MASTER'S PAPER

SIMPLIFIED ANTIBIOTIC REGIMENS FOR TREATING YOUNG INFANTS IN THE DEMOCRATIC REPUBLIC OF CONGO WITH POSSIBLE SEVERE INFECTION: A COMPARATIVE EFFECTIVENESS TRIAL

by

Adrien Lokangaka Longombe

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ABSTRACT

One-quarter of neonatal and infant deaths are due to infection, and the majority of these deaths occur in developing countries. A significant reduction in infant mortality in these countries will not occur without a reduction in deaths due to infection. We participated in a multi-national study that demonstrated the effectiveness of three simplified antibiotic regimens compared to standard treatment. For this report, we examined the site-specific data for the Democratic Republic Congo (DRC), the most impoverished of the countries that participated in the study, to determine if outcomes in the DRC were similar to outcomes across all sites. This randomized controlled trial enrolled 1,842 infants, of whom 1805 met the per-protocol criteria for study analysis. The main outcome was treatment failure within the first week of enrollment. Treatment failure occurred in 123 (6.7%) infants: 30 (6.6%) in Arm A, 36 (8.2%) in Arm B (risk difference 1.6%; 95% CI -1.8% to 5%), 29 (6.3%) in C (-0.3%, -3.4% to 3%), and 28 (6.1%) in C (-0.5%, -3.6% to -2.7%). The risk difference between each of the experimental treatments and the reference treatment suggests equivalence. These findings suggest that a simplified antibiotic regimen can be used for the community-based management of possible severe infection in young infants where referral to a hospital for standard care is often not possible. We speculate that the widespread use of a simplified, community-

based treatment could result in increased coverage with treatment and improved survival in poor areas.

INTRODUCTION

Among the Millennium Development Goals (MDGs), those that target significant reductions in maternal and child mortality have proven the most difficult to achieve. There has been only limited progress towards these goals in many parts of the world. An estimated 3.1 million neonatal deaths occurred in 2010. These accounted for 40% of deaths in children. The persistent high neonatal mortality rate in many countries is a major obstacle to the achievement of MDG4, reduction in child mortality.[1]

Although neonatal mortality has declined in high-income countries over the past several decades, it is still one of the main public health problems in developing countries. Neonatal mortality fell from 33 deaths per 1,000 live births in 1990 to 21 deaths per 1,000 births in 2012, but the magnitude of reductions in South Asia and sub-Saharan Africa (39% and 28%, respectively) was lower than in other regions.[2] In 2009 more than 50 percent of all neonatal deaths occurred in five countries: India 27.8%, Nigeria 7.2%, Pakistan 6.9%, China 6.4%, and the Democratic Republic of the Congo 4.6%.[3] Achieving MDG4 will require effective interventions to reduce neonatal mortality in these countries.

Infection is one of the leading causes of neonatal mortality, accounting for about 25 percent of neonatal deaths.[4] Early-onset neonatal sepsis, defined as occurring within the first 72 hours after birth, is associated with vertical transmission of microorganisms present in the mother's genitourinary tract.[5] *Group B Streptococcus (GBS), Escherichia coli, Haemophilus influenza,* and *Listeria monocytogenes* are among the microorganisms commonly identified in early-onset neonatal sepsis.[4] Late-onset sepsis is more likely to result from an unhygienic environment and is commonly due to *Coagulase-negative Staphylococcus, Staphylococcus aureus, Escherichia coli, Klebsiella, Pseudomonas,* and *Enterobacter.*

A number of preventive strategies appear to reduce the likelihood of infection. These include clean delivery practices, prompt treatment of chorioamnionitis, early and exclusive breastfeeding, eye prophylaxis, and hygienic skin and umbilical cord care.[6-8] A set of simple, preventive interventions reduced the incidence of sepsis by 30 percent in a remote district of India.[9] Umbilical cord cleansing with chlorhexidine and emollient therapy for preterm babies are promising interventions.[10-12]

When prevention of infection fails, neonatal sepsis often results in death. Case fatality can be as high as 22 percent without effective therapy.[13] It is estimated that appropriate treatment could reduce infection-specific mortality by 30-70 percent, making it an important intervention for improving child survival and meeting the MDG4 targets.[14]

In the U.S., infants with suspected infections are generally treated with intravenous antibiotics for at least10 days in an inpatient setting.[15] Ampicillin along with an aminoglycoside is generally used as initial therapy, because these antibiotics are appropriate for the common pathogens, i.e., GBS, *Listeria monocytogenes, and E. coli.*[16, 17] According to the World Health Organization (WHO), infants with possible serious bacterial infections should be referred to a hospital and treated with a combination of injectable gentamicin and penicillin/ampicillin for at least 7-10 days.[18]

While there is little doubt about the efficacy of the recommended treatment in reducing the risk of death of young infants with possible serious bacterial infection, most of these infants do not currently receive inpatient care in most developing countries, including the Democratic Republic of Congo (DRC). There are several reasons for the lack of compliance in the DRC with this WHO recommendation. First, nearly all health care in rural areas is provided through health centers, and these centers do not typically provide inpatient care. Health centers refer some patients to their area hospital if inpatient care is advisable and feasible. However, distances from health centers to hospitals vary widely, ranging from less than 1 mile to 60 miles, and transportation is challenging. In addition, inpatient care is often not available because of inadequate and poorly equipped hospitals.[19]

From 2010 to 2013, a rural area of the DRC participated in a multi-national study that examined the effectiveness of four simplified regimens of antibiotic

therapy for the treatment of serious bacterial infection in neonates and young infants. The results of that study suggest that these infections could be treated effectively in health centers or homes. However, each of the five sites in three countries had unique demography, geography and healthcare infrastructure that might predict variation in effectiveness among sites. The objective of this report was to examine the comparative effectiveness of these treatment regimens in the cohort enrolled in the DRC, the most rural and impoverished environment among the study sites, by examining the DRC site-specific data from the multi-national study.

