health workers	Urban: ANM-263, ASHA-457 Rural: ANM-345, ASHA-1688

Table 1. Key Population & Health System Indicators

The district has 3 district-level health facilities – all 3 of them are equipped with Sick Newborn Care Units (SNCU), and primarily serve the population of Kanpur city, with Dufferin Women's Hospital serving as the referral facility for deliveries and Hailet Hospital serving as the referral facility for newborns and infants from rural blocks of the district.

We propose to initially set up the Hailet District Hospital as the clinical management site for the trials, which is currently the referral SNCU facility for all the rural Community Health Centers (CHCs). We expect that our required sample size will be met with a catchment population of Kanpur city and the rural blocks of Kalyanpur, Chaubepur and Shivrajpur (marked in green in Figure 3). In addition, if the need arises, we will additionally also include the rural block of Bilhaur. The rural blocks have been chosen based on highway connectivity with CHCs and number of referrals to Hailet Hospital. We plan to refer cases from other secondary care facilities in the rest of the catchment area to this facility. Our catchment facilities, therefore, include all 3 district hospitals in Kanpur city and the 3 CHCs from the rural blocks. Based on our experience and lessons from the PSBI unit & research set up at Hailet Hospital, we will consider also including one or both of the other 2 district hospitals as study facilities for enrolment and management of young infants.

The farthest CHC of Shivrajpur is at a distance of 30kms from Hailet by road, and the farthest district hospital MKCH is at a distance of 11kms. Travel time from anywhere within the study catchment area to Hailet does not exceed 1.5 hours. Table 5 summarizes the case load and staffing at the various catchment facilities.

Area	Facility	Deliveries (per mth)	OPD/ Emergency/ SNCU cases: 0-59d babies (pm)	Pediatricians	Nurses (PNC, SNCU, KMC)	ANM	ASHA + Sangini
Kanpur city	Hailet DH + SNCU	360	600	7	63	263	457
	Dufferin DWH + SNCU	730	1,104	4	60		
	MKCH DWH + SNCU	260	551	6	18		
	Total:	1,350	2,255	12			
Kalyanpur	CHC	175	120	1	5	40	162 + 7
Shivrajpur	CHC	150	264	1	6	28	140 + 6
Chaubepur	CHC	187	88	1	6	27	134 + 6
Bilhaur	CHC	267	176	0	6	42	182 + 9

Table 2. Existing case load and staffing at the various clinical catchment facilities

While the normal flow of OPD, Emergency and SNCU cases into the district level facilities from the study catchment area will likely be able to provide us sufficient cases for Study 2, we will strengthen case identification and referral by ASHA workers in order to meet the sample size for Study 1. An enrolment rate of 37 cases per month for Study 1 and 27 cases per month for Study 2 (total of 64 PSBI cases per month) will help us meet the study sample size requirements for our site. We expect that our strengthened health system surveillance should be able to capture at least 50% of expected PSBI cases from the population of infants born in public health facilities in our study catchment area. Table 6 estimates the PSBI case load within the study catchment area and anticipates the PSBI capture rate per month.

Catchment Area	**Birth cohort (per month)**	**Expected PSBI (per month)**	**Deliveries in govt. Facilities (pm)**	**Expected PSBI in govt. Facilities (pm)**	**Anticipated PSBI capture @ 50% loss due to missed detection or refusal(pm)**
Kanpur city	4,667	467	1,080*	108	54
Kalyanpur	310	31	195	20	10
Shivrajpur	249	25	157	16	8
Chaubepur	215	22	187*	19	9
Bilhaur	287	29	267*	27	13

*These delivery figures are based on actual number of deliveries in secondary-level facilities. Others are based on estimates from NHFS-4 proportion of 63% deliveries in govt. facilities in rural areas of Kanpur Nagar district.

Table 3. Anticipated PSBI capture rate per month from study catchment areas

For the smooth conduct of the study, we plan to set up a 14-bedded PSBI ward in the chosen district hospital(s) as a model unit for managing young infants with PSBI. The ward will provision for family participatory care and access to washroom and dining areas for caregivers (as per latest Mother-Newborn Care Unit guidelines laid out by government of India). An enrolment and consenting station will be placed inside the ward. The ward will be run under the supervision of existing pediatricians providing services at the district hospital.

