Safety and efficacy of alternative antibiotic regimens compared with 7 day injectable procaine benzylpenicillin and gentamicin for outpatient treatment of neonates and young infants with clinical signs of severe infection when referral is not possible: a randomised, open-label, equivalence trial

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Summary

Background Severe infections remain one of the main causes of neonatal deaths worldwide. Possible severe infection is diagnosed in young infants (aged 0–59 days) according to the presence of one or more clinical signs. The recommended treatment is hospital admission with 7–10 days of injectable antibiotic therapy. In low-income and middle-income countries, barriers to hospital care lead to delayed, inadequate, or no treatment for many young infants. We aimed to identify effective alternative antibiotic regimens to expand treatment options for situations where hospital admission is not possible.

Methods We did this randomised, open-label, equivalence trial in four urban hospitals and one rural field site in Bangladesh to determine whether two alternative antibiotic regimens with reduced numbers of injectable antibiotics combined with oral antibiotics had similar efficacy and safety to the standard regimen, which was also used as outpatient treatment. We randomly assigned infants who showed at least one clinical sign of severe, but not critical, infection (except fast breathing alone), whose parents refused hospital admission, to one of the three treatment regimens. We stratified randomisation by study site and age (<7 days or 7–59 days) using computer-generated randomisation sequences. The standard treatment was intramuscular procaine benzylpenicillin and gentamicin once per day for 7 days (group A). The alternative regimens were intramuscular gentamicin once per day and oral amoxicillin twice per day for 7 days (group B) or intramuscular procaine benzylpenicillin and gentamicin once per day for 2 days, then oral amoxicillin twice per day for 5 days (group C). The primary outcome was treatment failure within 7 days after enrolment. Assessors of treatment failure were masked to treatment allocation. Primary analysis was per protocol. We used a prespecified similarity margin of 5% to assess equivalence between regimens. This study is registered with ClinicalTrials.gov, number NCT00844337.

Findings Between July 1, 2009, and June 30, 2013, we recruited 2490 young infants into the trial. We assigned 830 infants to group A, 831 infants to group B, and 829 infants to group C. 2367 (95%) infants fulfilled per-protocol criteria. 78 (10%) of 795 per-protocol infants had treatment failure in group A compared with 65 (8%) of 782 infants in group B (risk difference –1·5%, 95% CI –4·3 to 1·3) and 64 (8%) of 790 infants in group C (–1·7%, –4·5 to 1·1). In group A, 14 (2%) infants died before day 15, compared with 12 (2%) infants in group B and 12 (2%) infants in group C. Non-fatal relapse rates were similar in all three groups (12 [2%] infants in group A *vs* 13 [2%] infants in group B and 10 [1%] infants in group C).

Interpretation Our results suggest that the two alternative antibiotic regimens for outpatient treatment of clinical signs of severe infection in young infants whose parents refused hospital admission are as efficacious as the standard regimen. This finding could increase treatment options in resource-poor settings when referral care is not available or acceptable.

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Introduction

Although many developing countries have achieved substantial decreases in deaths in the post-neonatal period and in children aged 1–4 years, neonatal death rates have decreased more slowly, with an estimated 3 million neonatal deaths worldwide every year.[1,2] Most of these neonatal deaths are in developing countries,[3] which are characterised by high rates of home delivery by unskilled attendants and high rates of infections in neonates.[4] Up to one in five neonates in developing

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countries develop life-threatening infections.[5] Several preventive interventions against neonatal infections, including tetanus toxoid immunisation of pregnant women, early and exclusive breastfeeding, use of clean delivery practices, and umbilical cord cleansing with chlorhexidine, have been identified and incorporated into many health-care programmes.[4,6–8] However, infections remain one of the main causes of neonatal deaths worldwide, accounting for roughly a quarter of neonatal deaths.[2] In settings characterised by high neonatal mortality, the proportion of neonatal deaths caused by infections has been estimated to be up to 50%.[9–11] Therefore, strategies for timely identification and management of infections in neonates and young infants (aged 0–59 days) are urgently needed.

WHO recommends that all cases of clinical signs of severe infection in young infants (aged 0–59 days) are treated in hospital with a 7–10 day course of injectable antibiotics—penicillin (or ampicillin) and gentamicin. However, in many low-income and middle-income countries, this care is often not available, accessible, or acceptable to families. Furthermore, the quality of care in peripheral facilities is often inadequate because of scarcity of trained personnel or necessary supplies.[12,13] These constraints lead to delayed or inadequate treatment or no treatment at all for many young infants in low-income and middle-income countries.

