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Day clinic versus hospital care of pneumonia and severe malnutrition in children under five: a randomized trial

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Corresponding Author:	Mohammod Jobayer Chisti, MBBS, MMed (Pediatrics), PhD (Ped. Resp. Med) International centre for Diarrhoeal Disease Resaerch, Bangladesh (ICDDR,B) Dhaka, BANGLADESH
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	International centre for Diarrhoeal Disease Resaerch, Bangladesh (ICDDR,B)
Corresponding Author's Secondary Institution:	
First Author:	Hasan Ashraf, MBBS
First Author Secondary Information:	
Order of Authors:	Hasan Ashraf, MBBS
	Nur H. Alam, MBBS, MD
	Marufa Sultana, MBBS, MPH
	Selina A. Jahan, MBBS
	Nurshad Begum, MBBS
	Sharmin Farzana, MPH
	Mohammod Jobayer Chisti, MBBS, MMed (Pediatrics), PhD (Ped. Resp. Med)
	Tahmeed Ahmed, MBBS, PhD
	Jahangir A. M. Khan, PhD
	George J Fuchs, MD
	Trevor Duke, MD, FRACP
	Niklaus Gyr, MD, MPH, MD
Order of Authors Secondary Information:	
Manuscript Region of Origin:	BANGLADESH
Abstract:	Objectives: To evaluate the clinical outcomes and costs of managing pneumonia and severe malnutrition in a day clinic management (DC) model (outpatient) compared to hospital care (inpatient). Methods: A randomized clinical trial where children aged 2 months to 5 years with pneumonia and severe malnutrition were randomly allocated to DC or inpatient hospital care. We used block randomization of variable length from 8-20 and produced computer-generated random numbers that were assigned to one of the two interventions. Successful management was defined as resolution of clinical signs of pneumonia and being discharged from the model of care (DC or hospital) without need for referral to a hospital (DC), or referral to another hospital. All the children in both DC and hospital received intramuscular ceftriaxone, daily nutrition support and

	micronutrients. Results: 470 children were randomly assigned to either DC or hospital care. Successful management was achieved for 184 of 235 (78.3%) by DC alone, compared to 201 of 235 (85.5%) by hospital inpatient care [RR (95% CI) = 0.79 (0.65 – 0.97), p=0.02]. During 6-months of follow-up, 30/235 (12.8%) and 36/235 (15.3%) required readmission to hospital in the DC and hospital care groups respectively [RR (95% CI) = 0.89 (0.67 – 1.18), p=0.21]. The average overall health care and societal cost was 34% lower in DC (US$ 188±11.7) compared to hospital (US$ 285±13.6) (p<0.001), and 33% lower cost for households. Conclusions: There was a 7% greater probability of successful management of pneumonia and severe malnutrition when inpatient hospital care rather than the outpatient day clinic care was the initial method of care. However, where timely referral mechanisms were in place, 94% of children with pneumonia and severe malnutrition were successfully managed initially in a DC, and costs were substantially lower than with hospital admission.

Author statement

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I have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

I have drafted the work or revised it critically for important intellectual content; AND

I have approved the final version to be published; AND

I agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All persons who have made substantial contributions to the work reported in the manuscript, including those who provided editing and writing assistance but who are not authors, are named in the Acknowledgments section of the manuscript and have given their written permission to be named. If the manuscript does not include Acknowledgments, it is because the authors have not received substantial contributions from nonauthors.

Attachment: Yes No (circle)

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Author signature

Hasan Ashraf (deceased) _____

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Day clinic versus hospital care of pneumonia and severe malnutrition in children under five: a randomized trial

Short title: Day clinic versus hospital care management

Hasan Ashraf, MBBS, MCPH, MD[a*], Nur H. Alam, MBBS, MD[a], Marufa Sultana, MBBS, MPH[a], Selina A. Jahan, MBBS[a], Nurshad Begum, MBBS[a], Sharmin Farzana, MPH[a], Mohammod J. Chisti, MBBS, MMed, PhD[a], Mohiuddin Kamal, MBBS[b], Abu Shamsuzzaman, MBBS[c], Tahmeed Ahmed, MBBS, PhD[a], Jahangir A. M. Khan, PhD[a], George J Fuchs, MD[d], Trevor Duke, MD, FRACP[e], Niklaus Gyr, MD, MPH[f]

Affiliations:
[a] icddr,b (International Centre for Diarrhoeal Disease Research, Bangladesh)
[b] Radda Maternal and Child Health (MCH)-Family Planning (FP) Centre, Dhaka, Bangladesh
[c] ICHSH (Institute of Child Health and Shishu Sasthya Foundation Hospital, Dhaka, Bangladesh)
[d] Department of Pediatrics, University of Kentucky College of Medicine, Lexington, KY, USA
[e] Centre for International Child Health, University of Melbourne, MCRI, Melbourne, Australia
[f] Faculty of Medicine, University of Basel, Switzerland

*Dr Hasan Ashraf tragically died of colon cancer in 2015 after drafting the original manuscript. Publication of this study pays tribute to Dr Ashraf's tireless work over two decades to research and improve child health and nutrition in Bangladesh.

Address of correspondence to: Dr Mohammod Jobayer Chisti, Senior Scientist, Dhaka Hospital, Nutrition and Clinical Services Division, icddr,b; 68 Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka 1212, Bangladesh; Email: chisti@icddrb.org

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Abbreviations:

DC	Day care management
WFL	Weight for Length
NCHS	National Center for Health statistics
RR	Relative Risk
CI	Confidence interval
SD	Standard Deviation
IQR	Inter-quartile Range
US$	United States Dollar
SAM	Severe Acute Malnutrition
MAM	Moderate Acute Malnutrition
RCT	Randomized Clinical Trial
RDI:	Recommended Daily Intake
MCH	Maternal and Child Health
ICHSH	Institute of Child Health and Shishu Saystha Foundation Hospital
WHO	World Health Organization
WAZ/ZWA	Weight for Ag Z score
HAZ/ZHA	Height/Length for Ag Z score
WHZ/ZWH	Weight for Height/Length Z score
MUAC	Mid-Upper Arm Circumference
RRC	Research Review Committee
ERC	Ethical Review Committee
SpO_2	Arterial Oxygen Saturation
NRU	Nutritional Rehabilitation Unit
SPSS	Statistical Package for Social Sciences
CHD	Congenital Heart Disease

Table of Contents Summary: We reported management of children with severe pneumonia and severe malnutrition by day clinic approach compared to hospital care.

What is known on this subject: Three studies including one RCT on severe pneumonia excluding severe malnutrition indicated that the day clinic approach is safe, effective and a less expensive alternative to hospitalization if the patients in the clinic are closely monitored.

What this study adds: Children with pneumonia and severe malnutrition were managed successfully by a day clinic approach, as long as timely and effective referral mechanisms were in place. Costs were substantially lower with DC compared to hospital care, including household costs.

Contributor`s statements

Hasan Ashraf: Dr. Ashraf conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and died before the submission of the final manuscript.

Nur H. Alam: Dr Alam also carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Marufa Sultana: Ms Marufa carried out initial analyses especially in cost analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Selina A. Jahan: Dr Jahan is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Nurshad Begum: Dr Begum is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Sharmin Farzana: Dr Farzana is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Mohammod J. Chisti: Dr Chisti helped to carry out the initial analyses, reviewed and revised the manuscript, coordinated with all the authors to compile all the revised drafts and approved the final manuscript as submitted.

Mohiuddin Kamal: Dr Kamal is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Abu Shamsuzzaman: Dr Shamsuzzaman is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Tahmeed Ahmed: Dr Ahmed helped in analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Jahangir A. M. Khan: Dr Khan helped in analyses especially in cost analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

George J Fuchs: Dr Fuchs helped in analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Trevor Duke: Professor Duke helped in analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Niklaus Gyr: Professor Gyr conceptualized and designed the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: To evaluate the clinical outcomes and costs of managing pneumonia and severe malnutrition in a day clinic management (DC) model (outpatient) compared to hospital care (inpatient).

Methods: A randomized clinical trial where children aged 2 months to 5 years with pneumonia and severe malnutrition were randomly allocated to DC or inpatient hospital care. We used block randomization of variable length from 8-20 and produced computer-generated random numbers that were assigned to one of the two interventions. Successful management was defined as resolution of clinical signs of pneumonia and being discharged from the model of care (DC or hospital) without need for referral to a hospital (DC), or referral to another hospital. All the children in both DC and hospital received intramuscular ceftriaxone, daily nutrition support and micronutrients.

Results: 470 children were randomly assigned to either DC or hospital care. Successful management was achieved for 184 of 235 (78.3%) by DC alone, compared to 201 of 235 (85.5%) by hospital inpatient care [RR (95% CI) = 0.79 (0.65 – 0.97), p=0.02]. During 6-months of follow-up, 30/235 (12.8%) and 36/235 (15.3%) required readmission to hospital in the DC and hospital care groups respectively [RR (95% CI) = 0.89 (0.67 – 1.18), p=0.21]. The average overall health care and societal cost was 34% lower in DC (US$ 188±11.7) compared to hospital (US$ 285±13.6) (p<0.001), and 33% lower cost for households.

Conclusions: There was a 7% greater probability of successful management of pneumonia and severe malnutrition when inpatient hospital care rather than the outpatient day clinic care was the initial method of care. However, where timely referral mechanisms were in place, 94% of children with pneumonia and severe malnutrition were successfully managed initially in a DC, and costs were substantially lower than with hospital admission.

Clinical Trial Registration**:** www.clinicaltrials.gov (identifier NCT00968370)

INTRODUCTION

The fourth Millennium Development Goal identified priority areas for improving child survival globally with the aim of reducing national child mortality rates by two-thirds from 1990-2015. This was substantially achieved in many countries, however the commonest causes of child death still include pneumonia and malnutrition.(1-3). Each year ~~T~~there are over 150 million cases of pneumonia in children under the age of 5 years, including over 60 million cases in South Asia~~, each year~~. There are 1.7 and 3.6 million annual child deaths in developing countries associated with severe acute malnutrition (SAM) and moderate acute malnutrition (MAM), respectively (4). There is substantial overlap: 22-40% of children with severe pneumonia also have malnutrition (5, 6). Children who present with both pneumonia and malnutrition are among the most vulnerable with a mortality rate as high as 23% that is up to 15 times higher than children with pneumonia who do not have severe malnutrition (7). Treatment of such children therefore must include nutritional rehabilitation, and careful follow-up and monitoring to detect complications and the deteriorating patient if mortality is to be minimized.