METHODS

Study design

The multi-national study was an individually randomized, open-label, equivalence trial.[20] The data reported here are from the DRC site only. The study randomized young infants with signs of serious bacterial infection to one of four community-based antibiotic treatment regimens.

Description of the study site

The study was conducted in the province of Equateur which is in the north-west part of the country. Infants resided in the North and South Ubangi health districts. In these districts, we selected the following health zones: Karawa, Bominenge, Bogose-Nubea, and Budjala. We enrolled infants in the following communities (clusters): Karawa, Gbosasa, Bodadi, Bominenge, Takaya, Bongo,

and Budjala. The target population in those clusters was 322,746 inhabitants, averaging approximately 16,000 births per year over the past decade.

Study participants

Young infants, 0 to 59 days of age, with possible serious bacterial infection and whose families did not accept or could not access inpatient hospital care were considered for participation in the study.

Inclusion criteria:

- any of the following: not feeding well, movement only when stimulated, severe chest indrawing and axillary temperature >38.0°C or <35.5°C
- parents not accepting hospital referral
- parents giving consent to participate in the study

Exclusion criteria:

- having very low weight (<1500g at the time of presentation)
- being hospitalized for illness in the previous two weeks or prior inclusion in the study
- exhibiting any sign of critical illness: unconscious, convulsions, unable to feed at all, apnea, unable to cry, cyanosis, dehydration, bulging fontanel
- having any of the following conditions: major congenital malformations inhibiting oral antibiotic intake, active bleeding requiring transfusion, surgical conditions needing hospital referral, persistent vomiting defined

as vomiting following three attempts to feed the baby within one-half

hour

Active surveillance

A system of active surveillance for the identification of pregnancies, births, and sick infants was established in all study communities. Before the beginning of the trial, community health workers (CHWs) conducted a household census in order to identify all births and pregnant women. Household censuses were repeated every three to four months. Other methods were also used to discover pregnancies and births: self-reporting to a CHW, identification at antenatal clinics in the community health facilities, and information from traditional birth attendants (TBAs) or other key informants. CHWs visited the homes of newborns on days 1, 3, 7, 14, 21, 28, 35, 42, 49 and 60 after birth. During these home visits, the CHWs provided standardized advice regarding newborn care, as described in the WHO/UNICEF Joint Statement on home-based care of newborns, [21] including: early and exclusive breastfeeding, maintenance of body temperature using skin-to-skin contact, hand-washing prior to handling infant, hygienic umbilical cord care, and recommendations regarding adherence to a vaccination schedule. At each home visit, CHWs assessed the newborn for signs of illness and counseled the families on recognition of danger signs (stops feeding well, convulsions, fast breathing, severe chest in-drawing, temperature > 37.5°C or < 35.5°C, movements only on stimulation, yellow soles, or pus from

umbilicus, eye or skin). Young infants who exhibited any of these signs were advised to go to a health center.

Informed consent procedure, screening and enrollment

Infants referred to health centers by CHWs, as well as those who were self-referred by their parents or guardians, were seen by a study nurse. If the study nurse confirmed the danger sign, the infant was referred to facility local hospital, as recommended in the WHO Integrated Management of Children Illness (IMCI) guidelines.[22]

If the family refused to accept hospital referral despite the best efforts of the study nurse, they were considered for enrollment in the study if all other inclusion criteria were met, and none of the exclusion criteria were present. Consent for study participation was obtained by the study nurse at the health facility or at home in the presence of a witness. Consent included detailed oral communication in the study participant's native language to ensure comprehension of the trial and study procedures. Illiterate parents were asked to provide a thumbprint on the consent form; literate parents were requested to sign the consent form.

Randomization and allocation concealment

Prior to randomization, infants were categorized by type of presentation as having either severe infection or fast breathing only. Severe infection included all presenting signs and symptoms except fast breathing only. Infants were

stratified on type of presentation and age at presentation (< 7 days old and 7 to 59 days old). Four block-randomization schemes in block sizes of 8 were computer-generated off-site using STATA version 10.0 by a person not involved with the study. For allocation concealment, the treatment code for each study infant was sealed in an envelope; one color for each age stratum. Two color-coded envelopes for within age stratum were used to randomize infants within each stratum of presentation (severe infection and fast breathing only). Each cluster was given envelopes for a set of blocks, and used blocks were regularly replaced so that a constant number of envelopes were always available in the community. When the first infant was enrolled in a community in a stratum, the first envelope of the first block for that presentation and age stratum and age category at the health center was opened and the infant was treated according to the treatment code inside. When the next infant was enrolled, the next envelope of the block was opened.