Strategies for community-based management of infections in young infants by trained community health workers have been developed, assessed, and shown to be effective.[10,14–17] In Bangladesh, our group, Projahnmo, showed that identification and treatment of neonates with suspected severe infection by trained community health workers who used injectable procaine benzylpenicillin and gentamicin for 7 days substantially reduced neonatal mortality, compared with no care or untrained care.[10] Although treatment of ill neonates by community health workers has been shown to be safe and effective in low-resource settings, major obstacles are associated with large-scale implementation of injectable therapy in the community or at first-level facilities. First, difficulties exist in ensuring availability of trained health workers and supplies, and in implementation of quality assurance for safe injectable antibiotic treatment every day for 7–10 days. Second, a 7–10 day regimen of parenteral antibiotic therapy presents challenges to community acceptance and compliance. Third, unsupervised use of injections at the community level might be unsafe and could increase the risk of transmission of HIV, hepatitis, and other viral diseases through use of contaminated needles.[18] Therefore, reduction of the number of injections to be used is important. Furthermore, the justification for 7–10 days of parenteral antibiotic therapy has not been fully established. 7 days of injectable therapy is perceived to be the most efficacious regimen in treatment of severe infections. However, for some neonates with infections, alternative regimens—eg, those that include a combination of parenteral and oral therapy or that switch to an oral antibiotic after initial treatment with injectable antibiotics for 2–3 days—might be equally effective, as has been shown in older children.[19] We aimed to determine whether two antibiotic regimens with a reduced number of injections are equivalent to the standard outpatient course of parenteral antibiotics for the treatment of clinical signs of severe infections in young infants in Bangladesh, whose parents sought care but refused hospital admission.

Methods

Study design

We did this randomised, open-label, equivalence trial at the outpatient departments of four urban hospitals and one rural field site in Bangladesh. The centres were the Dhaka Shishu (children's) Hospital, Shishu Sasthya Hospital, and the Institute of Child and Mother Health Hospital in urban Dhaka; Ma O' Shishu Hospital in urban Chittagong; and rural surveillance sites in the Sylhet district, Bangladesh. Details of the design and implementation of the study have been reported previously.[20]

The institutional review boards of the Bangladesh Institute of Child Health, Johns Hopkins Bloomberg School of Public Health, London School of Hygiene & Tropical Medicine, and WHO reviewed and approved this study.

Participants

In the urban hospitals, we screened infants who were brought to outpatient departments and enrolled those who met the eligibility criteria, whose parents or guardians refused hospital admission and consented to the study. In the rural site, trained female community health workers visited all young infants on days 0, 2, 6, 13, 20, 27, 34, 41, 48, and 59 after birth to identify infants who were unwell based on history and clinical assessments. Community health workers referred all unwell infants to one of the two designated hospitals within the study area for further assessment and care. Research assistants screened young infants presenting to the outpatient departments of these participating hospitals to identify those who met the age and residence criteria. These infants were then screened by the study physician for clinical signs of severe infection according to the inclusion and exclusion criteria. Infants with one or more inclusion criteria and no exclusion criteria were clinically eligible. At all sites, we offered all clinically eligible infants hospital admission or referral to another hospital if no hospital bed was available. If the infant's family did not comply with hospital admission or referral, the study physician offered the option for home treatment through study participation.

The inclusion criteria were age 0–59 days, residence within a predefined geographical area based on feasibility of follow-up visits, and the presence of at least one of five

clinical signs of severe infection: severe lower chest wall indrawing; axillary temperature 38·0°C or more (≥100·4°F) confirmed by a second reading; axillary temperature of 35·5°C or less (≤95·9°F) confirmed by a second reading; lethargy, defined as movement only on stimulation by the examining physician; and history of feeding problems, confirmed by poor suck on examination. Infants with fast breathing alone (respiratory rate ≥60 breaths per min) were excluded because data from previous studies in Bangladesh[10] suggest that this sign alone is not predictive of severe illness. Infants with signs of critical illnesses were excluded, because outpatient treatment was judged to be potentially unsafe for this group. Critical illness was defined as the presence of any of the following signs: unconsciousness; history or presence of convulsions at assessment; inability to feed; apnoea; inability to cry; cyanosis; bulging fontanelle; major congenital malformations; major bleeding; surgical conditions needing hospital referral; persistent vomiting after three attempts to feed the baby within 30 min; and physician's suspicion of meningitis. Infants were also excluded from the study if they weighed less than 1500 g, had been admitted to hospital for illness in the past 2 weeks, or had previously been included in the study. We obtained written informed consent for study participation from caregivers of infants who met the eligibility requirements.

Randomisation and masking

We randomly assigned eligible infants to receive either the standard antibiotic treatment or one of two alternative treatments. The standard treatment was intramuscular procaine benzylpenicillin and gentamicin (group A), which were given once per day for 7 days. The two alternative regimens were intramuscular gentamicin once per day and oral amoxicillin twice per day for 7 days (group B), and intramuscular procaine benzylpenicillin and gentamicin once per day for 2 days, then oral amoxicillin twice per day for 5 days (group C).