We will conduct formative research in order to provide inputs towards the planning and smooth conduct of the study. Formative research will seek to understand: patient flow within district

hospitals; current screening & treatment protocols, standardization & compliance; factors influencing family adherence to referral, hospitalization, out-patient treatment & follow-up; quality of care, capacity of health workers, etc.

Specifically, it will be important to finalize the study area. We will track all patients presenting at the district level facilities and record their assessment against the inclusion and exclusion criteria for study 1 and 2. This will help us understand how many cases we will be able to recruit through the normal patient flow, and how many more we will need to screen and refer in order to meet the sample size requirement. We need to meet a recruitment rate – after accounting for refusals and loss to follow-up – of 40 and 30 young infants per month respectively for Studies 1 and 2, in order to fulfil site-specific sample size requirements.

Another key factor would be to understand referral and care-seeking patterns of young infants in the study catchment area. Preferred private pediatricians/ physicians providing low-cost OPD services for young infants of the catchment population will also be identified, and if needed, engaged.

Close participation of the government and the National Health Mission in this study gives us an opportunity to strengthen existing services for identification, referral and management of infants with PSBI. We have identified the following health system components for strengthening:

- Accurate measurement and recording of birth weight (all newborns in public health facilities)
- Improving assessment and counseling at the time of discharge of the mother-baby dyad from public health facilities after delivery
- Improving the quality and timeliness of home visitations by ASHA as per the IMNCI-based 'home-based newborn care' program of the government
- Improving the facility registration process for mothers and infants to ensure recording of detailed address and contact information.
- Improving the quality of care, infection prevention and adherence to protocols of facility-based newborn care provided in outpatient, emergency and sick newborn care units in public health facilities
- Ensuring unbroken supply chain of essential medications, in particular, antibiotics for young infants as per WHO guidelines
- Strengthening referral management of young infants through existing channels

Common study procedures for both studies

Screening

Young infants < 2 months old at outpatient or emergency department or SNCU will be examined, triaged and stabilised by the consulting paediatrician or physician of the participating hospital. If the paediatrician/ physician observes signs of CSI during their initial assessment and clinical condition of the infant is stable, the infant will be assessed by the study Screening and Enrolment team after

obtaining due consent from parents (see section on Informed Consent below). Screening of sick young infants will be performed by a study nurse/physician in outpatient or emergency department or SNCU of the participating hospital. Those who fulfil the above-mentioned Study 1 inclusion criteria and don't have any exclusion criteria will be enrolled in Study 1 (after due consent) after confirmation of clinical signs by the treating physician. Infants who are not eligible for enrolment will be managed as per treatment protocols of the hospital. All young infants with any high-mortality-risk sign of CSI or multiple signs of CSI will be admitted for administration of injectable antibiotics as per WHO protocols by the treating physician. These young infants will be followed up by the Screening and Enrolment team and screened for enrolment in Study 2 after 48 hours of therapy.

Informed consent

An informed written consent will be obtained from parents/caregivers by a study nurse/ physician at two stages for both studies, first at the time of screening and later at the time of enrolment, for study 1 on the same day while for study 2 after 48 hours of admission, in the presence of a witness and will involve detailed verbal communication in the study participants' native language to ensure comprehension of the trial and study procedures. All consent forms will be translated into local languages. Parents/caregivers of sick young infants will be provided basic information about the study and invited to consent for screening. Parents/caregivers of infants found to be eligible after screening will be provided full information about the study and invited to have their infant participate in the study. The eligible infants will be enrolled if their parents provide an informed consent and will be randomized to either one of the treatment arms according to study approach. Illiterate parents/caregivers will be asked to give a thumbprint on the consent form; literate parents/caregivers will be requested to sign the consent form.

Randomization

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 (CRF).

Training of research staff

The study staff who will perform screening, enrolment, and outcome measurement will be trained using a standardized study Manual of Operations. Data will be collected by research staff onto standardized data collection forms. During training, emphasis will be placed on maintaining Good Clinical Practice (GCP) standards. All research staff will be trained in rapport building and communication with mothers/caregivers. The screening and enrolment study staff will be trained in introducing the study to potential participants, administering the consent form, assessing for clinical signs and eligibility, and correctly completing all relevant study forms. The outcome measurement staff will be trained in the definitions of outcomes and on their standardized assessment, as well as completion of the outcome assessment forms.