Treatment Regimens

Treatment Regimen A (reference treatment): injection of gentamicin once daily and injection of procaine penicillin once daily for 7 days (14 injections in total).

Treatment Regimen B: injection of gentamicin once daily and oral amoxicillin twice daily for 7 days (7 injections in total).

Treatment Regimen C: injection of gentamicin once daily and injection of procaine penicillin once daily for 2 days; thereafter oral amoxicillin for 5 days (4 injections in total).

Treatment Regimen D: injection of gentamicin once daily and oral amoxicillin twice daily for 2 days; thereafter oral amoxicillin twice daily for 5 days (2 injections in total).

Treatment

This was an open (un-blinded) study because a multiple injection regimen was compared to single injection-oral regimen combinations; blinding participants and investigators by using placebo injections would thus not be justifiable (Figure 1).

All treatments were given at a health center or at home. The injections were given once daily by the study nurse at a health center or at home, while oral medicines were given under supervision of CHWs at home. Mothers observed the first dose being given, then were instructed to provide the second daily dose of oral amoxicillin at home in the same manner. Daily assessment by the study nurse was conducted to identify worsening of any critical signs. Home visits to assess the outcome of the treatment were conducted by an independent outcome assessment nurse at day 4, 8, 11 and15 to detect any treatment failure.

Study outcomes

Treatment failure within day 1-8 following enrollment was the primary outcome and was defined as any one of the following:

- Death

- Clinical deterioration (hospitalization, emergence of any sign of critical illness, a new sign of severe infection, or re-emergence of a sign of severe infection on day 4 after it had initially disappeared)

- No improvement in clinical condition by day 4 (if single sign of severe infection at enrollment, persistence of the sign, and if multiple signs at enrollment, persistence of >1 sign)

- Not cured by day 8 (persistence of any sign of severe infection on day 8 of enrollment)

- Development of a serious adverse effect to the study antibiotics

- Withdrawal of informed consent, any time between days 1-8

Data collection

Standard case report forms were used to collect data. Data were double-entered into a SQL database. A clean copy of the database was sent monthly to the central data coordination center at the London School of Hygiene and Tropical Medicine (LSHTM) for quality checks.

Sample size and analysis plan

For the DRC site, a sample size of approximately 450 per group ensures 86% statistical power to demonstrate equivalence between treatments based on the 95% confidence interval for the risk difference of treatment failure.

The analysis was conducted using STATA version 13.0. The primary analysis was per-protocol, which is considered a more conservative analysis than

intention to treat (ITT) analysis for equivalence studies. The primary outcome was treatment failure. The difference in the risk of treatment failure between the reference arm (Regimen A) and all other treatment arms together with a 95% confidence interval was calculated. Secondary analyses were performed to investigate adverse events including death and other serious outcomes.

RESULTS

From April 2011 to May 2013, we enrolled 1842 infants. Among these, 779 (42.3%) were enrolled in their first week of life. The randomization process allocated 464 infants to Arm A, 447 infants to Arm B, 465 infants to Arm C, and 466 infants to Arm D.

Table 1 lists the baseline characteristics of study infants. All of these were similar among the four treatment regimens. With regard to the place of birth, 421 (22.8%) infants were born at home and 1213 (65.8%) infants were born at health centers. The mean weight-for-age z score study infants was below zero, the mean of the reference population used by WHO (Figure 2). About 21% were stunted (weight-for-age Z score <-2). The mean age of mothers was 25, and 339 (18.4%) mothers were less than 20 years old. Approximately one-third of mothers (33.6%) had more than 4 living children, and 96% of mothers attended at least one antenatal clinic visit. The majority of mothers (52.3%) had no formal education, and 46.8% had less than 12 years of education.

The signs commonly present at enrollment were fever (32.9%) and fast breathing (32.7%) (Figure 3); 314 (17.0%) infants were enrolled with two or more signs.

We excluded 37 infants from our analysis of treatment effect because they did not receive all treatment doses and adequate follow-up as required by the study protocol. Infants whose parents declined treatment at some point (n=12) but who had adequate assessment and follow up were categorized as treatment failures. Most of these infants were in Arm (n=5).

Among the 1805 infants who met the treatment and assessment criteria, 454 (25.2%) were allocated to Arm A, 437 (24.2%) to Arm B, 457 (25.3%) to Arm C, and 457 (25.3%) to Arm D. Almost all infants (98%) received all treatment doses as per-protocol analysis, and 1804 (98%) infants received all independent outcome assessment visits (Table 2).

Treatment failure occurred in 123 (6.7%) infants: 30 (6.6%) infants allocated to Arm A, 36 (8.2%) to Arm B (risk difference: 1.6%; 95% CI: -1.8%–5%), 29 (6.4%) to Arm C (-0.3%; -3.4%–3%), 28 (6.1%) to Arm D (-0.5%; -3.6%–2.7%) (Table 3).

Among treatment failures, 32 infants died; 23 had the appearance or a sign of critical illness; 17 had a new sign of serious infection; 17 were hospitalized; and 35 had no improvement in clinical condition by day 4. The signs that either did not improve or were new and resulted in the classification of

treatment failure were fast breathing (31%) and chest indrawing (23%) (Figure 4). Treatment failure occurred mostly on day 4 of enrollment (Figure 5).