We randomly assigned infants to one of the three treatment regimens, stratified by study site and age (<7 days or 7–59 days), using computer-generated randomisation sequences (generated by SC, who was not involved in the field implementation) with randomly permuted block sizes of 6, 9, and 12. We placed the allocation sequence for each site and age group in serially numbered, sealed, opaque envelopes, and delivered them to each site. After we had obtained consent for enrolment,

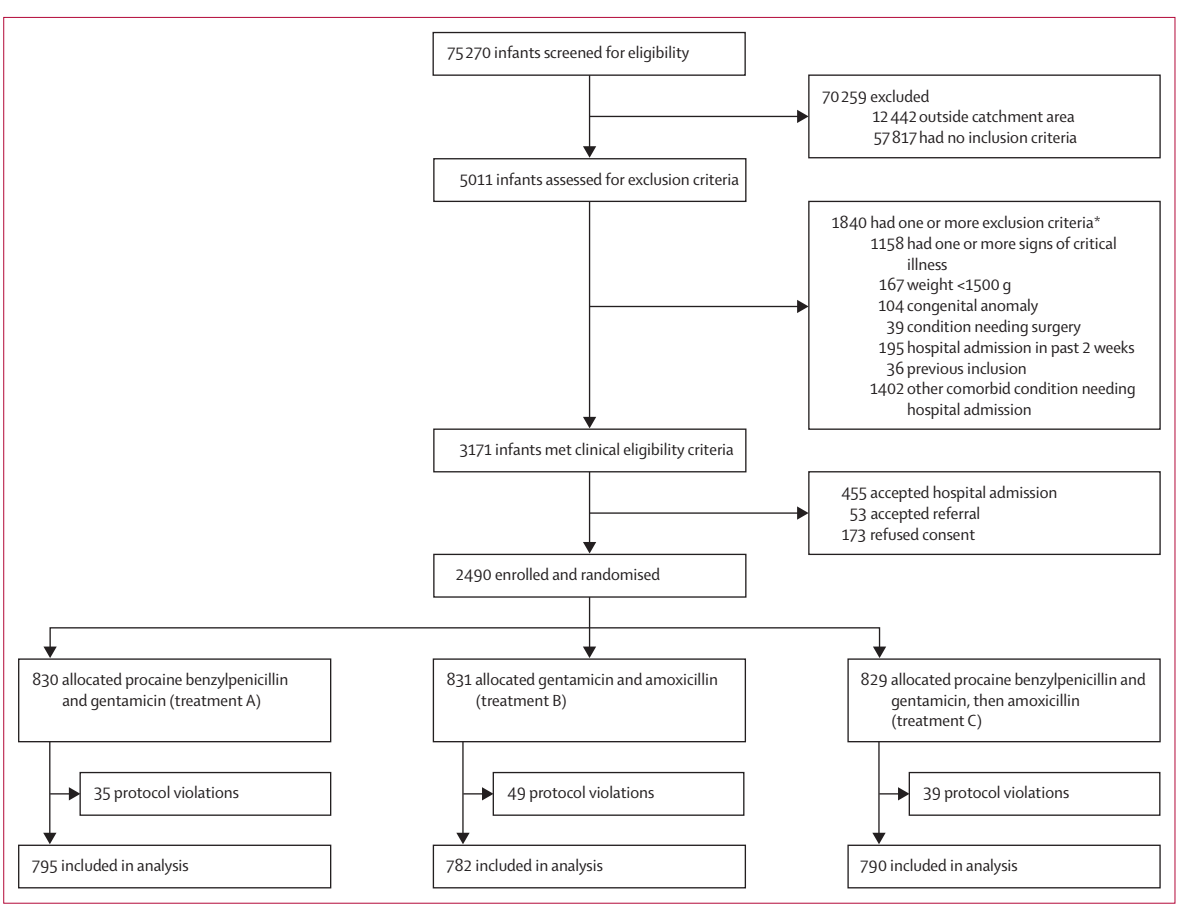

Figure: **Trial profile**
*Exclusion criteria add up to more than 1840 because some infants had more than one.

the study physician selected the next envelope in the sequence, and the infant was assigned to the treatment corresponding to the allocation code printed within the envelope. We did not deem it ethical to give placebo injections to such young infants and therefore, we were not able to mask the study participants or study physicians to treatment group allocation.

Procedures

We selected doses of antibiotics to optimise efficacy, safety, and feasibility. We used extended-interval (every 24 h) gentamicin regimens at doses of 4·0–6·5 mg/kg per 24 h and intramuscular procaine benzylpenicillin each day at doses of 40 000–50 000 IU/kg.[21–23] For amoxicillin, the target dose was 75–100 mg/kg per day divided into two doses each day.[23] All enrolled infants received the first doses of the assigned antibiotics and we discharged them home after counselling their caregivers on appropriate home management. Study physicians made home visits every day for the next 7 days to assess the infants to identify treatment failure, provide intramuscular injections (if allocated), and measure treatment adherence. During each visit, doctors taught caregivers of infants allocated to oral amoxicillin treatment how to give the oral amoxicillin. If an infant vomited within 20 min of oral dosing, the caregiver's instructions were to give another complete dose. If the infant vomited within 20 min of the second oral dose, the instructions were for caregivers to seek medical attention. Additionally, study physicians made home visits on days 11 and 15 to identify relapse and death.