Day clinic management

Many low-income countries including Bangladesh do not have enough hospital beds to accommodate all children with pneumonia and severe malnutrition. In addition, there are disadvantages for families if hospitalization is prolonged. These include the cost of transportation, lost wages, long distances from hospital, the care of other children and other household responsibilities. Further, prolonged hospitalization carries substantial risks of nosocomial infections.

We developed a model of day clinic management (DC) (8-10). While DC of childhood illnesses is not new, it is typically reserved for children with illnesses of low severity. Previous studies of DC management include two uncontrolled observational studies, one on children with severe malnutrition (9), another on children with pneumonia (8) and one randomized controlled trial of children with pneumonia excluding severe malnutrition (10). These indicate that DC management ~~is~~ can be a safe, effective and a less expensive alternative to hospitalization if a clinic is well equipped with skilled staff and good supervision and close monitoring on a daily basis. However, no trials have examined whether DC management is superior/non-inferior to hospitalization for children with both pneumonia and severe malnutrition.

We report the results of a randomized controlled trial comparing DC in a well-equipped and well-staffed clinic with hospital care for children with both severe pneumonia and severe malnutrition. Thus, we hypothesized that successful management of children with severe pneumonia (previous WHO classification, of cough and difficult breathing and chest indrawing without hypoxaemia or emergency signs) in DC would be as good as inpatient h~~H~~ospital care.

PATIENTS AND METHODS

Study settings

The Radda Maternal and Child Health Family Planning Centre (Radda clinic) in Dhaka was the site for DC. Radda clinic is run by a non-government organization that has provided maternal and child health (MCH) services since 1974. It is located in the Mirpur area in urban Dhaka, approximately 2 Km away from the referral hospital. The clinic is open from 8am to 5pm daily. The clinic has eight beds, one physician, two nurses and four health care workers. In this study

hospital care was at the Institute of Child Health and Shishu Saystha Foundation Hospital (ICHSH). This has eight beds, two physicians, four nurses, two research assistants and four health care workers providing 24-hours inpatient care (10). Same ~~R~~resources for the management of pneumonia and malnutrition were available at both sites, including oxygen therapy, pulse oximetry, suction equipment, nebulizer, glucometer, and weighing scales.

Study design

This was a parallel type of RCT where our allocation ratio was 1:1. This trial was designed to compare clinical outcomes and cost of DC with that of hospital care for the treatment of children with pneumonia and severe malnutrition. The Research Review Committee (RRC) and Ethical Review Committee (ERC) of icddr,b approved the study. This trial was registered at www.clinicaltrials.gov (identifier NCT00968370).

Participants

Children 2-59 months of age with WHO defined pneumonia and severe malnutrition were enrolled from November 2008 to April 2013. Severe pneumonia was defined as cough or difficult breathing with lower chest wall in-drawing, according to the previous WHO criteria for severe pneumonia (11) (this classification was amended as pneumonia, or chest-indrawing pneumonia in 2013 (12)). We excluded all children with what was previously classified as very severe pneumonia (the presence of cyanosis or danger signs). Severe malnutrition, one of our inclusion criteria, was defined as one or more of the following criteria: (i) weight for height/length less than minus 3 Z-scores (<-3 WHZ), (ii) weight for age less than minus 3 Z-scores (<-3 WAZ), (iii) height/length for age less than minus 3 Z-scores (<-3 HAZ), (iv) bilateral

pitting oedema, (v) mid upper arm circumference (MUAC) <115 mm in children 6-59 months old. Children with suspected severe sepsis (Severe sepsis was defied as sepsis plus the presence of poor peripheral perfusion (weak or absent peripheral pulses), and capillary refill time greater than 3 sec or hypotension (5). Sepsis was defined as the presence or presumed presence of infection with hyperthermia or hypothermia (rectal temperature >38·5°C or <35·0°C, respectively) and tachycardia (5)), meningitis, convulsions or other life threatening illness, and those living more than 5km from the DC clinic were excluded from the study.

Intervention

Case management was carried out in stages: an acute phase management of pneumonia with severe malnutrition followed by a nutrition rehabilitation phase, then follow-up for at least 6 months after discharge (9, 13). This followed the WHO protocol for severely malnourished children (14) and for severe pneumonia (11) modified for DC management(8-10). Interventions were assigned in DC and Hospital care management.

DC intervention: At Radda day clinic parents brought their sick children at 8am and returned home at 5pm daily, including on weekends and public holidays. Oxygen saturation was measured using pulse oximetry and oxygen was administered to children with SpO_2<90%. If a patient had hypoxemia after 5 pm, that patient was referred to another hospital with higher greater facilities. They received once-daily injections of ceftriaxone: 75-100 mg/kg for 5 days (15). This is the only deviation ofrom the WHO protocol that we have purposefully done for this trial mainly to have adequateto maintain compliance of the patients/care givers by avoiding daily four doses of injections of aAmpicillin/pPenicillin as this is not practical for this trialper day. Mothers were encouraged to breast feed. As we did not screen for the nutritional status of the

mothers we thus are unable to correlate their nutritional status with that of their children.

Children who were not being breast fed were offered milk-based therapeutic diets: milk-suji, milk-suji 100 (mixture of cow's milk, rice powder, sugar, soy oil, 100 Kcal/100 g boiled for 7-10 minutes), infant formula, vitamin A, multivitamins, folic acid, zinc, potassium, and magnesium(9). Mothers and caretakers received practical training in the preparation of diets.

Hospital care intervention: Children assigned randomly to hospital care received similar treatment: daily ceftriaxone and supportive care including ~~where needed~~ oxygen therapy, micronutrients and therapeutic diet.

DC and hospital management continued until the child fulfilled the following criteria for at least 5 days: afebrile, respiratory rate within the normal range, no or mild chest wall indrawing, no danger signs, and SpO_2>90% off oxygen for at least 24 hours (10). The patients were then transferred to a nutritional rehabilitation diet and received culturally acceptable meals of khichuri, halwa, and milk-suji 100 (9). Children of both groups received this diet until they attained adequate weight targets [weight for height (W/H) of 80% of National Centre for Health Statistics (NCHS) median]. An ~~approximate~~ estimated daily energy intake during the nutritional rehabilitation phase ranged from 150 to 250 Kcal/kg per day.

Follow-up: At the time of discharge from clinic or hospital, parents were advised to attend follow-up clinic each week for two weeks, then every two weeks for three months and finally on a monthly basis for six months. At each follow up visit, a study physician interviewed mothers or guardians about signs/symptoms of specific morbidities since the previous visit. Morbidity

data, including subsequent respiratory and diarrhoea illnesses were recorded (8-10). The weight for age Z score (ZWA), weight for length/height Z score (ZWH) and height for age Z score (ZHA) were calculated. We also recorded unscheduled visits, readmission to hospitals, and deaths.

Outcomes

The primary outcome was the success of management and components of this are deaths/discontinuation/referral and readmission.

~~The primary outcome was the successful management of study children in both the interventions. The success of management was defined as a composite of discharge from the model of care (DC or hospital) after disappearance of clinical signs of severe pneumonia without need for referral to another hospital, and overall weight for length/height (WFL) ≥80% of the NCHS median at the time of discharge.~~

~~Primary outcome measures were the proportion of children successfully managed at respective study sites, the proportion of children requiring referral or readmission to hospitals, the proportions of children who died or discontinued the study, and the proportions of children who required referral or readmission to hospital during 6 months of follow-up. The study groups were compared at discharge from the clinic/hospital and during 6 months of follow-up.~~

The secondary outcomes were ~~of~~ the ~~study was an average overall~~ health care, provider and ~~societal~~ household costs ~~among~~ between the groups.

~~C~~In the cost analysis

~~A~~an "i~~I~~ngredient approach" was used to calculate the cost of treatments for both facilities. According to this approach, all inputs related to the treatment need to be identified, quantified and valued (16). Applying this method, listing all resources were done whether they were measurable or not, then quantified and finally valued them with their unit price. The calculation of the total cost borne by each facility was done by quantities of resources multiplied by the unit prices of those resources by respective facility (16). Direct costs measured the costs incurred directly during treatment procedure. Direct medical cost is healthcare-related costs spent for the prevention, detection, treatment, continuing care, rehabilitation, or terminal care of patients (17). Direct non-medical costs were considered as cost for non-healthcare related services such as transportation costs, food costs, lodging, and other costs related to hospitalization (e.g. plates, soaps, glasses, mugs etc.). To determine provider costs, medical and non-medical costs such as cost ~~of medicine~~of medicine, diagnostic tests, oxygen, micronutrients, therapeutic diet, transportation, and food cost were ~~estimated and~~estimated and summed-up for measuring total costs borne by each provider. Unit price of the medical equipment and other inputs were taken from the project's financial document and then calculated according to their measurement unit. Facility costs were estimated by summing the capital and recurrent cost items. Capital cost was considered as assets that are usually invested in bulk and used over time (for more than one year) (18). Annual values of capital items were estimated from their expected useful life years by applying 3% discounting rate. Items ~~those~~ purchased regularly within a year were considered as recurrent costs. Facility costs per patient were calculated by dividing the total facility costs with the number of patients treated by the respective facility. Costs incurred for referred cases from

DC to hospital care, costs borne for the additional treatment pathway was calculated and added as DC cost.

Household costs was estimated by including direct medical costs incurred by families, direct non-medical costs and indirect costs where indirect costs or loss of productivity were measured by applying a human capital approach (19). Indirect costs included lost wages due to lost work time by the patients, their caregivers, and their substitutes. The human capital method measures any lost production, in terms of lost earnings of a patient or caregiver (19). Self reported salary was applied to value their lost time. Societal cost resulted from the summation of net provider cost (excluding any fees received from households) and household costs for treating severe pneumonia with SAM. Results expressed as average cost (mean, SD) per patient treated.