DISCUSSION

A multi-national study investigated the safety and effectiveness of simplified regimens for the management of possible serious bacterial infection among infants in resource-poor community settings. This study enrolled 3564 infants in five sites (Kenya, DRC, and Nigeria: Ibadan, Zaria, Ile-Ife). Four week-long treatment regimens were compared. The outcomes of infants treated with three regimens of antibiotics that included combinations of parenteral (intramuscular) and oral antibiotics were compared to outcomes in a reference group treated with daily doses of parental antibiotics, the standard care. Among the 3364 infants, treatment failure occurred in 229 (6.8%) infants, but the risk differences between the experiment treatment regimens and the reference treatment was not statistically different, falling within the pre-specified +5% similarity margin. The conclusion from this study was that treatment with these regimens was equivalent to the standard care.

These findings were similar to results from previous studies. Community-based interventions involving CHWs in the prevention and promotion of maternal and newborn health proved effective in rural Pakistan and in Gadchiroli, India.[13, 23] A field trial conducted in rural India decreased case fatality of neonatal sepsis from 16.6% to 2.8% after the intervention of CHWs, thus confirming the feasibility, the acceptability, and the relevance of home-based strategies for

newborn care, as well as the management of neonatal severe infection in poor settings.[24, 25] A cluster-randomized trial demonstrated that pregnancy and postnatal surveillance visits by CHWs reduced neonatal mortality rate by 53% in Uttar Pradesh, India.[26] All these studies were observational and not individually randomized. However, a randomized controlled study evaluating the effectiveness of three simplified, community-based antibiotic regimens demonstrated the superiority of the combination of procaine penicillin and gentamicin over oral antibiotics. [27] Interestingly, ceftriaxone proved less effective. Although this study suggests that oral antibiotics may not be as effective as parental antibiotics, and would contradict the findings of our multi-national trial, the sample size was small, increasing the likelihood that results occurred by chance alone.

The purpose of the study reported in this manuscript was to determine whether the results from the multi-national study could be reasonably extrapolated to the DRC. The DRC is a unique environment compared to the other sites in terms of several factors. First, mothers had less education compared to other sites. The majority of mothers (52.3%) had no formal education, whereas the mean for all sites was about 17%. This is consistent with the DHS 2007 which found 41% and 50.3% of illiterate women of reproductive age in the DRC and in the Equateur province, respectively.[28] Second, the socio-economic status is lower in the DRC. Despite the abundant natural resources of the country, the population of the DRC is among the poorest in the world.[29, 30] According to the 2013 Human Development Report,

the DRC ranks last with a poverty ratio of about 80%.[31] Third, the DRC has high fertility rates and bigger families. The total fertility rate in the DRC is 6.3,[28] which is the highest among all the study sites.

As in the multi-national study, we examined the safety and efficacy of simplified antibiotic regimens compared with the reference treatment for the management of neonates and young infants with suspected severe bacterial infection. Our study found evidence for similarity between each of the experimental treatment regimens and the reference treatment. Treatment failure varied among groups from 6.1% to 8.2%. Treatment regimen D, which had only two injections of gentamicin, had the smallest proportion (6.1%) of treatment failure. The risk difference in treatment among the three simplified regiments and the reference treatment varied from -0.5% to 1.6%. Neither the rate of treatment failure nor the risk difference was statistically different among treatment groups. Among the danger signs for which infants were recruited, chest fast breathing (31%) and chest indrawing (23%) were the leading causes of treatment failure. Most treatment failures occurred on day 4, and the most common reason for treatment failure was the persistence of the danger signs on day 4. These findings are similar to those observed in the multi-national study. In view of these findings, it can reasonably be inferred that treatment regimens tested in the multi-national study would be equally effective in the DRC.

Strengths and limitations

This is the first study in the DRC that compared treatment regimens for the management of neonatal severe bacterial infection. The study was conducted within the context of the existing health structure. Therefore, the study methodology could be used as a model for capacity-building of the existing health system, and we believe that this strategy of care could be scaled up without difficulty. The study was conducted in one of the poorest regions of the country. The confirmation of effectiveness in this area suggests that the effectiveness of these simplified treatments can be generalized to more affluent areas of the country. The protocol was highly supervised; eligibility was confirmed by specially trained study nurses and assessment visits were conducted by the most qualified nurses among them who were not part of the clinical care team.

This study also had some limitations. Although we had sufficient statistical power to demonstrate equivalence between treatments, the multi-national study was not powered for site-specific outcomes. Therefore, the results should be interpreted with some caution. The low mortality rate among all treatment groups may reflect the intense surveillance of the population. This close surveillance may have resulted in earlier identification of high-risk infants and earlier referral for health care. Later identification might have occurred in the absence of the study resulting in more severe illness at the initiation of

antibiotic treatment. This might result in less effectiveness of simplified treatment regimens and higher mortality.

Implications of the results

Community-based treatments are more practical because they do not require inpatient care that is not available to many children in rural areas of the DRC. The most simplified treatment regimen may be particularly useful because it is based primarily on oral treatment. We speculate that the widespread use of this strategy for treating neonates and young infants with serious bacterial infection would result in more infants treated more effectively. This, in turn, would reduce mortality among young infants.