	Procaine benzylpenicillin and gentamicin (group A, n=830)	Gentamicin and amoxicillin (group B, n=831)	Procaine benzylpenicillin and gentamicin, then amoxicillin (group C, n=829)
Study site			
Dhaka Shishu (children's) Hospital	150 (18%)	150 (18%)	150 (18%)
Shishu Sasthya Hospital	225 (27%)	224 (27%)	225 (27%)
Ma O' Shishu Hospital	170 (20%)	170 (20%)	170 (21%)
Institute of Child and Mother Health Hospital	117 (14%)	117 (14%)	116 (14%)
Sylhet	168 (20%)	170 (20%)	168 (20%)
Age at enrolment (days)			
0–6	86 (10%)	85 (10%)	82 (10%)
7–59	744 (90%)	746 (90%)	747 (90%)
Sex			
Male	517 (62%)	516 (62%)	497 (60%)
Female	313 (38%)	315 (38%)	332 (40%)
Weight-for-age *Z* score at enrolment	–1·62 (1·19)	–1·62 (1·15)	–1·58 (1·18)
Number of signs present			
1	508 (61%)	517 (62%)	518 (62%)
2	294 (35%)	279 (34%)	271 (33%)
>2	28 (3%)	35 (4%)	40 (5%)
Fever present			
In isolation	179 (22%)	195 (23%)	210 (25%)
With or without another sign	329 (40%)	337 (41%)	369 (45%)
Hypothermia present			
In isolation	11 (1%)	10 (1%)	13 (2%)
With or without another sign	18 (2%)	18 (2%)	16 (2%)
Lethargy present			
In isolation	1 (<1%)	0 (0%)	2 (<1%)
With or without another sign	17 (2%)	19 (2%)	21 (3%)
Severe chest indrawing present			
In isolation	273 (33%)	266 (32%)	252 (30%)
With or without another sign	501 (60%)	500 (60%)	477 (58%)
Poor feeding (suck) present			
In isolation	44 (5%)	46 (6%)	41 (5%)
With or without another sign	316 (38%)	306 (37%)	298 (36%)
Local infection present	48 (6%)	50 (6%)	55 (7%)
Mother's age (years)	24·0 (4·8)	24·3 (4·8)	24·1 (4·6)
Maternal education (years)	5·0 (3·5)	5·1 (3·7)	5·0 (3·6)

Data are n (%) or mean (SD).

Table 1: **Baseline characteristics of all enrolled infants**

The study had internal and external quality assurance mechanisms. A clinical supervisor at each study site monitored activities with respect to quality and consistency of study procedures. A random sample of 5% of eligibility assessments was repeated by a second study physician; the second physician assessor was masked to the first physician's assessment. The assessment of the second physician did not routinely affect study procedures or outcome ascertainment. However, if the second physician identified danger signs that were missed by the first physician, a supervising physician assessed and managed the infant.

If infants who were not admitted to hospital survived, and study physicians identified them as meeting the criteria for clinical treatment failure on routine follow-up visits, we designated them as provisional treatment failures, and transported them to the hospital accompanied by study personnel. At the hospital, the infant received a repeat examination by a second study physician. The second physician assessor was masked to the treatment allocation and any previous assessments of the infant. If the second assessment supported the decision of treatment failure, the infant was deemed to have confirmed treatment failure. If the second medical assessment disagreed with the first assessment, the assessors referred the decision to a supervising physician, whose decision was judged to be final. Infants who had treatment failure were referred for further hospital care according to standard hospital practices.

A technical steering committee and a data safety monitoring board provided independent oversight to the study. The technical steering committee members and independent clinical monitors deployed by the technical steering committee made site visits once per year to ensure adequate implementation of the study procedures and gave feedback to the study team. We used the feedback from the technical steering committee to further standardise study procedures including clinical assessments, as needed.

Outcomes

The primary outcome was treatment failure in the 7 days (up to the day 8 visit) after enrolment. We defined treatment failure as one or more of the following criteria: death at any time before the day 8 assessment; clinical deterioration at or before the day 8 assessment based on the occurrence of at least one of eight critical signs reported by the study physician based on physical examination (unconsciousness, convulsions [diagnosed by observation or clinical history], inability to feed, apnoea, cyanosis, bulging fontanelle, major bleeding, and persistent vomiting [defined as vomiting after three attempts to feed the infant within 30 min, as assessed by study physician]); change of antibiotic or addition of another antibiotic by a study physician on or before day 8 because of new-onset infectious comorbidity (eg, severe omphalitis, bone or joint infection, or severe skin or soft tissue infection), or serious non-fatal antibiotic-associated adverse event (eg, dehydration-associated severe diarrhoea, Stevens-Johnson syndrome, anaphylaxis, or acute renal failure); hospital admission for any reason at or before the day 8 assessment; occurrence of new clinical signs of severe infection at or after day 3; presence of at least two of the signs that were present on enrolment at day 4 in infants with multiple signs at enrolment; presence of the sign on day 4 in infants with a single sign on enrolment; recurrence of any one of the five inclusion signs on or after day 5; or persistence of any one of the five signs of severe infection that was present at enrolment on day 8.