Sample size

The sample size was estimated based on a success rate of 88% in a study conducted by Ashraf et al. wher~~en~~ severe pneumonia (previous WHO classification) in children was treated by DC management (10), and a maximal ~~expected~~ estimated hospital success rate of 96%. With 90% power and 5% significance, the required sample size was 235 for each of the two treatment groups.

In order to assess the cost and characteristics of the two management strategies, we used a process of opportunistic sampling. According to central limit theorem, at least 30 cases are required for calculation of means with an assumption of normal distribution(16). Therefore, we targeted double i.e. 60 from each facility, estimating a total of 120 such children.

Randomisation

After fulfilling eligibility criteria and obtaining written informed parental consent, children were randomly assigned to either DC at Radda clinic or hospital care at ICHSH. We used block randomization of variable length from 8-20 and produced computer-generated random numbers that were assigned to one of the two interventions.

Blinding

The random numbers corresponding to specific interventions were sealed in sequentially numbered envelopes arranged in an ascending order. Treatment was assigned at enrollment through opening of sequentially numbered envelopes. Until envelopes were opened, neither parents/legal guardian nor physicians/nurses were aware of treatment groups.

Statistical Methods

All data were collected on case report forms and entered into a personal computer and analyzed using statistical software Statistical Package for Social Sciences for Windows (Version 20.0. Armonk, NY, IBM Corp) and Epi Info (version 7.0, Epi Info™ software; Center for Disease Control and Prevention, Atlanta, GA, USA). Continuous variables were compared between groups using Student's t-test and Mann Whitney test. Dichotomous variables were analyzed using x2-test or Fisher's exact test, as appropriate. A probability of <0.05 was considered statistically significant.

RESULTS

Between November 2008 and April 2013, 1338 children were screened at Radda clinic and ICHSH; 868 were not eligible (Figure 1). The cost analysis was carried out among patients recruited between January 1st 2012 and February 28th 2013. Four hundred and seventy children

with severe pneumonia and severe malnutrition were enrolled: 24% recruited at the Radda Clinic and 76% at the hospital, and 235 were assigned to each treatment group. No significant differences in patient characteristics or nutritional status were observed at baseline (Tables 1 and 2). The median age was 10.1 months (inter-quartile range: 6.0-16.5 months). Sixty-five percent of children came from poor families, as defined by a monthly income of less than US$100. Fifty-four percent of the fathers were day labourers, rickshaw pullers, or garments workers, and 74% of the mothers were engaged in home duties and had no outside employment. Eleven percent of children had hypoxemia (Table1) and 32 (7%) had oedema (Table 2).

Primary clinical outcomes

Successful management was achieved for 184 of 235 (78.3%) by DC alone, compared to 201 of 235 (85.5%) by hospital inpatient care [RR (95% CI) = 0.79 (0.65 – 0.97), p=0.02]. Management was successful overall for children in DC plus hospital referral when needed in 220 (93.6%), and inpatient hospital care plus referral to a higher facility in 223 (94.9%) respectively. The mean (± SD) time (days) required to treatment success with DC was marginally longer compared to hospital care [7.9 (5.5) vs. 7.1 (3.1), p=0.04] (Table 4).

Of the remaining 51 (22%) DC patients, 36 (15%) were referred to hospital and 15 (6%) were withdrawn from the study (causes of withdrawal listed in the trial profile) (Table 3). Of the remaining 34 (15%) hospital care children, 22 (9%) were referred to other hospitals and 10 (4%) discontinued treatment (Table 3). Differences in referral and discontinuation of treatment between the interventions were statistically not significant (Table 3).

Three deaths occurred among children in the DC group and four deaths among the hospital group. Over the 6 months of follow-up 30 (13%) and 36 (15%) required readmission to hospital and three (1.3%) and two (0.9%) died in the DC and hospital groups, respectively (Table 3). Readmissions were due to severe pneumonia (n=30), very severe pneumonia with hypoxaemia (n=17), diarrhoea and dehydration (n=8). Other causes of readmission were typhoid fever (n=3), congenital heart disease (CHD) (n=3), pulmonary tuberculosis (n=1), asthma (n=1), influenza (n=1), intracranial haemorrhage (n=1), and pseudotumour cerebri (n=1). All the readmitted children had severe malnutrition.

Cost of treatment

One hundred and twenty children were evaluated as part of the cost analysis. Both DC and hospital care groups were similar with regard to age, sex distribution and socio-economic status. The mean household income per month was US$141 and US$136 for the DCA and hospital care respectively. The average monthly expenditure of the household was US$9 and US$6 for DCA and hospital care respectively.

The average societal cost per child treated was 34.4% lower in DC (US$ 184.27±11.7) compared to hospital care (US$ 280.88±13.6). Including all clinical procedures as well as follow up, the average provider cost per child was US$165.17 ±30.29 in DCA and US$252.08 ±24.20 in hospital (Table 5). Distribution ~~of the Breakdown~~ of provider costs per child across types of care showed that facility costs were highest for both service providers (DC Vs Hospital care: 54% Vs 66%) followed by direct medical costs (DC Vs Hospital care: 43% Vs 32%). Non-medical costs from provider aspect ~~s~~ caused a minor part of total cost only~~had minor contribution amongst total expense~~ (3% and 2% for DC and hospital care respectively). ~~showed medical, non-medical and~~

~~facility costs constituting approximately 43%, 3% and 54% for DC, and 32%, 2% and 66% for hospital care respectively~~. Medical cost comprised of all direct costs incurred by the provider like personnel, medicine, equipments, oxygen, diagnostic and other direct costs.

Among the medical costs, personnel costs were highest, amounting to US$58.30 for DCA and US$65.16 for hospital care. Antibiotics, micronutrients, diagnostic tests and supportive care resulted in 19% of medical cost per child in both facilities. Facility cost incorporated all capital and recurrent cost items that were used during the study period. Costs incurred by the household including follow-up were also lower (33.8%) in case of DC (US$ 19.1±5.6) compared to hospital care (US$ 28.8±8.9) ($p<0.001$). This equates to 14% and 21% of average monthly household incomes respectively. Travel costs were a major ~~cost driver~~contribution among household costs and constituted 60% and 45% of average household costs for DCA and hospital respectively. Further, estimated productivity loss (income loss during care giving) was ~~higher~~ double that in ~~case of~~the hospital care group compared to DCA (Table 5).

DISCUSSION

To our knowledge, this study is the first randomised controlled trial comparing the clinical and costs of outpatient day clinic with primary hospital management for children with both pneumonia and severe malnutrition. There was a 7% greater probability of successful management when children were managed in hospitals than only in DC. However the overall outcome of children managed in the health service system *as a whole*, i.e. outpatient DC plus hospital referral if needed, and inpatient hospital care plus referral to a higher facility were similar with successful management in 94% and 95% respectively.

There were no differences in deaths during either active treatment phase or 6 months of follow up (total of 6 deaths in each group). The relatively low mortality rate was mostight have been likely due to exclusion of children with high-risk co-morbidities, and the close monitoring that was provided in the context of a trial. Outpatient management was made safer by checking for danger signs and for hypoxemia using pulse oximetry, providing health education for mothers, and close daily follow-up.

Overall, the time needed to reach target weight gain in both groups was short. The predominant stunted character of our study population might explain this on enrolment. As the study children were severely undernourished and simultaneously most of them were stunted, there is potential to have a limited incremental body-mass. This is common finding in the Indian sub-continent.

Duration of resolution of clinical signs of pneumonia in both groups was at least five days, which was reasonably long. All the children in the study had severe malnutrition and might be immune-compromised which potentially required longer time for antibiotics and other supportive therapy to work for the normalization of clinical signs of pneumonia. Another important aspect of this study is the requirement of less than one-day duration for treatment success in DC compared to hospital care, although the difference was statistically significant. Still, this signifies that the treatment in the day care may be convenient.

Readmission was common in both groups. Persistence of a relatively poor nutritional status impairs immunity and increases the risk of new infections (20), such as pneumonia and diarrhea

(21), even after apparent recovery from the primary illness. So even if the target weight was reached, the children's poor nutritional state continued to affect their health.

The average societal cost per patient for treatment was significantly lower among the DC group of children compared to hospital group (p=0.001), and there were cost savings for families from DC. The calculation of DC costs were all-inclusive, including costs of the referral hospital in case of DC failure. Medical and health facility costs were the highest component; health care facilities providing services to patients for 24 hours a day will understandably cost more than outpatient clinics that provide care for 9 hours per day. Other studies have shown that pneumonia treatment is more expensive when inpatient care is required (19, 22). A study from south India found that the average outpatient costs to treat a child with pneumonia was US$13 while inpatient costs were estimated to be US$71 and US$235 for pneumonia and severe pneumonia, respectively (19) .

Analysis showed that travel cost was higher amongst hospital care group, However, this ~~dissimilarity~~ difference may~~ight~~ be explained by the cultural ~~and real life aspect while patients~~factors such as patients' requiring assistance from ~~needs to be assisted by~~ caregivers and being provided food from the other members of ~~taken by them usually bring from~~ household. These frequent visits by different members of the household may increase travel costs.

~~Frequent visits to hospital by different members of the households throughout the treatment period might increase the travel cost of the households.~~

Societal costs were 34% lower ~~regarding~~ in the DC group and ~~while~~ households had 33% lower economic costs ~~could save 33% economic costs if receive treatment from DC.~~if receiving

treatment in this group. If cost savings of a similar magnitude as well as clinical effectiveness are maintained after scaling up, then this could be allocated to other essential areas. ~~If cost savings of similar magnitude as well as clinical effectiveness could be possible to maintain through scale up of the model, it would be possible to allocate valuable resources efficiently to other essential areas.~~ Generalisability and scaling however may be a challenge in rural areas as the DC model for managing severe pneumonia with severe malnutrition requires close monitoring, checking for danger signs, pulse oximetry, health literacy education for mothers and close daily follow up.~~However DC management is only safe if children are consistently checked for danger signs and pulse oximetry is used daily to check for hypoxemia, where appropriate health education is provided for mothers, and where there is close daily follow-up, although, generalisability of this management in rural settings may be pose a challenge.~~

Apart from the lower household expenses ~~in~~ the DC demonstrated the wider benefits to families were not systematically evaluated. Nevertheless, the field research team reported the impression that mothers appeared to prefer DC to hospital management mostly because they were better able to cope with their household responsibilities.