Dosage of drugs to be used in the study

Table 4: Dosage of injection gentamicin and ampicillin (control arm in study 1 and study 2)

	Gentamicin *(Give once a day for 7 days)*	**Ampicillin**[1] *(Give 50 mg/kg body weight twice daily for 7 days)*
Weight (kg)	Volume per dose (mL)	Volume per dose (mL)
	Strength, 20 mg/mL	Strength 250 mg/1.5mL
1.5 – 2.4	0.4	0.8
2.5 – 3.9	0.8	1.2
4.0 – 5.9	1.2	1.5

[1] To a vial of 250 mg, add 1.3 mL of sterile water

Table 5: Dosage of injection gentamicin and oral amoxicillin (intervention arm in study 1)

	Gentamicin (I/M) *(Give once a day for 2 days)*	**Amoxicillin** *(Give twice daily for 7 days)*
Weight (kg)	Volume per dose (mL)	Dispersible tablet
	Strength, 20 mg/mL	250 mg per dose
1.5 – 2.4	0.4	1/2
2.5 – 3.9	0.8	1/2
4.0 – 5.9	1.2	1

Table 6: Dosage of oral amoxicillin (intervention arm in study 2)

	Amoxicillin *(Give twice daily for 7 days)*
Weight (kg)	Dispersible tablet
	250 mg per dose
1.5 – 2.4	1/2
2.5 – 3.9	1/2
4.0 – 5.9	1

Further, the team of investigators across all study sites will explore ways to standardise the medicine procurement from a pharmacological quality perspective.

Quality assurance

All study teams (screening, enrolment, and outcome assessment teams) will have study supervisors who will support adherence to the manual of operations. Regular standardization exercises, oversight and monitoring of all study activities will be conducted by the quality assurance team through regular and random visits and checks of proportion (10%) of all completed study forms. Site preparation review will be conducted before the initiation of the study. This will include standardization of practices and measurements. External oversight and support will be provided by the WHO staff and study consultants to ensure quality of study implementation.

Quality of Care in Hospitals

The hospital infant care services will be strengthened in terms of manpower, capacity building through trainings, processes and standard operating procedures (SOPs), ensuring continuous availability of standard quality antibiotics and basic support for routine care. The “minimum” quality of care will be according to WHO pocketbook for hospital care for children, which includes keeping the baby warm and providing kangaroo mother care to prevent hypothermia, encouraging mother to breastfeed frequently to prevent hypoglycaemia, fluid management when required, basic laboratory support, and oxygen therapy when needed(4). The hospital team will be oriented on the study protocol and recommended treatment protocols including information on indications for changing the treatment regime. Regular visits to assess the quality of care at the hospitals will be made by experienced Paediatrician/ Neonatologist.

Documentation, reporting and response to adverse events

Any adverse event that occurs after enrolment will be recorded on an adverse event reporting form by the treating nurse/physician. A serious adverse event like death, anaphylactic reaction, severe diarrhoea, disseminated or severe rash will be reported to WHO within 48 hours of the occurrence. These cases will be considered to have treatment failure and they (except of course the ones who unfortunately die) will be referred for appropriate treatment. In case of other minor adverse effects such as mild rash etc. the treatment will be continued.

The WHO team will report the incidence of severe adverse events (SAE) to the DSMB on a regular basis for their ongoing review.

Safety Considerations

- Counsel and empower the mother/caregivers/families at enrolment and at all follow up visits to:
  - recognise danger signs or signs of illness and seek care
  - when to return to the hospital for follow up care
- Provide a central contact number to mothers/caregivers of all the enrolled young infants.
- Train the mother/caregiver/family on the quantity, frequency and process of giving oral antibiotic at home. Systems are in place in the hospital to provide emergency and rescue care in case of any adverse event
- Facilitate referral to higher facility if required.
- Any adverse event that occurs after enrolment will be recorded on an adverse event reporting form by the study nurse/physician. A serious adverse event like death, anaphylactic reaction, severe diarrhoea, disseminated or severe rash will be reported to WHO within 48 hours of the

occurrence. These cases will be considered to have treatment failure and they will be referred for appropriate treatment. In case of other minor adverse effects such as mild rash etc. the treatment will be continued.

- The DSMB will monitor SAEs on a regular basis.