The secondary outcomes were the proportions of infants who died and of those who had non-fatal relapse, defined as young infants who were deemed to be cured within 7 days but developed any of the clinical signs of severe infection after 7 days and within 14 days.

Statistical analysis

We postulated that the alternative therapies would be equivalent to the standard therapy and that the treatment failure proportion would be 10% in all groups. For each comparison (group B *vs* group A and group C *vs* group A), we planned the analysis to be based on the difference in the risk of failure between the two treatment groups. We used a two-sided 95% CI to assess the similarity of the two treatments. We judged the alternative therapies to be equivalent to the reference therapy if the upper bound of the confidence interval for the difference in treatment failure was less than 5%. We used Stata 13.0 software for all statistical analysis. We calculated κ to determine agreement, which is the standard statistical technique.[24]

We estimated the sample sizes for this three-armed study using Blackwelder's method.[25] We assumed that the true failure rate in the standard treatment regimen and the alternative regimens would be 10%. We estimated that enrolment of 750 evaluable infants in each of the three groups (2250 infants in total) would yield 90% power to show similarity within 5%, if the true failure rates were identical. Based on previous experience in similar settings, we allowed for up to 15% loss to follow-up, and therefore, aimed to enrol 866 infants to each group or 2598 infants in total.

In our primary analysis, we included infants who met predefined per-protocol criteria based on treatment compliance and completeness of clinical follow-up. Infants were fully adherent to study treatment if they received all doses of scheduled antibiotics on all 7 days or by the time of treatment failure (if treatment failure occurred), and were not known to have received any other antibiotic from a study or non-study physician. We deemed infants who were not fully adherent as partly adherent if they received all scheduled antibiotics on days 1–3 or by the time of treatment failure; received at least half of the scheduled doses of each antibiotic during days 4–7, or by the time of treatment failure; were not known to have received any non-study injectable antibiotic before day 8 assessment; and were not known to have received any non-study oral antibiotic on days 1–3. Infants who did not fulfil the criteria of being either fully or partly adherent were regarded as non-adherent. Infants who received scheduled follow-up on all 7 days or up to the time of treatment failure (if treatment failure occurred) had complete clinical follow-up. Infants had partly complete clinical follow-up if they had one or more days of follow-up missing, but follow-up was completed on assessment days 2–4 and at least one of days 5–8, and vital status was known on day 8. Infants who did not fulfil the criteria of complete or partly complete clinical follow-up had incomplete clinical follow-up. The per-protocol analysis included infants who had either complete or partly complete follow-up and who were either fully or partly adherent. We deemed infants with either incomplete clinical follow-up or who were non-adherent to be not per

	Procaine benzylpenicillin and gentamicin (group A, n=830)	Gentamicin and amoxicillin (group B, n=831)	Procaine benzylpenicillin and gentamicin, then amoxicillin (group C, n=829)
Clinical follow-up			
Complete	791 (95%)	801 (96%)	790 (95%)
Partly complete	16 (2%)	10 (1%)	14 (2%)
Incomplete	23 (3%)	20 (2%)	25 (3%)
Treatment adherence			
Completely adherent	784 (94%)	757 (91%)	765 (92%)
Partly adherent	13 (2%)	26 (3%)	30 (4%)
Non-adherent	33 (4%)	48 (6%)	34 (4%)
Per-protocol status*			
Per protocol	795 (96%)	782 (94%)	790 (95%)
Not per protocol	35 (4%)	49 (6%)	39 (5%)
Met intention-to-treat criteria†	819 (99%)	821 (99%)	820 (99%)

Data are n (%). *Infants were classified as per protocol if they had complete or partly complete clinical follow-up and complete or partly complete treatment adherence. †Received first dose of treatment and were followed up on at least one of days 2–8.