~~The main limitation of the study was to use of inj. ceftriaxone as the first line of treatment of severe pneumonia instead of ampicillin/penicillin and gentamicin mainly due to practical purpose. Another limitation was the use of a number of exploratory analyses, as those were not mentioned in the registered protocol.~~

CONCLUSIONS

Though successful management was slightly greater with hospital than with DC management

(86% HC vs 78% DC), with proper triage, supervision and monitoring, and referral when needed children with pneumonia and severe malnutrition were treated as successfully in DC as in hospitals (94% and 95% respectively)~~With proper triage, supervision and monitoring, and referral when needed children with pneumonia and severe malnutrition were treated as successfully in DC as in hospitals (94% and 95% respectively)~~. In environments with limited resources, a functioning DC model will- increase bed availability in hospitals for higher acuity admissions~~free up hospital beds to treat other and higher risk illnesses~~. With a modest investment to upgrade clinic facilities, train staff, and procure appropriate pulse oximetry monitoring and nutrition-care equipment, the DC approach is low cost and effective, as long as systems are in place for identifying children ~~who are~~ failing treatment and- requiring ~~appropriate~~ referral ~~systems are in place~~.

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Day clinic versus hospital care of pneumonia and severe malnutrition in children under five: a randomized trial

Short title: Day clinic versus hospital care management

Hasan Ashraf, MBBS, MCPH, MD[a*], Nur H. Alam, MBBS, MD[a], Marufa Sultana, MBBS, MPH[a], Selina A. Jahan, MBBS[a], Nurshad Begum, MBBS[a], Sharmin Farzana, MPH[a], Mohammod J. Chisti, MBBS, MMed, PhD[a], Mohiuddin Kamal, MBBS[b], Abu Shamsuzzaman, MBBS[c], Tahmeed Ahmed, MBBS, PhD[a], Jahangir A. M. Khan, PhD[a], George J Fuchs, MD[d], Trevor Duke, MD, FRACP[e], Niklaus Gyr, MD, MPH[f]

Affiliations:
[a] icddr,b (International Centre for Diarrhoeal Disease Research, Bangladesh)
[b] Radda Maternal and Child Health (MCH)-Family Planning (FP) Centre, Dhaka, Bangladesh
[c] ICHSH (Institute of Child Health and Shishu Sasthya Foundation Hospital, Dhaka, Bangladesh)
[d] Department of Pediatrics, University of Kentucky College of Medicine, Lexington, KY, USA
[e] Centre for International Child Health, University of Melbourne, MCRI, Melbourne, Australia
[f] Faculty of Medicine, University of Basel, Switzerland

*Dr Hasan Ashraf tragically died of colon cancer in 2015 after drafting the original manuscript. Publication of this study pays tribute to Dr Ashraf's tireless work over two decades to research and improve child health and nutrition in Bangladesh.

Address of correspondence to: Dr Mohammod Jobayer Chisti, Senior Scientist, Dhaka Hospital, Nutrition and Clinical Services Division, icddr,b; 68 Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka 1212, Bangladesh; Email: chisti@icddrb.org

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Abbreviations:

DC	Day care management
WFL	Weight for Length
NCHS	National Center for Health statistics
RR	Relative Risk
CI	Confidence interval
SD	Standard Deviation
IQR	Inter-quartile Range
US$	United States Dollar
SAM	Severe Acute Malnutrition
MAM	Moderate Acute Malnutrition
RCT	Randomized Clinical Trial
RDI:	Recommended Daily Intake
MCH	Maternal and Child Health
ICHSH	Institute of Child Health and Shishu Saystha Foundation Hospital
WHO	World Health Organization
WAZ/ZWA	Weight for Ag Z score
HAZ/ZHA	Height/Length for Ag Z score
WHZ/ZWH	Weight for Height/Length Z score
MUAC	Mid-Upper Arm Circumference
RRC	Research Review Committee
ERC	Ethical Review Committee
SpO_2	Arterial Oxygen Saturation
NRU	Nutritional Rehabilitation Unit
SPSS	Statistical Package for Social Sciences
CHD	Congenital Heart Disease

Table of Contents Summary: We reported management of children with severe pneumonia and severe malnutrition by day clinic approach compared to hospital care.

What is known on this subject: Three studies including one RCT on severe pneumonia excluding severe malnutrition indicated that the day clinic approach is safe, effective and a less expensive alternative to hospitalization if the patients in the clinic are closely monitored.

What this study adds: Children with pneumonia and severe malnutrition were managed successfully by a day clinic approach, as long as timely and effective referral mechanisms were in place. Costs were substantially lower with DC compared to hospital care, including household costs.

Contributor`s statements

Hasan Ashraf: Dr. Ashraf conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and died before the submission of the final manuscript.

Nur H. Alam: Dr Alam also carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Marufa Sultana: Ms Marufa carried out initial analyses especially in cost analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Selina A. Jahan: Dr Jahan is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Nurshad Begum: Dr Begum is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Sharmin Farzana: Dr Farzana is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Mohammod J. Chisti: Dr Chisti helped to carry out the initial analyses, reviewed and revised the manuscript, coordinated with all the authors to compile all the revised drafts and approved the final manuscript as submitted.

Mohiuddin Kamal: Dr Kamal is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Abu Shamsuzzaman: Dr Shamsuzzaman is one of the authors who designed the data collection instruments, and coordinated and supervised data collection at the site, critically reviewed the manuscript, and approved the final manuscript as submitted.

Tahmeed Ahmed: Dr Ahmed helped in analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Jahangir A. M. Khan: Dr Khan helped in analyses especially in cost analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

George J Fuchs: Dr Fuchs helped in analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Trevor Duke: Professor Duke helped in analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Niklaus Gyr: Professor Gyr conceptualized and designed the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: To evaluate the clinical outcomes and costs of managing pneumonia and severe malnutrition in a day clinic management (DC) model (outpatient) compared to hospital care (inpatient).

Methods: A randomized clinical trial where children aged 2 months to 5 years with pneumonia and severe malnutrition were randomly allocated to DC or inpatient hospital care. We used block randomization of variable length from 8-20 and produced computer-generated random numbers that were assigned to one of the two interventions. Successful management was defined as resolution of clinical signs of pneumonia and being discharged from the model of care (DC or hospital) without need for referral to a hospital (DC), or referral to another hospital. All the children in both DC and hospital received intramuscular ceftriaxone, daily nutrition support and micronutrients.

Results: 470 children were randomly assigned to either DC or hospital care. Successful management was achieved for 184 of 235 (78.3%) by DC alone, compared to 201 of 235 (85.5%) by hospital inpatient care [RR (95% CI) = 0.79 (0.65 – 0.97), p=0.02]. During 6-months of follow-up, 30/235 (12.8%) and 36/235 (15.3%) required readmission to hospital in the DC and hospital care groups respectively [RR (95% CI) = 0.89 (0.67 – 1.18), p=0.21]. The average overall health care and societal cost was 34% lower in DC (US$ 188±11.7) compared to hospital (US$ 285±13.6) (p<0.001), and 33% lower cost for households.

Conclusions: There was a 7% greater probability of successful management of pneumonia and severe malnutrition when inpatient hospital care rather than the outpatient day clinic care was the initial method of care. However, where timely referral mechanisms were in place, 94% of children with pneumonia and severe malnutrition were successfully managed initially in a DC, and costs were substantially lower than with hospital admission.

Clinical Trial Registration**:** www.clinicaltrials.gov (identifier NCT00968370)

INTRODUCTION

The fourth Millennium Development Goal identified priority areas for improving child survival globally with the aim of reducing national child mortality rates by two-thirds from 1990-2015. This was substantially achieved in many countries, however the commonest causes of child death still include pneumonia and malnutrition.(1-3). Each year there are over 150 million cases of pneumonia in children under the age of 5 years, including over 60 million cases in South Asia. There are 1.7 and 3.6 million annual child deaths in developing countries associated with severe acute malnutrition (SAM) and moderate acute malnutrition (MAM), respectively (4). There is substantial overlap: 22-40% of children with severe pneumonia also have malnutrition (5, 6). Children who present with both pneumonia and malnutrition are among the most vulnerable with a mortality rate as high as 23% that is up to 15 times higher than children with pneumonia who do not have severe malnutrition (7). Treatment of such children therefore must include nutritional rehabilitation, and careful follow-up and monitoring to detect complications and the deteriorating patient if mortality is to be minimized.

Day clinic management

Many low-income countries including Bangladesh do not have enough hospital beds to accommodate all children with pneumonia and severe malnutrition. In addition, there are disadvantages for families if hospitalization is prolonged. These include the cost of transportation, lost wages, long distances from hospital, the care of other children and other household responsibilities. Further, prolonged hospitalization carries substantial risks of nosocomial infections.

We developed a model of day clinic management (DC) (8-10). While DC of childhood illnesses is not new, it is typically reserved for children with illnesses of low severity. Previous studies of DC management include two uncontrolled observational studies, one on children with severe malnutrition (9), another on children with pneumonia (8) and one randomized controlled trial of children with pneumonia excluding severe malnutrition (10). These indicate that DC management can be a safe, effective and a less expensive alternative to hospitalization if a clinic is well equipped with skilled staff and good supervision and close monitoring on a daily basis. However, no trials have examined whether DC management is superior/non-inferior to hospitalization for children with both pneumonia and severe malnutrition.

We report the results of a randomized controlled trial comparing DC in a well-equipped and well-staffed clinic with hospital care for children with both severe pneumonia and severe malnutrition. Thus, we hypothesized that successful management of children with severe pneumonia (previous WHO classification, of cough and difficult breathing and chest indrawing without hypoxaemia or emergency signs) in DC would be as good as inpatient hospital care.