Follow Up

All infants will be followed up till day 15 after initiation of therapy. In Study 1, infants in the intervention arm will be asked to return to the hospital for treatment and assessment by the hospital physician/nurse on Days 2 and 4 of treatment initiation. In Study 2, infants in the intervention arm will be asked to return to the hospital on day 5 of initiation of therapy (i.e., 3 days after discharge) for assessment by hospital physician/nurse. The infants will be assessed for the presence of any adverse event. Transportation for hospital visits will be arranged by the study team, using the government's emergency transport system.

Adverse events identified during scheduled follow up visits to the hospital OPD, hospital visit by the family for care-seeking any time during the follow up period, reported to the IOA team during home visit and referred for care to be managed by the treating physician as per routine practice and followed up till resolution.

Infants in the control arm will be followed up and managed as per routine hospital procedures.

All efforts will be made to follow all the enrolled young infants in both studies. In case young infant will not come to hospital/health facility on the day of follow-up, study team will contact them through phone and counsel parents/caregivers to bring the infant to hospital/health facility.

Treatment Documentation

Study Treatment Documentation and Compliance Team (TDCT) will document the treatment received in the hospital and home on day 1, 2, 4 and 8 of initiation of therapy in both studies. For infants in the control arm the documentation of treatment received will be captured from the hospital in-patient treatment charts***.**

For infants in the intervention arm, the documentation of treatment received on days 1, 2, 4 and 8 will be captured in the OPD physician notes and as reported by the mother on day 8.

Ethical Considerations

Safety of enrolled children in these studies will be ensured by close monitoring and follow-up by the treating physician/nurses and study staff. The trial protocol and all associated questionnaires and consent forms will be reviewed by the Institutional Review Boards (IRBs) of CEL and GSVM Medical College (Hailet Hospital), as well as by the Ethical Review Committee of WHO. The trial will also be registered in the international Trial Registry. The trial will follow CIOMS and Good Clinical Practice guidelines. An independent Data Safety Monitoring Board will be constituted to monitor the trial at regular intervals. Written informed consent from the parent/guardian of the child will be obtained before inclusion in the study, as mentioned above.

Data management

The data collection tool for screening, enrolment, treatment documentation and outcome measurement will be common for all study sites, for ease of data collation and management for this multi-centre trial. The tool will have in-built checks for missing values, consistency, skips, etc. All effort will be made to minimize missing data. There will be no imputation of missing data. All incoming data will be reviewed on a daily basis for errors and inconsistencies by a data analyst based on a

comprehensive set of predefined algorithms. As per the outcome measurement protocol, the evidence against every sign recorded by the outcome assessment team will be reviewed for correctness within 24 hours by a trained physician. Any discrepancies identified will be reported back within 24 hours to the respective team for correction. Cleaned data will be synchronized from the site server to the WHO server on a monthly basis.

Data Handling and confidentiality

Data will be collected prospectively using electronic devices. Protecting the confidentiality of the data will be a high priority. The following safety measures will be employed to ensure data protection and safe handling. At the time of enrolment into any of the above-mentioned studies, each participant will be given a unique participant ID number. The consent form, and any other forms linking participant personal information to study ID code number will be kept in securely locked filing cabinets. The key linking participant name and ID will be kept confidential in a secured location at the PI's office where only the PI and co-investigators will have access to this list. Proper documentation and storage of the metadata and any files or protocols relevant to data management will be handled with utmost care. Regular backups of the existing data will be done in appropriate intervals. All computers being used in the study will be password protected and will have restricted access to specific study staff to protect confidentiality. None of the participants' names or identifiers will be used in any publications or discussions regarding the study. Data will be primarily accessible only to the 'Research Team'. The data/records will be kept until its use in any form including secondary analyses.

Approach to analysis

The analysis for Study 1 will be by both intention to treat (for testing the superiority hypothesis) and per protocol (for testing the non-inferiority hypothesis). The analysis for Study 2 will be per protocol since only the non-inferiority hypothesis will be tested. The primary outcome rates will be compared between the intervention and control groups and differences in these rates and their confidence intervals will be calculated. All planned analysis will use 5% significant level. No adjustment will be made for control of type I error due to two primary outcomes, because the two outcomes are complementary and therefore a correction is not warranted.