Table 2: **Per-protocol population**

	Procaine benzylpenicillin and gentamicin (group A, n=795)	Gentamicin and amoxicillin (group B, n=782)	Procaine benzylpenicillin and gentamicin, then amoxicillin (group C, n=790)
Treatment failure by day 8 visit	78 (10%)	65 (8%)	64 (8%)
Risk difference	..	−1·5% (−4·3 to 1·3)	−1·7% (−4·5 to 1·1)
Initial reason for treatment failure			
Death	6/78 (8%)	5/65 (8%)	5/64 (8%)
Admitted to hospital	25/78 (32%)	14/65 (22%)	15/64 (23%)
Clinical deterioration	13/78 (17%)	13/65 (20%)	11/64 (17%)
New sign on/after day 3	4/78 (5%)	10/65 (15%)	7/64 (11%)
Persistence of sign(s) at day 4	15/78 (19%)	8/65 (12%)	11/64 (17%)
Recurrence of signs on/after day 5	10/78 (13%)	13/65 (20%)	14/64 (22%)
Persistence at day 8	0/78	1/65 (2%)	0/64
Severe adverse event	3/78 (4%)	0/65	0/64
Antibiotic change because of infectious comorbidity	2/78 (3%)	1/65 (2%)	1/64 (2%)
Admitted to hospital during first week	50 (6%)	34 (4%)	39 (5%)
Risk difference	..	−1·9% (−4·2 to 0·3)	−1·4% (−3·6 to 0·9)
Died during first week	13 (2%)	9 (1%)	6 (1%)
Risk difference	..	−0·5% (−1·6 to 0·7)	−0·9% (−1·9 to 0·2)
Died at any time before day 15 follow-up	14 (2%)	12 (2%)	12 (2%)
Risk difference	..	−0·2% (−1·5 to 1·0)	−0·2% (−1·5 to 1·0)
Treatment successes with follow-up on days 11 or 15	709	700	718
Admitted to hospital during second week*	5 (1%)	2 (<1%)	4 (1%)
Risk difference	..	−0·4% (−1·1 to 0·3)	−0·1% (−1·0 to 0·7)
Died during second week*	1 (<1%)	1 (<1%)	6 (1%)
Risk difference	..	0·0% (−0·4 to 0·4)	0·7% (−0·0 to 1·4)
Non-fatal relapse during second week*	12 (2%)	13 (2%)	10 (1%)
Risk difference	..	0·2% (−1·2 to 1·5)	−0·3% (−1·6 to 1·0)

Data are n (%) or risk difference (95% CI). *Percentages calculated from total number of treatment successes with follow-up on days 11 or 15.

Table 3: **Primary and secondary treatment outcomes in children in the per-protocol analysis**

protocol and we excluded them from the primary per-protocol analysis. All infants who received the first doses of the assigned antibiotics and received at least one follow-up visit were included in the intention-to-treat analysis.

The data safety monitoring board reviewed the trial data every 3 months and met in person once per year. The London School of Hygiene & Tropical Medicine was the data centre. This study is registered with ClinicalTrials.gov, number NCT00844337.

Role of the funding source

The funders of the study had a role in study design, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

See Online for appendix

Results

Between July 1, 2009, and June 30, 2013, we screened 75 270 young infants in the outpatient departments of the study hospitals (figure). We excluded 72 099 (96%) infants. 5011 young infants who were from the predefined catchment areas had one or more inclusion signs, 1158 of whom had signs of very severe disease and 682 had other exclusion signs. We assigned similar numbers of per-protocol infants to the three study groups (795 in group A, 782 infants in group B, and 790 infants in group C).

1984 (80%) enrolled infants were from urban study hospitals and 506 (20%) infants were from the rural surveillance site. The urban and rural infants presenting to the study hospitals were mostly similar, although rural infants were younger (aged <7 days: 134 [26%] of 506 rural infants *vs* 253 [10%] of 2490 infants overall), less often had multiple presenting signs (65 [13%] of 506 infants *vs* 947 [38%] of 2490 infants overall), and were more often clinically eligible (713 [11%] of 6339 infants *vs* 3171 [4%] of 75 270 infants overall) than were infants from urban sites. Almost all of the hypothermia cases were identified in the rural hospitals (appendix).

The distribution of enrolled infants was similar across treatment groups with respect to age, sex, weight for age at enrolment, and mothers' age and education. Similarly, the distributions of presenting signs of enrolled infants were also similar across treatment groups (table 1). 2382 (96%) infants in all three groups had complete clinical follow-up and an additional 40 (2%) infants had partly complete clinical follow-up. 2306 (93%) infants were fully adherent to the study drugs and another 69 (3%) infants were partly