PATIENTS AND METHODS

Study settings

The Radda Maternal and Child Health Family Planning Centre (Radda clinic) in Dhaka was the site for DC. Radda clinic is run by a non-government organization that has provided maternal and child health (MCH) services since 1974. It is located in the Mirpur area in urban Dhaka, approximately 2 Km away from the referral hospital. The clinic is open from 8am to 5pm daily. The clinic has eight beds, one physician, two nurses and four health care workers. In this study

hospital care was at the Institute of Child Health and Shishu Saystha Foundation Hospital (ICHSH). This has eight beds, two physicians, four nurses, two research assistants and four health care workers providing 24-hours inpatient care (10). Same resources for the management of pneumonia and malnutrition were available at both sites, including oxygen therapy, pulse oximetry, suction equipment, nebulizer, glucometer, and weighing scales.

Study design

This was a parallel type of RCT where our allocation ratio was 1:1. This trial was designed to compare clinical outcomes and cost of DC with that of hospital care for the treatment of children with pneumonia and severe malnutrition. The Research Review Committee (RRC) and Ethical Review Committee (ERC) of icddr,b approved the study. This trial was registered at www.clinicaltrials.gov (identifier NCT00968370).

Participants

Children 2-59 months of age with WHO defined pneumonia and severe malnutrition were enrolled from November 2008 to April 2013. Severe pneumonia was defined as cough or difficult breathing with lower chest wall in-drawing, according to the previous WHO criteria for severe pneumonia (11) (this classification was amended as pneumonia, or chest-indrawing pneumonia in 2013 (12)). We excluded all children with what was previously classified as very severe pneumonia (the presence of cyanosis or danger signs). Severe malnutrition, one of our inclusion criteria, was defined as one or more of the following criteria: (i) weight for height/length less than minus 3 Z-scores (<-3 WHZ), (ii) weight for age less than minus 3 Z-scores (<-3 WAZ), (iii) height/length for age less than minus 3 Z-scores (<-3 HAZ), (iv) bilateral

pitting oedema, (v) mid upper arm circumference (MUAC) <115 mm in children 6-59 months old. Children with suspected severe sepsis (Severe sepsis was defied as sepsis plus the presence of poor peripheral perfusion (weak or absent peripheral pulses), and capillary refill time greater than 3 sec or hypotension (5). Sepsis was defined as the presence or presumed presence of infection with hyperthermia or hypothermia (rectal temperature >38·5°C or <35·0°C, respectively) and tachycardia (5), meningitis, convulsions or other life threatening illness, and those living more than 5km from the DC clinic were excluded from the study.

Intervention

Case management was carried out in stages: an acute phase management of pneumonia with severe malnutrition followed by a nutrition rehabilitation phase, then follow-up for at least 6 months after discharge (9, 13). This followed the WHO protocol for severely malnourished children (14) and for severe pneumonia (11) modified for DC management(8-10). Interventions were assigned in DC and Hospital care management.

DC intervention: At Radda day clinic parents brought their sick children at 8am and returned home at 5pm daily, including on weekends and public holidays. Oxygen saturation was measured using pulse oximetry and oxygen was administered to children with SpO_2<90%. If a patient had hypoxemia after 5 pm, that patient was referred to another hospital with greater facilities. They received once-daily injections of ceftriaxone: 75-100 mg/kg for 5 days (15). This is the only deviation from the WHO protocol to maintain compliance by avoiding four injections of Ampicillin/Penicillin per day. Mothers were encouraged to breast feed. As we did not screen for the nutritional status of the mothers we thus are unable to correlate their nutritional status with that of their children. Children who were not being breast fed were offered milk-based

therapeutic diets: milk-suji, milk-suji 100 (mixture of cow's milk, rice powder, sugar, soy oil, 100 Kcal/100 g boiled for 7-10 minutes), infant formula, vitamin A, multivitamins, folic acid, zinc, potassium, and magnesium(9). Mothers and caretakers received practical training in the preparation of diets.

Hospital care intervention: Children assigned randomly to hospital care received similar treatment: daily ceftriaxone and supportive care including oxygen therapy, micronutrients and therapeutic diet.

DC and hospital management continued until the child fulfilled the following criteria for at least 5 days: afebrile, respiratory rate within the normal range, no or mild chest wall indrawing, no danger signs, and SpO_2>90% off oxygen for at least 24 hours (10). The patients were then transferred to a nutritional rehabilitation diet and received culturally acceptable meals of khichuri, halwa, and milk-suji 100 (9). Children of both groups received this diet until they attained adequate weight targets [weight for height (W/H) of 80% of National Centre for Health Statistics (NCHS) median]. An estimated daily energy intake during the nutritional rehabilitation phase ranged from 150 to 250 Kcal/kg per day.

Follow-up: At the time of discharge from clinic or hospital, parents were advised to attend follow-up clinic each week for two weeks, then every two weeks for three months and finally on a monthly basis for six months. At each follow up visit, a study physician interviewed mothers or guardians about signs/symptoms of specific morbidities since the previous visit. Morbidity data, including subsequent respiratory and diarrhoea illnesses were recorded (8-10). The weight

for age Z score (ZWA), weight for length/height Z score (ZWH) and height for age Z score (ZHA) were calculated. We also recorded unscheduled visits, readmission to hospitals, and deaths.

Outcomes

The primary outcome was the success of management and components of this are deaths/discontinuation/referral and readmission. The secondary outcomes were the health care, provider and household costs between the groups.

In the cost analysis an "ingredient approach" was used to calculate the cost of treatments for both facilities. According to this approach, all inputs related to the treatment need to be identified, quantified and valued (16). Applying this method, listing all resources were done whether they were measurable or not, then quantified and finally valued them with their unit price. The calculation of the total cost borne by each facility was done by quantities of resources multiplied by the unit prices of those resources by respective facility (16). Direct costs measured the costs incurred directly during treatment procedure. Direct medical cost is healthcare-related costs spent for the prevention, detection, treatment, continuing care, rehabilitation, or terminal care of patients (17). Direct non-medical costs were considered as cost for non-healthcare related services such as transportation costs, food costs, lodging, and other costs related to hospitalization (e.g. plates, soaps, glasses, mugs etc.). To determine provider costs, medical and non-medical costs such as cost of medicine, diagnostic tests, oxygen, micronutrients, therapeutic diet, transportation, and food cost were estimated and summed-up for measuring total costs borne by each provider. Unit price of the medical equipment and other inputs were taken from the project's financial document and then calculated according to their measurement unit.

Facility costs were estimated by summing the capital and recurrent cost items. Capital cost was considered as assets that are usually invested in bulk and used over time (for more than one year) (18). Annual values of capital items were estimated from their expected useful life years by applying 3% discounting rate. Items purchased regularly within a year were considered as recurrent costs. Facility costs per patient were calculated by dividing the total facility costs with the number of patients treated by the respective facility. Costs incurred for referred cases from DC to hospital care, costs borne for the additional treatment pathway was calculated and added as DC cost.

Household costs was estimated by including direct medical costs incurred by families, direct non-medical costs and indirect costs where indirect costs or loss of productivity were measured by applying a human capital approach (19). Indirect costs included lost wages due to lost work time by the patients, their caregivers, and their substitutes. The human capital method measures any lost production, in terms of lost earnings of a patient or caregiver (19). Self reported salary was applied to value their lost time. Societal cost resulted from the summation of net provider cost (excluding any fees received from households) and household costs for treating severe pneumonia with SAM. Results expressed as average cost (mean, SD) per patient treated.

Sample size

The sample size was estimated based on a success rate of 88% in a study conducted by Ashraf et al. where severe pneumonia (previous WHO classification) in children was treated by DC management (10), and a maximal estimated hospital success rate of 96%. With 90% power and 5% significance, the required sample size was 235 for each of the two treatment groups.

In order to assess the cost and characteristics of the two management strategies, we used a process of opportunistic sampling. According to central limit theorem, at least 30 cases are

required for calculation of means with an assumption of normal distribution (16). Therefore, we targeted double i.e. 60 from each facility, estimating a total of 120 such children.

Randomisation

After fulfilling eligibility criteria and obtaining written informed parental consent, children were randomly assigned to either DC at Radda clinic or hospital care at ICHSH. We used block randomization of variable length from 8-20 and produced computer-generated random numbers that were assigned to one of the two interventions.

Blinding

The random numbers corresponding to specific interventions were sealed in sequentially numbered envelopes arranged in an ascending order. Treatment was assigned at enrollment through opening of sequentially numbered envelopes. Until envelopes were opened, neither parents/legal guardian nor physicians/nurses were aware of treatment groups.

Statistical Methods

All data were collected on case report forms and entered into a personal computer and analyzed using statistical software Statistical Package for Social Sciences for Windows (Version 20.0. Armonk, NY, IBM Corp) and Epi Info (version 7.0, Epi Info™ software; Center for Disease Control and Prevention, Atlanta, GA, USA). Continuous variables were compared between groups using Student's t-test and Mann Whitney test. Dichotomous variables were analyzed using x2-test or Fisher's exact test, as appropriate. A probability of <0.05 was considered statistically significant.

RESULTS

Between November 2008 and April 2013, 1338 children were screened at Radda clinic and ICHSH; 868 were not eligible (Figure 1). The cost analysis was carried out among patients recruited between January 1st 2012 and February 28th 2013. Four hundred and seventy children with severe pneumonia and severe malnutrition were enrolled: 24% recruited at the Radda Clinic and 76% at the hospital, and 235 were assigned to each treatment group. No significant differences in patient characteristics or nutritional status were observed at baseline (Tables 1 and 2). The median age was 10.1 months (inter-quartile range: 6.0-16.5 months). Sixty-five percent of children came from poor families, as defined by a monthly income of less than US$100. Fifty-four percent of the fathers were day labourers, rickshaw pullers, or garments workers, and 74% of the mothers were engaged in home duties and had no outside employment. Eleven percent of children had hypoxemia (Table1) and 32 (7%) had oedema (Table 2).

Primary clinical outcomes

Successful management was achieved for 184 of 235 (78.3%) by DC alone, compared to 201 of 235 (85.5%) by hospital inpatient care [RR (95% CI) = 0.79 (0.65 – 0.97), p=0.02]. Management was successful overall for children in DC plus hospital referral when needed in 220 (93.6%), and inpatient hospital care plus referral to a higher facility in 223 (94.9%) respectively. The mean (± SD) time (days) required to treatment success with DC was marginally longer compared to hospital care [7.9 (5.5) vs. 7.1 (3.1), p=0.04] (Table 4).