CONCLUSION

Simplified antibiotic regimens for treating infants in rural DRC with possible severe bacterial infection appear to be acceptable, feasible, safe, and effective. Since the most simplified regimen using mainly oral antibiotic and only two injections proved as effective as the WHO-recommended treatment, scaling up this regimen will more likely result in more infants treated effectively and result in reduced mortality in poor areas where hospital care is costly and inaccessible.

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Table 1: Baseline characteristics of enrolled infants

		Arm A (%)	Arm B (%)	Arm C (%)	Arm D (%)
				Study interventions	
	Total enrolled	464	447	465	466
Age (days)	Mean (SD)	15.8 (15.5)	15.6 (15.3)	15.5 (16.1)	15.9 (15.8)
	< 7 days	196 (42.2)	187 (41.8)	203 (43.6)	193 (41.4)
	≥ 7 days	268 (57.8)	260 (58.2)	262 (56.4)	273 (58.6)
Sex	Males	251 (54.1)	235 (52.6)	245 (52.7)	243 (52.1)
	Females	213 (45.9)	212 (47.4)	220 (47.3)	223 (47.9)
Weight for age (Z score)	Mean Z score (SD)	-1.2 (1.2)	-1.03 (1.2)	-1.3 (1.3)	-1.2 (1.2)
	< -2z scores	94 (20.3)	81 (18.1)	110 (23.7)	105 (22.5)
	>=-2z scores	370 (79.7)	366 (81.9)	355 (76.3)	361 (77.5)
Respiratory rate	Mean (SD)	67.7 (18.3)	67.9 (19.3)	67.3 (19.3)	66.4 (18.2)
	< 60	180 (38.8)	177 (39.6)	194 (41.7)	199 (42.7)
	60-70	76 (16.4)	73 (16.3)	80 (17.2)	66 (14.2)
	70-79	88 (19)	79 (17.7)	80 (17.2)	93 (20)
	80-89	65 (14)	55 (12.3)	52 (11.2)	59 (12.7)
	90-99	31 (6.7)	30 (6.7)	32 (6.9)	27 (5.8)
	≥ 100	24 (5.2)	33 (7.4)	27 (5.8)	22 (4.7)
Temperature	< 35.5	53 (11.4)	61 (13.6)	79 (17)	64 (13.7)
	35.5–37.9	125 (26.9)	146 (32.7)	117 (25.2)	123 (26.4)
	≥38.0–38.9	260 (56)	217 (48.5)	245 (52.7)	248 (53.2)
	≥39.0	26 (5.6)	23 (5.1)	24 (5.2)	31 (6.7)
Poor feeding		98 (13.6)	98 (21.9)	93 (20)	111 (23.8)
Movement only on stimulation		19 (26.7)	17 (3.8)	12 (2.6)	16 (3.4)
Severe chest indrawing		103 (60.1)	107 (23.9)	97 (20.9)	94 (20.2)
Number of signs at enrollment	1	381 (82.1)	375 (83.9)	391 (84.1)	381 (81.8)
	2	72 (15.5)	66 (14.8)	62 (13.3)	74 (15.9)
	3	11 (2.4)	5 (1.1)	8 (1.7)	10 (2.1)
	4	0 (0)	1 (0.2)	4 (0.9)	1 (0.2)
Maternal age (years)	Mean (SD)	25.9 (6.6)	24.9 (6.5)	25.2 (6.3)	24.8 (5.9)
	< 20 years	82 (17.7)	88 (19.7)	84 (18.1)	85 (18.2)
	≥ 20 years	310 (66.8)	284 (63.5)	320 (68.8)	308 (66.1)
	Unknown	72 (15.5)	75 (16.8)	61 (13.1)	73 (15.7)
Place of birth	Home	94 (20.3)	104 (23.3)	106 (22.8)	117 (25.1)
	Hospital	40 (8.6)	33 (7.4)	32 (6.9)	24 (5.2)
	Health center	303 (65.3)	296 (66.2)	306 (65.8)	308 (66.1)
	Other	26 (5.6)	14 (3.1)	21 (4.5)	17 (3.6)
	Unknown	1 (0.2)	0 (0)	0 (0)	0 (0)
Number of live births	1	110 (23.7)	118 (26.4)	114 (24.5)	114 (24.5)
	2-3	178 (38.4)	187 (41.8)	198 (42.6)	200 (42.9)
	≥4	175 (37.7)	141 (31.5)	152 (32.7)	152 (32.6)

	Unknown	1 (0.2)	1 (0.2)	1 (0.2)	0 (0)
At least one antenatal clinic attendance	Yes	442 (95.3)	434 (97.1)	449 (96.6)	446 (95.7)
	No	22 (4.7)	13 (2.9)	16 (3.4)	20 (4.3)
Religion	Christian	464 (100)	446 (99.8)	463 (99.6)	466 (100)
	Muslim	0 (0)	0 (0)	1 (0.2)	0 (0)
	Other	0 (0)	1 (0.2)	1 (0.2)	0 (0)
Maternal education (in years)	Mean (SD)	5.1 (2.7)	5 (2.5)	5.4 (2.4)	5.2 (2.3)
	No formal school attendance	243 (52.4)	241 (53.9)	238 (51.2)	242 (51.9)
	< 12 years	213 (45.9)	201 (45)	224 (48.2)	221 (47.4)
	≥ 12 years	8 (1.7)	5 (1.1)	3 (0.6)	3 (0.6)
	Unknown	1 (0.2)	0 (0)	0 (0)	0 (0)
Cooking place	Indoor with solid fuel	262 (56.5)	243 (54.4)	256 (55.1)	266 (57.1)
	Outdoor with solid fuel	202 (43.5)	204 (45.6)	209 (44.9)	200 (42.9)