	Procaine benzylpenicillin and gentamicin (group A, n=819)	Gentamicin and amoxicillin (group B, n=821)	Procaine benzylpenicillin and gentamicin, then amoxicillin (group C, n=820)
Treatment failure by day 8 visit	83 (10%)	82 (10%)	70 (9%)
Risk difference	..	–0·1% (–3·1 to 2·7)	–1·6% (–4·4 to 1·2)
Initial reason for treatment failure			
Death	6/83 (7%)	7/82 (9%)	5/70 (7%)
Admitted to hospital	30/83 (36%)	24/82 (29%)	18/70 (26%)
Clinical deterioration	13/83 (16%)	14/82 (17%)	13/70 (19%)
New sign on/after day 3	4/83 (5%)	11/82 (13%)	7/70 (10%)
Persistence of sign(s) at day 4	15/83 (18%)	10/82 (12%)	11/70 (16%)
Recurrence of signs on/after day 5	10/83 (12%)	13/82 (16%)	15/70 (21%)
Persistence at day 8	0/83	1/82 (1%)	0/70
Severe adverse event	3/83 (4%)	1/82 (1%)	0/70
Antibiotic change because of infectious comorbidity	2/83 (2%)	1/82 (1%)	1/70 (1%)
Admitted to hospital during first week	55 (7%)	47 (6%)	44 (5%)
Risk difference	..	–1·0% (–3·3% to 1·3%)	–1·3% (–3·7 to 1·0)
Died during first week	14 (2%)	11 (1%)	7 (1%)
Risk difference	..	–0·4% (–1·6 to 0·8)	–0·9% (–1·9 to 0·2)
Died at any time before day 15 follow-up	15 (2%)	14 (2%)	13 (2%)
Risk difference	..	–0·1% (–1·4 to 1·1)	–0·2% (–1·5 to 1·0)
Treatment successes with follow-up on days 11 or 15	719	714	730
Admitted to hospital during second week*	5 (1%)	2 (<1%)	5 (1%)
Risk difference	..	–0·4% (–1·1% to 0·3%)	0·0% (–0·9% to 0·8%)
Died during second week*	1 (<1%)	1 (<1%)	6 (1%)
Risk difference	..	0·0% (–0·4 to 0·4)	–0·7% (–0·0 to 1·4)
Non-fatal relapse during second week*	12 (2%)	14 (2%)	11 (2%)
Risk difference	..	0·3 (–1·1 to 1·7)	–0·2 (–1·4 to 1·1)

Data are n (%) or risk difference (95% CI). *Percentages calculated from total number of treatment successes with follow-up on days 11 or 15.

Table 4: **Primary and secondary treatment outcomes in children in the intention-to-treat analysis**

adherent in all three groups. Most infants met the per-protocol criteria (table 2).

Similar to the all enrolled infants, the distribution of per-protocol infants with respect to age, sex, weight-for-age at enrolment, and mothers' age and education were similar across treatment groups. The distributions of presenting signs in per-protocol infants were also similar across study groups (appendix).

In group A, 78 (10%) infants had treatment failure, compared with 65 (8%) infants in group B and 64 (8%) infants in group C (table 3). Risk difference between groups C and A was –1·5% (95% CI –4·3 to 1·3) and risk difference between groups B and A was –1·7% (–4·5 to 1·1). Therefore, the upper bound of both confidence intervals was less than the predefined 5% equivalence margin. Hospital admission and deaths in the first week were slightly more common in group A than in groups B and C. Death in the second week was slightly more common in group C than in groups A and B, but risk of death at any time before the day 15 follow-up was less than 2% in all treatment groups. This risk was similar to that of infants who opted for hospital admission (5 [2%] of 272 infants for whom we had data died during hospital admission and another 3 [1%] infants died within 1 week of discharge). Risk of non-fatal relapse was less than 2% in all three groups (table 3). The risk of treatment failure among intention-to-treat infants was slightly higher than per-protocol infants but similar in all three groups (table 4). Non-fatal severe adverse events were rare. Three infants in group A, two infants in group B, and three infants in group C had severe diarrhoea. We detected no cases of Stevens-Johnson syndrome, anaphylaxis, or acute renal failure (data not shown).

We included 3719 infants in repeat quality assurance assessments at the time of screening. Agreement between the two physicians was nearly 100% for all inclusion and exclusion signs. The κ values for inclusion signs ranged from 0·86 to 1·0. The κ values for all exclusion signs were more than 0·8 except for persistent vomiting which had a κ value of 0·67 (appendix).

Discussion

This study is the first outpatient trial of alternative antibiotic regimens for infants with clinical signs of severe infection (panel). The data show that the alternative regimens were efficacious and safe for outpatient treatment of clinical signs of severe infection in young infants whose caregivers did not accept hospital

care. Notably, we did not assess the regimens in young infants with critical illnesses or in infants with clinical signs of severe infection whose caregivers accepted hospital admission.

Although the treatment failure rate of about 8–10% might seem high, similar rates were reported in an earlier community-based study[29] that compared three antibiotic regimens. To ensure safety of the infants in the study, we used highly sensitive criteria (eg, persistence of signs on day 4, hospital admission for any reason) to assess treatment failure. The risk of death was low, similar in all three groups, and similar to that of infants who opted for hospital admission.

This trial was individually randomised and we reached the desired sample size. The randomisation seemed to be effective because background characteristics and presenting signs were similar in all randomised treatment groups. We achieved very high follow-up completion and treatment adherence, and only 123 (5%) of the 2490 enrolled infants did not meet the per-protocol criteria. The trial had robust internal and external monitoring and quality assurance methods.[30] The low loss to follow-up and high treatment adherence, coupled with strong monitoring, supports the internal validity of the results. We did the study in varied populations (urban hospitals where infants were brought by caregivers and rural hospitals where cases were identified by trained community health workers and referred to hospitals), suggesting potential generalisability of the study results.