Of the remaining 51 (22%) DC patients, 36 (15%) were referred to hospital and 15 (6%) were withdrawn from the study (causes of withdrawal listed in the trial profile) (Table 3). Of the remaining 34 (15%) hospital care children, 22 (9%) were referred to other hospitals and 10 (4%)

discontinued treatment (Table 3). Differences in referral and discontinuation of treatment between the interventions were statistically not significant (Table 3).

Three deaths occurred among children in the DC group and four deaths among the hospital group. Over the 6 months of follow-up 30 (13%) and 36 (15%) required readmission to hospital and three (1.3%) and two (0.9%) died in the DC and hospital groups, respectively (Table 3). Readmissions were due to severe pneumonia (n=30), very severe pneumonia with hypoxaemia (n=17), diarrhoea and dehydration (n=8). Other causes of readmission were typhoid fever (n=3), congenital heart disease (CHD) (n=3), pulmonary tuberculosis (n=1), asthma (n=1), influenza (n=1), intracranial haemorrhage (n=1), and pseudotumour cerebri (n=1). All the readmitted children had severe malnutrition.

Cost of treatment

One hundred and twenty children were evaluated as part of the cost analysis. Both DC and hospital care groups were similar with regard to age, sex distribution and socio-economic status. The mean household income per month was US$141 and US$136 for the DCA and hospital care respectively. The average monthly expenditure of the household was US$9 and US$6 for DCA and hospital care respectively.

The average societal cost per child treated was 34.4% lower in DC (US$ 184.27±11.7) compared to hospital care (US$ 280.88±13.6). Including all clinical procedures as well as follow up, the average provider cost per child was US$165.17 ±30.29 in DCA and US$252.08 ±24.20 in hospital (Table 5). Distribution of provider costs per child across types of care showed that facility costs were highest for both service providers (DC Vs Hospital care: 54% Vs 66%)

followed by direct medical costs (DC Vs Hospital care: 43% Vs 32%). Non-medical costs from provider aspect caused a minor part of total cost only (3% and 2% for DC and hospital care respectively). . Medical cost comprised of all direct costs incurred by the provider like personnel, medicine, equipments, oxygen, diagnostic and other direct costs.

Among the medical costs, personnel costs were highest, amounting to US$58.30 for DCA and US$65.16 for hospital care. Antibiotics, micronutrients, diagnostic tests and supportive care resulted in 19% of medical cost per child in both facilities. Facility cost incorporated all capital and recurrent cost items that were used during the study period. Costs incurred by the household including follow-up were also lower (33.8%) in case of DC (US$ 19.1±5.6) compared to hospital care (US$ 28.8±8.9) ($p<0.001$). This equates to 14% and 21% of average monthly household incomes respectively. Travel costs were a major contribution among household costs and constituted 60% and 45% of average household costs for DCA and hospital respectively. Further, estimated productivity loss (income loss during care giving) was double that in the hospital care group compared to DCA (Table 5).

DISCUSSION

To our knowledge, this study is the first randomised controlled trial comparing the clinical and costs of outpatient day clinic with primary hospital management for children with both pneumonia and severe malnutrition. There was a 7% greater probability of successful management when children were managed in hospitals than only in DC. However the overall outcome of children managed in the health service system *as a whole*, i.e. outpatient DC plus hospital referral if needed, and inpatient hospital care plus referral to a higher facility were similar with successful management in 94% and 95% respectively.

There were no differences in deaths during either active treatment phase or 6 months of follow up (total of 6 deaths in each group). The relatively low mortality rate was most likely due to exclusion of children with high-risk co-morbidities, and the close monitoring that was provided in the context of a trial. Outpatient management was made safe by checking for danger signs and for hypoxemia using pulse oximetry, providing health education for mothers, and close daily follow-up.

Overall, the time needed to reach target weight gain in both groups was short. The predominant stunted character of our study population might explain this on enrolment. As the study children were severely undernourished and simultaneously most of them were stunted, there is potential to have a limited incremental body-mass. This is common finding in the Indian sub-continent.

Duration of resolution of clinical signs of pneumonia in both groups was at least five days. All the children in the study had severe malnutrition and might be immune-compromised which potentially required longer time for antibiotics and other supportive therapy to work for the normalization of clinical signs of pneumonia. Another important aspect of this study is the requirement of less than one-day duration for treatment success in DC compared to hospital care, although the difference was statistically significant. Still, this signifies that the treatment in the day care may be convenient.

Readmission was common in both groups. Persistence of a relatively poor nutritional status impairs immunity and increases the risk of new infections (20), such as pneumonia and diarrhea

(21), even after apparent recovery from the primary illness. So even if the target weight was reached, the children's poor nutritional state continued to affect their health.

The average societal cost per patient for treatment was significantly lower among the DC group of children compared to hospital group (p=0.001), and there were cost savings for families from DC. The calculation of DC costs were all-inclusive, including costs of the referral hospital in case of DC failure. Medical and health facility costs were the highest component; health care facilities providing services to patients for 24 hours a day will understandably cost more than outpatient clinics that provide care for 9 hours per day. Other studies have shown that pneumonia treatment is more expensive when inpatient care is required (19, 22). A study from south India found that the average outpatient costs to treat a child with pneumonia was US$13 while inpatient costs were estimated to be US$71 and US$235 for pneumonia and severe pneumonia, respectively (19) .

Analysis showed that travel cost was higher amongst hospital care group, However, this difference may be explained by the cultural factors such as patients' requiring assistance from caregivers and being provided food from the other members of household.
These frequent visits by different members of the household may increase travel costs.

Societal costs were 34% lower in the DC group and households had 33% lower economic costs if receiving treatment in this group. If cost savings of a similar magnitude as well as clinical effectiveness are maintained after scaling up, then this could be allocated to other essential areas. Generalisability and scaling however may be a challenge in rural areas as the DC model for

managing severe pneumonia with severe malnutrition requires close monitoring, checking for danger signs, pulse oximetry, health literacy education for mothers and close daily follow up. Apart from the lower household expenses the DC demonstrated the wider benefits to families were not systematically evaluated. Nevertheless, the field research team reported the impression that mothers appeared to prefer DC to hospital management mostly because they were better able to cope with their household responsibilities.

CONCLUSIONS

Though successful management was slightly greater with hospital than with DC management (86% HC vs 78% DC), with proper triage, supervision and monitoring, and referral when needed children with pneumonia and severe malnutrition were treated as successfully in DC as in hospitals (94% and 95% respectively). In environments with limited resources, a functioning DC model will increase bed availability in hospitals for higher acuity admissions. With a modest investment to upgrade clinic facilities, train staff, and procure appropriate pulse oximetry monitoring and nutrition-care equipment, the DC approach is low cost and effective, as long as systems are in place for identifying children failing treatment and requiring referral.

ACKNOWLEDGEMENTS

We are grateful to the physicians, nurses, research assistants and health workers for their contribution during patient enrolment and data collection. We are grateful to the parents of children involved in this study for their generous participation. Icddr,b is thankful to the UBS Optimus Foundation, Zürich, Switzerland for providing support.

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Author statement

Manuscript title: Day clinic versus hospital care of pneumonia and severe malnutrition in children under five: a randomized trial

I have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

I have drafted the work or revised it critically for important intellectual content; AND

I have approved the final version to be published; AND

I agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All persons who have made substantial contributions to the work reported in the manuscript, including those who provided editing and writing assistance but who are not authors, are named in the Acknowledgments section of the manuscript and have given their written permission to be named. If the manuscript does not include Acknowledgments, it is because the authors have not received substantial contributions from nonauthors.

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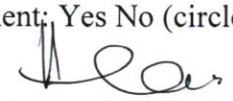

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Cover letter

Date: April 17, 2019

To: Helen Fletcher, BSc, PhD
Editor, Tropical Medicine & International Health

From: Mohammod Jobayer Chisti
Corresponding author,
TMIH Submission No. TMIH-D-18-00669

Subject: Response on the comments of the reviewers of Tropical Medicine & International Health on manuscript (TMIH-D-18-00669) entitled "Day clinic versus hospital care of pneumonia and severe malnutrition in children under five: a randomized trial"

Dear Dr Helen Fletcher,
Thank you for providing us the opportunity to submit our revised manuscript with after revision. We have revised the manuscript according to the suggestions of the respected reviewers. We are sending track change version of the manuscript which highlights the changes we have made for your convenience. We are also sending a clean version of this revised manuscript. We are also attaching this cover letter outlining a point-by-point response to the each point kindly raised by the reviewers.

We hope that our responses will be appropriate to qualify the manuscript for publication in your well reputed journal. We are expressing our sincere thanks to you and the respected reviewers for the overall positive comments.

Responses to the comments of the reviewers

Reviewer #1:

Comment: This well written manuscript reports an extension of previous work in the field, now demonstrating the effectiveness and efficiency of Day Clinic management with hospitalisation for children with pneumonia and severe malnutrition. The results are very informative and will have major implication for the management of such children in the developing world.
Response: Thank you very much for your valuable comment regarding the manuscript.

Reviewer #2:
Comment: Well designed study, important and worthy of publication, it needs some revision; below are both suggestions, comments and typos that need correcting; identification is by line on page.
Response: Thank you very much for your overall positive comments. We have revised the manuscript following your kind suggestions below.

Comment: P2 Line 23 (P2L23) NR should read NRU?
Response: We have corrected this on page 2 line 23.

Comment: P5 L5 "Each year there are over....". Remove "each year" at end of sentence
Response: Thanks. We have corrected accordingly.

Comment: P5 L11 what is the mortality rate? useful to include
Response: Thanks. We have included the information of mortality rate on page 5, line 11.

Comment: P6 L9 "...both pneumonia and severe malnutrition"
Response: We have corrected accordingly.

Comment: P7 L2 Were there differences between the resources either available or utilised; hopefully they were the same or else this is a flaw.
Response: Thanks. We have revised accordingly.