Table 2: Treatment adherence and follow up of enrolled infants

	Treatment regimens			
	Arm A	Arm B	Arm C	Arm D
Number of enrolled infants	464	447	465	466
Treatment adherence				
Received all treatment doses as per-protocol	452 (97.4)	441 (98.7)	455 (97.8)	457 (98.1)
Did not receive all doses, but met per-protocol analysis criteria	3 (0.6)	2 (0.4)	2 (0.4)	0 (0)
Did not meet per-protocol analysis criteria for treatment	9 (1.9)	4 (0.9)	8 (1.7)	9 (1.9)
Follow up by independent outcome assessor				
Received all independent outcome assessment visits	452 (97.4)	434 (97.1)	462 (99.4)	456 (97.9)
Did not receive all independent outcome assessment visits, but met per-protocol analysis criteria	6 (1.3)	6 (1.3)	2 (0.4)	6 (1.3)
Did not meet per-protocol analysis criteria for assessment	6 (1.3)	7 (1.6)	1 (0.2)	4 (0.9)
Included in per-protocol analysis (met both treatment and assessment criteria)	454 (97.8)	437 (97.8)	457 (98.3)	457 (98.1)

Table 3: Primary and secondary outcomes in enrolled infants–per-protocol analysis

Treatment regimens

	Arm A	Arm B	Arm C	Arm D
Total enrolled	464	447	465	466
Met per-protocol analysis criteria	454 (97.8)	437 (97.8)	457 (98.3)	457 (98.1)
First week after enrollment				
Primary outcome: treatment failure by per-protocol analysis	30 (6.6)	36 (8.2)	29 (6.3)	28 (6.1)
Risk difference (95% CI)	-	1.6% (-1.8%–5%)	-0.3% (-3.4%–3%)	-0.5% (-3.6%–2.7%)
Reason for treatment failure				
Death	3 (0.7)	11 (2.5)	12 (2.6)	6 (1.3)
Appearance of a sign of critical illness	6 (1.3)	6 (1.4)	7 (1.5)	4 (0.9)
Appearance of a new sign of serious infection	2 (0.4)	7 (1.6)	4 (0.9)	4 (0.9)
SAE other than death	0 (0)	0 (0)	0 (0)	1 (0.2)
Hospitalization	4 (0.9)	4 (0.9)	5 (1.1)	2 (0.4)
No improvement in clinical condition by day 4	14 (3.1)	10 (2.3)	2 (0.4)	9 (2)
Reappearance of inclusion sign between days 5-8	4 (0.9)	2 (0.5)	4 (0.9)	5 (1.1)
Presence of inclusion sign on day 8	1 (0.2)	0 (0)	0 (0)	0 (0)
Withdrawal from the study (per-protocol withdrawal excluded)	5 (1.1)	1 (0.2)	4 (0.9)	2 (0.4)
Risk difference	-	-40% (-76%, -3.8%)	0% (-46.4%, 46.4%)	-27.7% (-68.9%, 13.4%)
Second week after enrollment				
Death	0 (0)	0 (0)	2 (0.4)	1 (0.2)
SAE other than death	0 (0)	0 (0)	0 (0)	0 (0)
First and second week after enrollment				
Death (% out of all enrolled)	4 (0.9)	11 (2.5)	14 (3)	7 (1.5)