The trial has some limitations. The design of the trial was open-label; masking was not possible for ethical reasons. However, treatment failures were assessed by a second independent assessor who was masked to treatment allocation. The study sample included few infants aged 0–6 days, which limits the applicability of the results for this age group. We treated clinical signs of severe infection, which is a clinical syndrome instead of a confirmed bacterial infection. We believe that this approach was appropriate, because the purpose of the trial was to develop alternative treatment strategies for settings in which hospital care is either not accessible or not acceptable to the family. In these settings, laboratory-based diagnosis of bacterial infection will not generally be available. These infants are also the most likely to die from clinical signs of severe infection. Even in high-income settings, early treatment of clinical signs of severe infection is often based on clinical suspicion, because culture methods are slow and not sensitive. For ethical reasons, we recruited infants whose caregivers did not accept hospital admission. However, less than 20% of caregivers accepted hospital admission and the case fatality ratio in the infants enrolled in the study was similar to that in infants who were admitted to hospital.

In low-resource settings, reliance on a strategy of hospital admission for young infants with clinical signs of severe infection has several inherent disadvantages. In many settings, most young infants who are referred might not be able to get to a hospital and might not receive treatment, which increases their risk of death.[31] Furthermore, hospital beds are often not available for admission of all young infants with clinical signs of severe infection. To provide treatment options for such settings, and by building on WHO guidelines for treatment of pneumonia and previous community-based neonate research, we identified and provided evidence of the safety and efficacy of two antibiotic regimens that can be used to treat clinical signs of severe infection in young infants as hospital outpatients or in the community. The alternative regimens require fewer injections than standard outpatient care, which potentially makes them more feasible to deliver, more accessible, and more acceptable to families. These regimens provide a strategy for treatment of young infants with clinical signs of severe infection in resource-poor settings with poor access to hospital care.

The purpose of the study was not to show that outpatient treatment with antibiotic regimens is equivalent to hospital care. Instead, we aimed to provide evidence for care of young infants for whom hospital care is not accessible or acceptable. Safe delivery of these potential new treatment

Panel: Research in context

Systematic review

In September, 2007, WHO, USAID, and SNL/SCF convened an expert consultation[26] on community-based approaches to management of neonatal infection to discuss programme needs and identify crucial research to accelerate the availability and use of safe, effective, affordable, simple, and feasible community case-management approaches for neonatal infection among families with no or little access to facility-based care. The meeting objectives were to: review the evidence from recent studies on safety, efficacy or effectiveness, feasibility, acceptability, and use of community-based management approaches to neonatal sepsis including community identification of cases, antibiotic regimens, care-seeking behaviours, health-system challenges, and ethical issues; identify, review, and rank key issues that, if addressed, will lead to expanded access to care and enable development of focused short-term programme approaches and a research agenda to address the issues not answered by the completed or ongoing studies; and outline and design priority research studies that would support the development of programmes to increase access to management of sepsis in neonates. We participated in the consultation and presented primary data from our own research. The expert panel decided that research to assess simplified antibiotic therapies with reduced numbers of injections combined with oral antibiotics for the treatment of infections in neonates would be the crucial next step, because it would extend access to treatment in settings where hospital care is not accessible or acceptable.

Interpretation

To our knowledge, this is the first study to assess the safety and efficacy of simplified antibiotic regimens for outpatient treatment of clinical signs of severe infection in neonates and young infants. Two other studies with similar designs were done concurrently, one in Africa[27,28] and the other in Pakistan. Our results provide evidence that simplified antibiotic regimens with a reduced number of injections are as efficacious as the standard regimen for outpatient treatment of clinical signs of severe infection in young infants. The alternative regimens could provide treatment options for many more infants with clinical signs of severe infection who live in resource-poor settings where hospital care is not accessible.

options will need substantial input into training and strengthening of primary health-care systems. Development of context-specific delivery systems will be important to ensure availability of trained health workers, supply of commodities, and adequate monitoring, supervision, and support for primary health-care systems.

Contributors

AHB, SKS, REB, MSh, and NBr, had the original idea and designed the trial protocol. AHB wrote the final protocol with all members of the study team. AHB, SKS, ASMNUA, IQ, and DER prepared the case report forms and standard operating procedures. ASMNUA, IQ, DER, MSa, AM, MHR, AKMS, WA, SMSBT, DKM, NBe, MI, MIM, and SEA ran the trial. SC wrote the plan of analysis in collaboration with AHB, LCM, and SKS. SC and NBe did the statistical analysis. AHB wrote the manuscript with input from all authors.

Declaration of interests

We declare no competing interests.

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