Pilot study

The primary objective of the pilot study is to finalize the standard operating procedures and case report forms for both studies. We will test study procedures, data collection tools and follow-up procedures, including consent forms, case report forms, treatment and home visits in both studies. The pilot study will be conducted for up to two-month period at each site to test study procedures and tools in advance of initiating enrolment for the actual trial for both studies. Pilot testing will begin with screening of sick young infants in outpatient department and emergency room of the participating hospital. Consent will be obtained for enrolment. Patients enrolled in the pilot study will not be included in the actual study. The numbers are expected to be small and therefore there will be no formal analysis of study outcomes. However, the pilot data will be analysed to determine the following proportion of infants at each study site: i) who meet clinical eligibility criteria among all young infants screened; ii) who consent to be enrolled in the study and iii) who can be successfully followed up till day 15 of enrolment in both studies. This will help us estimate enrolment rate, revise our strategy to meet sample size requirements for both studies, standardize the consenting process, streamline study processes, etc.

Community and health sector engagement and dissemination of results

In clinicals settings where these studies will be conducted, before these studies are initiated the local investigators will engage in dialogue with hospital health staff, ministry of health staff, community representatives, community based-organizations and non-governmental organizations working in the area to explain to them various aspects of this study.

Public health administrators are already part of the research teams. The health facility administrators and professionals in health facilities linked with the study will also be sensitized about this research through personal contacts and sensitization meetings. They will be informed that some patients with PSBI would be referred to tertiary care hospitals and will be requested for facilitated management for those children.

Potential audience for dissemination will be government officials, policy makers, academics, researchers, local community and other voluntary organizations involved with community-based services. To reach these varies audiences, a multipronged dissemination strategy will be required. We will invite above audience to dissemination seminars, which will be organized at the end of project. For local communities we will hold meetings with the community members and their leaders. We would publish the findings of these studies in peer reviewed journals. We will submit abstracts in national and international conferences.

Study management and oversight

i. **WHO** Department of Maternal, Newborn, Child and Adolescent Health and Ageing (**MCA**), WHO will coordinate the study, ensuring arrangements in place to support teams in any challenges being faced to implement these studies. WHO technical staff will conduct monitoring visits to each site every year. There, a detailed structured review of study implementation at each visit will take place. Monitoring visits will have the dual function of identifying problems and supporting their solution in improving intervention delivery quality and data collection. MCA, WHO is responsible for developing technical guidelines, including the management of PSBI in newborn and young infants. The results of the proposed research, therefore, can be incorporated into the guidelines in an accelerated manner. MCA has the operational advantages of building on existing facilities and communications network and a managerial group with experience in successful handling of projects of a similar kind. For example, our department coordinated a large cohort harmonization project for newborn health in nine countries Africa and Asia (AMANHI). In the past our Department has coordinated large multi-centre, multi-country studies on various aspects of newborn health in Africa and Asia (NEOVITA(11), EMPIC[14], AFRINEST(6, 7) studies to name a few) and their data contributed to the global and national guidelines and policy for the management of young infants with infections. The Department is currently coordinating important newborn health trials (immediate KMC and antenatal corticosteroids trials).

ii. The study **Steering Committee** will comprise of all Principal Investigators from study sites, consultants (to be selected), BMGF representatives and WHO technical staff (secretariat). WHO will be responsible for organizing Steering Committee meetings prior to study

[14] Enhanced community case management to increase access to pneumonia treatment in children under 5 years of age in sub-Saharan Africa and South Asia. Available at http://www.anzctr.org.au/TrialSearch.aspx?searchTxt=EMPIC&isBasic=True.

implementation, 9-12 months into the study and at the end of the study. This committee will be responsible for designing and implementing the study in a harmonized way. Study **Principal Investigators** will be responsible for contributing to the development of the research proposal, study manual, data management system, implementation of the intervention, outcome measurement and data collection, data analysis and interpretation and dissemination of results. All activities will be facilitated and supported by WHO. On a monthly basis, the sites will submit a brief status report to WHO. A formal progress report will be submitted by each site every year.

iii. A **Technical Advisory Group (TAG)** will be setup that will include three external experts in the field. The TAG members will serve in their individual capacity and will review the final research protocol for any major concern prior to trial implementation. TAG members' terms of reference also include revision of manual of operations, study forms and consent forms and advise on practical issues in implementing the trial in the field. WHO will serve as secretariat to this group and organize two meetings, one before the study starts and one after one year of study.

iv. WHO will establish a **Data Safety Monitoring Board (DSMB)** as an independent group of external experts to advise WHO and local PIs in order to ensure safety, progress of the study and assessment of efficacy of the intervention. They will meet every six months towards the end of the trial. The DSMB will also advise on continuation, modification, or termination of the trial.

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