Figure 1: Subject recruitment, randomization, and treatment

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┌─────────────────────────────────────────────────┐
│     Identification of all births by CHWs & TBAs  │
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                        ▼
        ┌───────────────────────────────────┐
        │    Evaluation of sepsis by CHWs    │
        └───────────────────────────────────┘
                        │
                        ▼
    ┌───────────────────────────────────────────┐
    │  Confirmation of sepsis signs and screening for  │
    │       eligibility by study nurses          │
    └───────────────────────────────────────────┘
                        │
                        ▼
        ┌───────────────────────────────────┐
        │           Randomization            │
        └───────────────────────────────────┘
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        ┌───────────┬───────────┬───────────┐
        ▼           ▼           ▼           ▼
  ┌──────────┐ ┌──────────┐ ┌──────────┐ ┌──────────┐
  │Regimen A │ │Regimen B │ │Regimen C │ │Regimen D │
  └──────────┘ └──────────┘ └──────────┘ └──────────┘
        │           │           │           │
        └───────────┴─────┬─────┴───────────┘
                          ▼
        ┌───────────────────────────────────┐
        │  Provision of treatment at health center │
        │  or at home by study nurses for 7 days  │
        └───────────────────────────────────┘
                          │
                          ▼
    ┌───────────────────────────────────────────┐
    │  Outcome assessment by independent outcome  │
    │ assessment nurses by on days 4, 8, 11 & 15 of enrollment │
    └───────────────────────────────────────────┘
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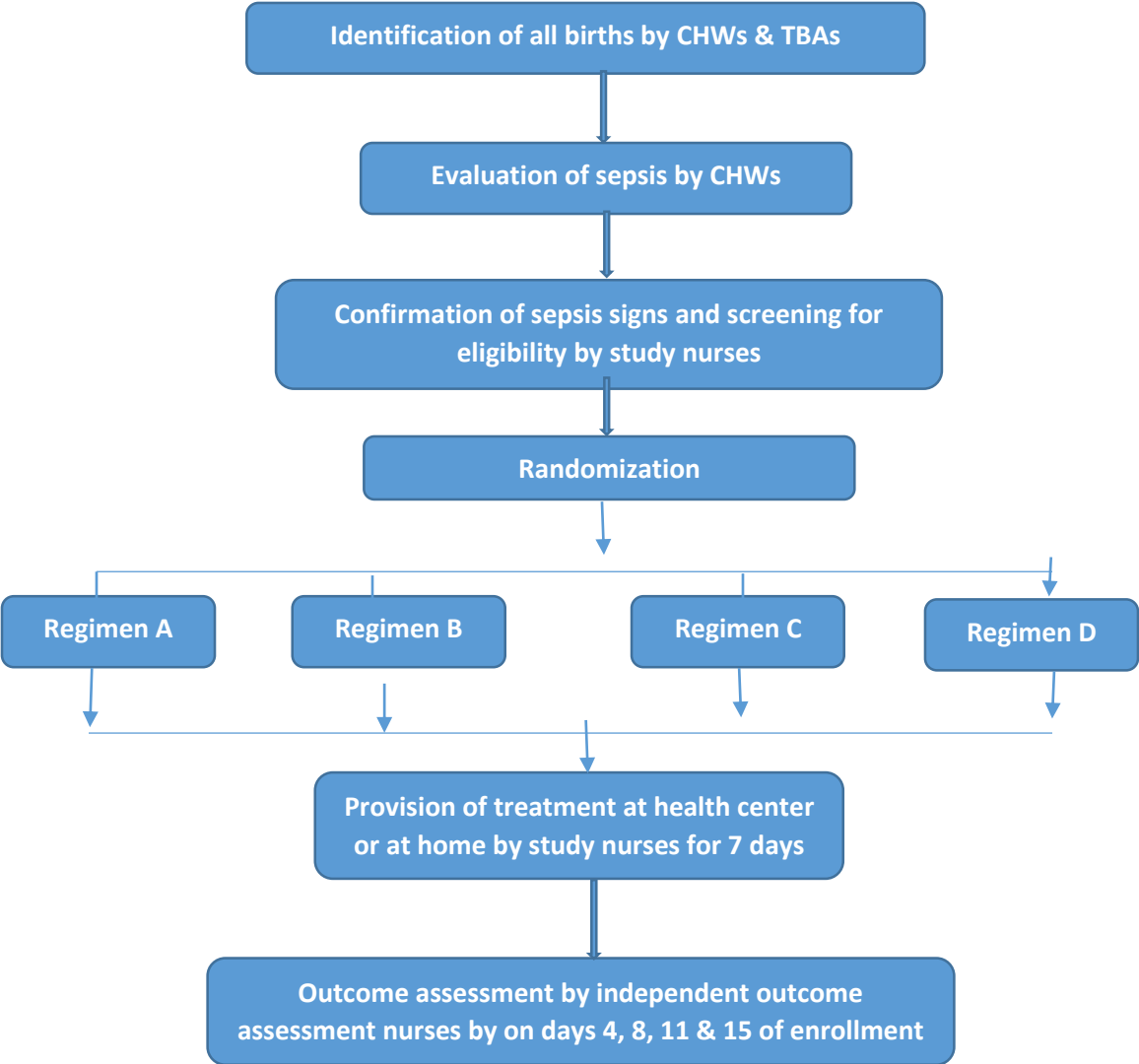
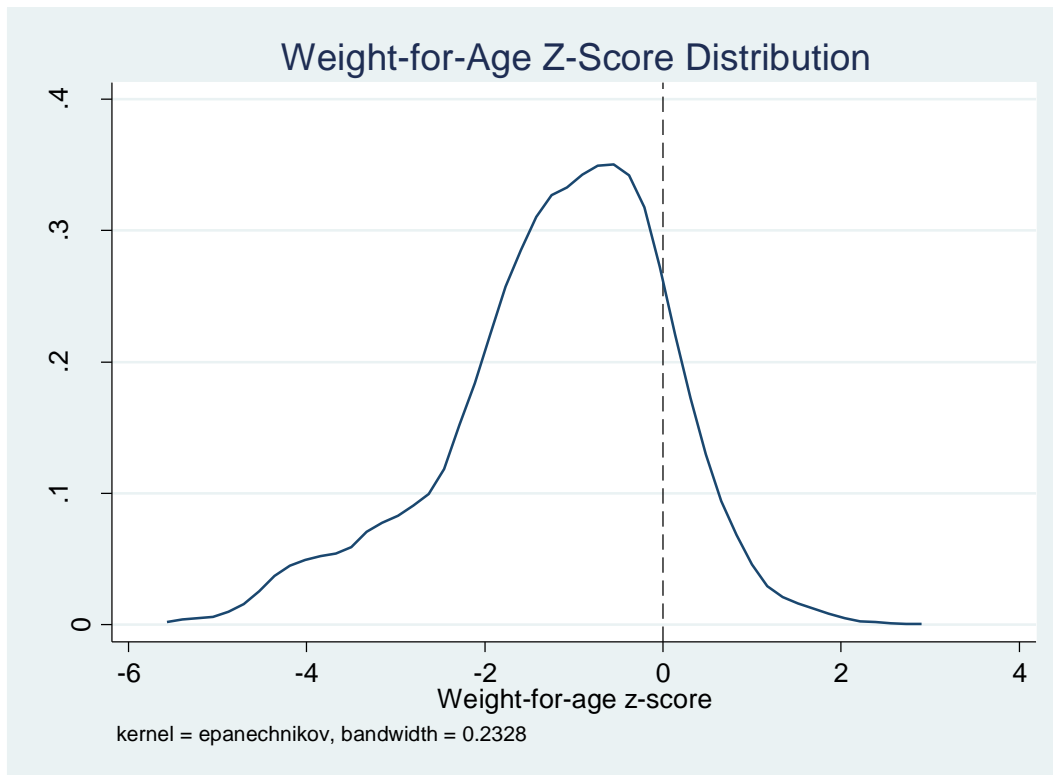**Figure 2: Weight-for-age z-score distribution**
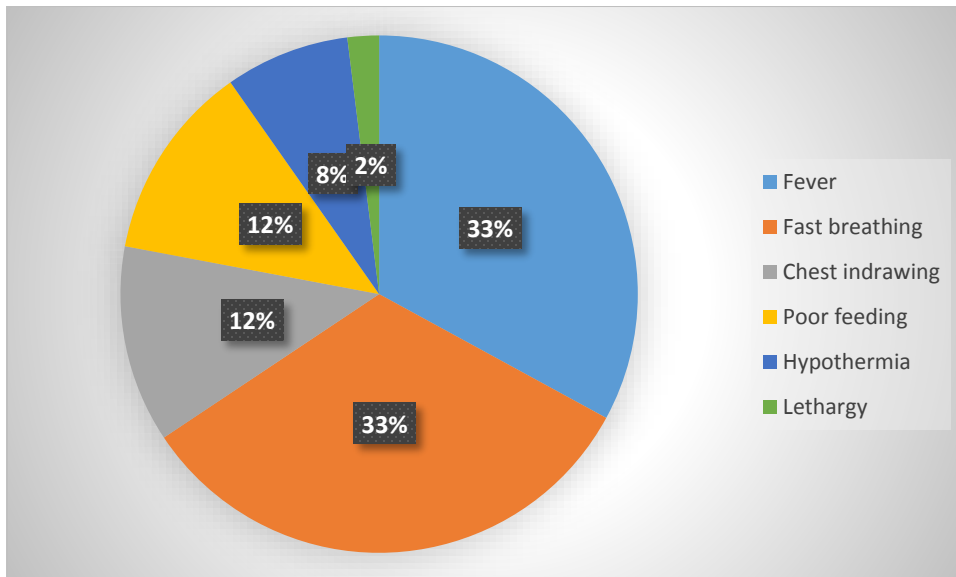