Comment: P7 L21 Bilateral pitting oedema could qualify as diagnostic; were other causes of this excluded?
Response: Actually bilateral pitting oedema was one of the diagnostic criteria of WHO defined severe malnutrition and it was one of the inclusion criteria, but not exclusion criteria. We have now revised the sentence for better clarity.

Comment: P8 L1 definition of "severe" sepsis? Many children with SAM have occult "severe sepsis" either define or remove word severe
Response: Thanks. We have included the definition.

Comment: P8 L13 "...that patient was referred....with greater facilities"
Response: Thanks. We have corrected accordingly.

Comment: P8 L15-18 change to:"This is the only deviation from the WHO protocol to maintain compliance by avoiding 4 injections of Amp/Penicillin per day."
Response: Thanks. We have revised accordingly.

Comment: P8 L17 Were mothers also screened nutritionally? were there differences btn the two groups in maternal status?
Response: As we did not screen for the nutritional status of the mothers we thus are unable to correlate their nutritional status with that of their children.. We have incorporated this information on page 9 (last sentence).

Comment: P9 L2 remove "where needed"
Response: We have corrected accordingly.

Comment: P9 L6: 5 days seems to be a long time to have essentially "resolved pneumonia" using all these parameters? Some comment re this req'd in discussion.
Response: Thanks. We have incorporated this in the discussion section on page 19.

Comment: P9 L12 The RDI measurements were measured how? It seems to be a rough estimate which is understandable. Were there any differences btn the 2 gps, if measurable...?
Response: Both the groups followed the WHO recommendations of RDI during rehabilitation phase but we did not collect that data for two groups. RDI was estimated to be ranging from 150 to 250 Kcal/kg per day. We have corrected the sentence on page 9.

Comment: P10: The primary outcome was the success of management and components of this are deaths/discontinuation/referral and readmission. I would reword Lines 2-11.
Response: Thanks. We have revised them on page 11.

Comment: P10 L13 "The secondary outcomes were the health care, provider and household costs between the groups"
Response: We have corrected accordingly.

Comment: P11 L12 remove "this"
Response: We have removed accordingly.

Comment: P12 L3 Where did the success rate of 88% come from? same for 96%
Response: Thanks. We have provided the information on page 13.

Comment: P13 L10 almost 1/3 of patients were recruited in the second time period which represents a fraction of the total study period; any particular reason for this? were there implications in terms of changed treatments, facilities, etc.?

Response:. We respect your concern. Actually we have recalculated the time and patient enrolment status and found that the second time period lasted 14 months or 25.9% of the total trial time (54 months) and included 120 patients or 25.5% of the total 470.

Comment: P14 L4 The time difference was less than one day. this should be highlighted in the discussion as it is an impt. finding; although the time to NRU was longer in the DC group.
Response: We have discussed this in the discussion section on page 19 (1st paragraph, last two sentences).

Comment: P14 L15 There were no admissions due to malnutrition presumably. this is worth stating.
Response: Although admissions were not due to malnutrition, actually all the children had severe malnutrition. We have incorporated this information on page 16 (first paragraph).

Comment: P14 L23 "...for the DCA and hospital care respectively" Also DCA and Dc are used interchangeably.
Response: We have corrected this accordingly on page 16 (second paragraph).

Comment: P15 L6-7 This data is best represented in a table or else directly stating them in comparison...3 numerical figures followed by 3 is confusing.
Response: Thanks. We agree. We have revised the text related to distribution of provider costs (Page 16, last paragraph) to make it clear. The percentage is already there in the table (Table 5).

Comment: P15 L16 "Travel costs were a major contribution among household..."
Response: Thanks. We have corrected this accordingly on page 17 (1st paragraph).

Comment: P15 L18 "...was double that in the hospital care group versus DCA (Table 5)"
Response: Thanks. We have corrected this accordingly on page 17 (1st paragraph).

Comment: P15 L20 "this study is the first randomised controlled trial.."
Response: Thanks. We have corrected this accordingly on page 17 (under discussion, 1st paragraph).

Comment: P15 L21 "... children with both pneumonia..."
Response: Thanks. We have corrected this accordingly on page 17 (under discussion, 1st paragraph).

Comment: P16 L1 remove italics for "overall" and italicise "as a whole" instead
Response: Thanks. We have corrected this accordingly on page 17 (under discussion, 1st paragraph).

Comment: P16 L 7 "The relatively low mortality rate was most likely due to..."
Response: Thanks. We have corrected this accordingly on page 17 (under discussion, 2nd paragraph).

Comment: P16 L9 "Outpatient management was made safe..."
Response: Thanks. We have corrected this accordingly on page 17 (under discussion, 2nd paragraph).

Comment: P16 L13:NRU phase 7.7 Vs 4.77. is there an explanation for this?
Response: Thanks. We have corrected this accordingly on page 17 (under discussion, 2nd paragraph).
Comment: P17 L12-22; "Analysis showed that travel costs were higher amongst the hospital care group, however this difference may be explained by cultural factors such as patients requiring assistance from care givers and being provided food from the family household. These frequent visits by different members of the household will increase travel costs.
Societal costs were 34% lower in the DC group and households had 33% lower costs if receiving treatment in this group. if cost savings of a similar magnitude as well as clinical effectiveness are maintained after scaling up, then this could be allocated to other essential areas theoretically. generalisability and scaling however may be a challenge in rural areas as the Dc model requires close monitoring, checking for danger signs, pulse oximetry, health literacy education for mothers and close daily follow up."
Response: Thanks for your thoughtful suggestions. We have revised the discussion section accordingly on pages 19 (last paragraph) and 20 (first paragraph).

Comment: P18 L4 "...lower household expenses the DC group demonstrated..."
Response: Thanks. We have corrected this accordingly on page 19 (3rd paragraph).

Comment: P18 L9. This is not the main limitation of the study, this needs to be removed.
Response: Thanks. We have deleted this sentence.

Comment: P18 L11-12 this needs explanation or removal.
Response: Thanks. We have deleted this sentence completely.

Comment: P18 L14-17 This requires changing; successful management was 78% DC vs. 86% HC. If needed one can then qualify the results by saying after appropriate referral patients were successfully managed 94% of the time.
Response: We agree. We have revised the sentence accordingly on page 21 in the conclusion.

Comment: P18 L17" a functioning DC model will increase bed availability in hospitals for higher acuity admissions."
Response: Thanks. We have corrected this sentence on page 21 in the conclusion.

Comment: P18 L20 " as long as systems are in place for identifying children failing treatment and requiring referral."
Response: Thanks. We have corrected this sentence on page 21 n the conclusion.

Table

Table 1 Baseline characteristics of the study children

Characteristics	Total (n=470)	Day-care (n=235)	Hospital-care (n=235)
Male	264 (56)	127 (54)	137 (58)
Infants 2-11 months, n (%)	250 (54)	124 (54)	126 (55)
Children 12-59 months, n (%)	195 (41)	98 (42)	97 (41)
Age in months: median (IQR)	10.1 (6.0-16.5)	10.1 (5.2-16.2)	10.1 (6.2-17.0)
Breast-fed	355 (75)	176 (75)	179 (76)
Weight, kg, mean (±SD)	5.8 (1.6)	5.8 (1.6)	5.9 (1.6)
Height, cm, mean ±SD)	65.0 (8.7)	64.7 (8.6)	65.2 (8.7)
MUAC, cm, mean (±SD)	11.5 (1.3)	11.5 (1.3)	11.5 (1.3)
Weight-for-Age Z score (WAZ), mean (±SD)	-3.45 (0.9)	-3.47 (0.8)	-3.42 (1.0)
Weight-for-Height/Length Z score (WHZ), mean (±SD)	-1.73 (1.1)	-1.75 (1.1)	-1.70 (1.1)
Height-for-Age Z score (HAZ), mean (±SD)	-3.43 (1.1)	-3.46 (1.1)	-3.38 (1.2)
Temperature ≥ 38^{o}C, n(%)	201 (43)	99 (42)	102 (43)
Pulse rate/minute, mean (±SD)	143 (19)	143 (19)	143 (18)
Pulse rate ≥ 160/min, n(%),	99 (21)	50 (21)	49 (21)
Respiratory rate/minute, mean (±SD)	55 (11)	55 (12)	56 (11)
Respiratory rate ≥60/min n(%)	171 (36)	80 (34)	91 (39)
Lower chest wall in-drawing n (%)	440 (94)	217 (92)	223 (95)
Rales/crepitation on auscultation n (%)	458 (97)	229 (97)	229 (97)
Hypoxaemia at admission, oxygen saturation <90%, n(%)	50 (11)	25 (11)	25 (11)

MUAC: mid upper arm circumference; WAZ: weight for age z score; WHZ: weight for height/length z score; HAZ: height for age z score

Table 2 Baseline nutritional status of study children

Nutritional status	Index	Total (n=470) n (%)	Day-care (n=235) n (%)	Hospital- care (n=235) n (%)
Oedematous malnutrition	Bi-pedal oedema	32 (7)	16 (7)	16 (7)
Severe wasting	Weight for height<-3 WHZ	55 (12)	28 (12)	27 (11)
Severe undernutrition	<-3 WAZ	228 (48)	117 (50)	111 (47)
Severe stunting	Height for age<-3 HAZ	68 (14)	34 (14)	34 (14)
Severe acute malnutrition (>6 months old)	MUAC< 115 mm	355/355 (100)	175/175 (100)	180/180 (100)

Table 3 Primary outcomes of the study children

Characteristic	Day-care (n=235) (%)	Hospital-care (n=235) (%)	Total (n=470) (%)	RR (95% CI)	p- value
Successfully managed at study sites	184 (78)	201 (86)	385 (82)	0.79 (0.65 – 0.97)	0.02
Referred to hospital due to lack of success	36 (15)	22 (9)	58 (12)	1.28 (1.02 – 1.60)	0.02
Discontinued treatment	15 (6)	10 (4)	25 (5)	1.21 (0.86 – 1.69)	0.15
Death during treatment phase	0	2 (1)	2 [0.4)	0	0.24
Total deaths over six months follow-up	3 (1)	4(2)	7(2)	0.85 (0.36 – 2.02)	0.50
Successfully managed within health service system*	220 (94)	223 (95)	443 (94)	0.89 (0.62 – 1.26)	0.28
Referred-readmitted during 6-months' follow-up period	30 (13)	36 (15)	66 (4)	0.89 (0.67 – 1.18)	0.21