Figure 3: Signs at enrollment
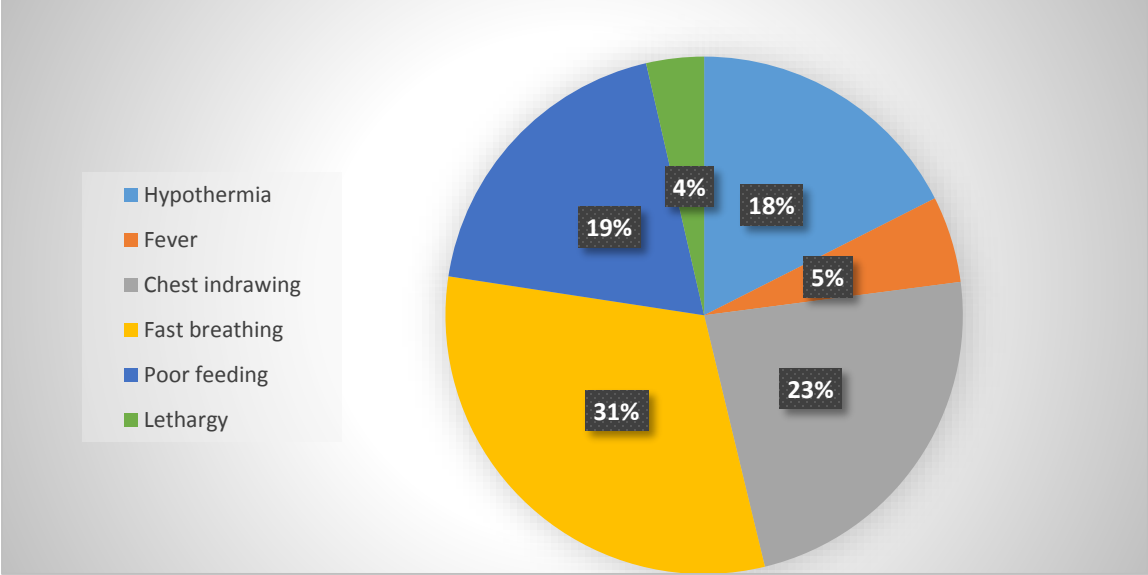
Figure 4: Percentage of treatment failure cause

Figure 5: Day on which treatment failure occurred