* Study sites plus referral hospitals; $p< 0.05$ was considered significant

Table 4 Secondary outcomes of the study children

Characteristics	Total (n=470)	Day-care (n=235)	Hospital-care (n=235)	p value
Duration of cough, days	5.84 (2.57)	6.04 (2.98)	5.63 (2.07)	0.08
Duration of fever, days	2.06 (1.70)	1.99 (1.38)	2.12 (1.96)	0.48
Duration of rapid breathing, days	3.48 (3.00)	3.54 (3.09)	3.42 (2.92)	0.70
Duration of lower chest wall in-drawing, days	4.53 (2.69)	4.60 (2.85)	4.46 (2.52)	0.59
Length of stay (days) until treatment success	7.5 (4.5)	7.9 (5.5)	7.1 (3.1) 1)	0.04
Duration of ceftriaxone therapy, days	6.3 (1.3)	6.3 (1.4)	6.3 (1.2)	0.69
Duration of oedema, days	4.10 (2.41)	3.53 (1.72)	4.63 (2.87)	0.21
Duration(admission to transfer to NRU) of acute phase, days	6.45 (2.05)	6.50 (1.96)	6.41 (2.13)	0.63
Duration(admission to NRU to discharge from NRU) of NRU phase, days	6.53 (8.32)	7.74 (9.93)	4.77 (4.80)	0.16
Weight gain in acute phase, g/kg/d	8.5 (13.7)	8.2 (15.6)	8.8 (11.8)	0.61
Weight gain in NR phase, g/kg/d	10.6 (12.0)	8.4 (4.0)	13.8 (17.9)	0.07
Total weight gain, g/kg/d	7.4 (12.6)	6.8 (14.4)	8.0 (10.5)	0.29
Duration of oxygen therapy for correction of hypoxaemia (median hr)	14.68 (19.18, 8.12)	12.37(13.69, 8.05)	16.88(23.25, 8.20)	0.30

Values are mean (SD), unless otherwise specified
*level of significance: $p < 0.05$

Table 5: Average total cost per patient managed by day care or hospital care

Societal cost	Day Care		Hospital Care		Difference	Significance of mean (P-value) difference
	Mean ± SD	(%)	Mean ± SD	(%)		
Medical cost	$72.3 ± $19.1	43.8	$81.4 ± 13.2	32.3		0.00
Personnel	$58.3 ± 12.3	35.3	$65.2 ± 9.8	25.9		0.00
Diagnosis	$3.4 ± 1.9	2.0	$2.9 ± 1.1	1.2		0.14
Medicine	$6.0 ± 2.2	3.7	$8.3 ± 3.2	3.3		0.00
*Supportive care**	$2.3 ± 1.3	1.4	$2.6 ±1.9	1.0		0.34
Therapeutic food	$2.3 ± 2.9	1.4	$2.4 ± 2.1	0.9		0.00
Non-medical cost (transportation ao)	$3.7 ± 2.4	2.2	$4.1 ± 1.6	1.6		0.28
Facility cost	$89.2 ± (-)	54.0	$166.6 ± (-)	66.1		-
Cost of Provider	$165.2 ± 30.3	100.0	$252.1 ± 24.2	100.0	34.4%	0.00
Travel cost	$11.4 ± 3.1	59.7	$13.0 ± 4.2	45.1		0.02
Food cost	$0.9 ± 1.2	4.7	$1.9 ± 2.9	6.6		0.02
Hotel cost	0 ± (-)	0.0	$ 0.1 ± (-)	0.4		-
Income loss	$6.8± 4.3	35.6	$13.9 ± 4.4	48.3		0.00
Cost of Household	$19.1 ± 5.6	100.0	$28.8± 8.9	100.0	33.7%	-
Total	$184.3 ± 11.7		$280.88 ± 13.6		34.4%	0.00

* Oxygen therapy and nebulisation with salbutamol; Values are means ± SD

Author statement

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Dr. Selina Akhter Jahan

11.24.2018

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NURSHAD BEGUM Nurshad Begum Nov. 22, 2018

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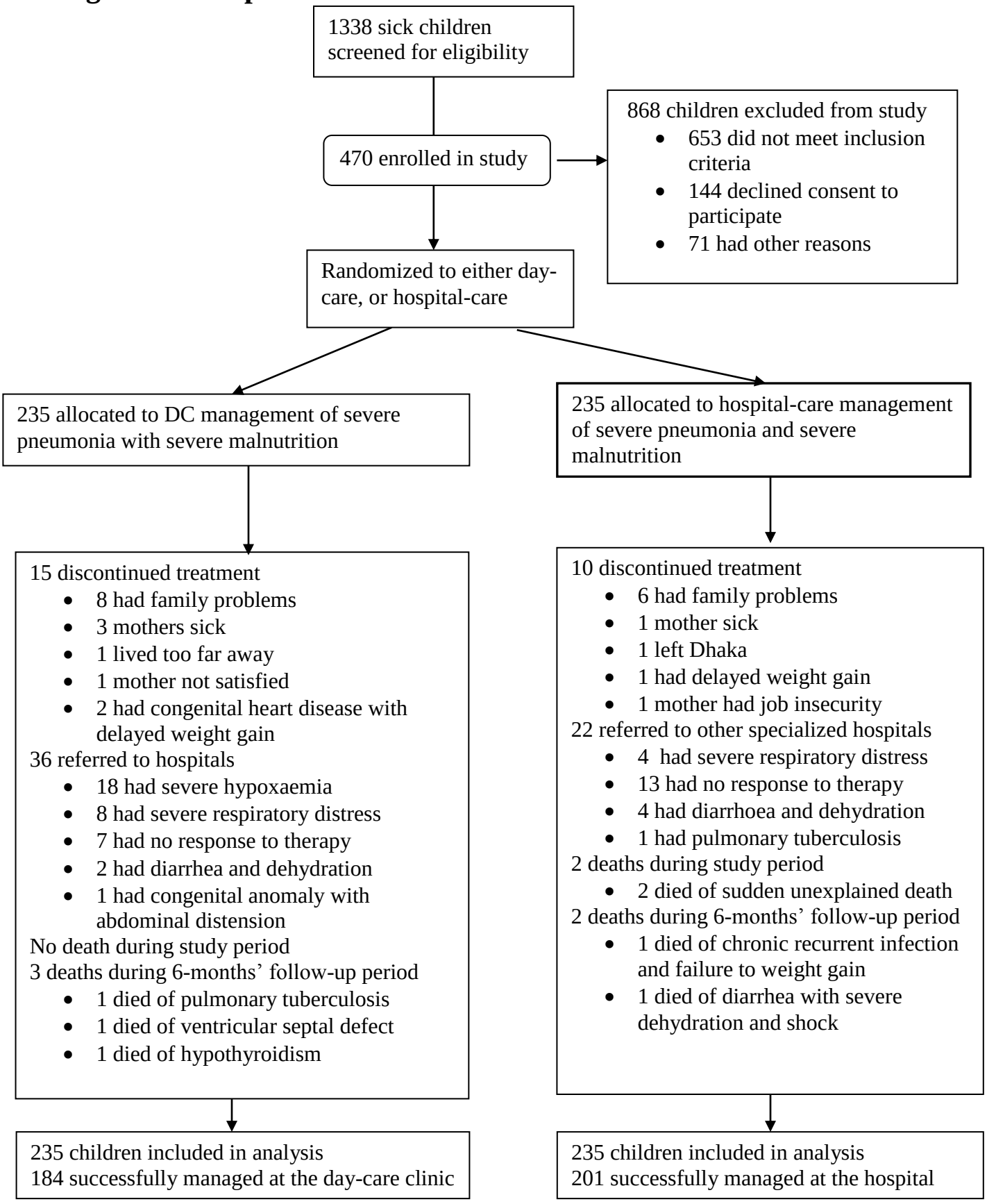
Figure

Figure 1 Trial profile



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Sharmin Farzana, 25/11/2018

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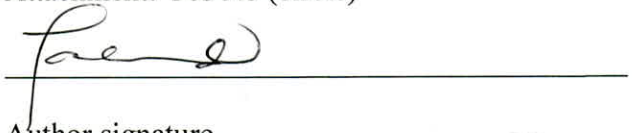

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Prof Trevor Duke. November 26, 2018

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Chief of Medicine
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Professorial Fellow - Paediatrics, University of Melbourne
Honorary Research Fellow - Murdoch Children's Research Institute
The Royal Children's Hospital Melbourne
50 Flemington Road | Parkville | 3052
Ph: 61 3 9345 5844 | F 61 3 9345 9154
Email: colin.robertson@rch.org.au

2. Dr. M. Santosham, Professor Dept of International Health-Health Systems Program John Hopkins Bloomberg school of Public Health 615 North Wolfe Street Baltimore, Maryland 21205 USA Fax: 001 410 614 1419 Email: msantosh@jhsph.edu

2. Dr. Michael Bennish Director, Africa Centre (Africa Centre for Health & Population Studies) PO Box 198, Mtubatuba 3935 South Africa Fax: (27) 35 550 1674 Tel: (27)35 550 7540 Email: mbennish@hotmail.com or Michael.Bennish@mrc.ac.za or MBennish@Lifespan.org.

4. Dr BE Golden: Child Health, University of Aberdeen, Royal Aberdeen Children's Hospital, Westburn Road, Aberdeen, AB25 2ZG, Mob: +447785512161, Fax: +441225551919 Email: b.e.golden@abdn.ac.uk.

5. Dr. Ahmed Youssef Ezeldin: Paediatrician, Cairo University146 A, El Nasr St. New Maadi, Baqlawy Building; Email: ayezzeldin@yahoo.com

6. Julian Kelly, MBBS, FRACP
Paediatrician (Asso. Professor), The Royal Children`s Hospital, The University of Melourne, Melbourne, Australia
julian.kelly@rch.org.au