Effectiveness, safety and economic viability of daycare versus usual hospital care management of severe pneumonia with or without malnutrition in children using the existing health system of Bangladesh: a cluster randomised controlled trial

Nur H. Alam,[a,*] Abu S. Faruque,[a] Hasan Ashraf,[a] Mohammod J. Chisti,[a] Tahmeed Ahmed,[a] Marufa Sultana,[a] Md Khalequzzaman,[b] Shahjahan Ali,[a] Shahnawaz Ahmed,[a] Sabiha Nasrin,[a] Md Tariqujjaman,[a] K. A. T. M Ehsanul Haque,[c] Ruhul Amin,[d] Abid Hossain Mollah,[e] Lutful Kabir,[f] Mohammod Shahidullah,[g] Wahida Khanam,[h] Khaleda Islam,[i] Minjoon Kim,[j] Maya Vandenent,[j] Trevor Duke,[k] Niklaus Gyr,[l,n] and George J. Fuchs[m,n]

[a]Nutrition and Clinical Services Division, icddr,b, Dhaka, Bangladesh
[b]Infectious Diseases Division, icddr,b, Dhaka, Bangladesh
[c]Graduate School of Biomedical and Health Sciences, Hiroshima University, Japan
[d]Dhaka Shishu Hospital, Dhaka, Bangladesh
[e]Dhaka Medical College Hospital, Dhaka, Bangladesh
[f]Sir Salimullah Medical College Hospital, Dhaka, Bangladesh
[g]Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[h]Institute of Child and Mother Health, Matuail, Dhaka, Bangladesh
[i]Primary Health Care, Ministry of Health and Family Planning, Government of Bangladesh, Bangladesh
[j]UNICEF Office, Dhaka, Bangladesh
[k]Melbourne Children Hospital, Melbourne, Australia
[l]University Hospital, Basel, Switzerland
[m]College of Medicine and College of Public Health, University of Kentucky, USA

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Summary

Background We aimed to define clinical and cost-effectiveness of a Day Care Approach (DCA) alternative to Usual Care (UC, comparison group) within the Bangladesh health system to manage severe childhood pneumonia.

Methods This was a cluster randomised controlled trial in urban Dhaka and rural Bangladesh between November 1, 2015 and March 23, 2019. Children aged 2–59 months with severe pneumonia with or without malnutrition received DCA or UC. The DCA treatment settings comprised of urban primary health care clinics run by NGO under Dhaka South City Corporation and in rural Union health and family welfare centres under the Ministry of Health and Family welfare Services. The UC treatment settings were hospitals in these respective areas. Primary outcome was treatment failure (persistence of pneumonia symptoms, referral or death). We performed both intention-to-treat and per-protocol analysis for treatment failure. Registered at www.ClinicalTrials.gov, NCT02669654.

Findings In total 3211 children were enrolled, 1739 in DCA and 1472 in UC; primary outcome data were available in 1682 and 1357 in DCA and UC, respectively. Treatment failure rate was 9.6% among children in DCA (167 of 1739) and 13.5% in the UC (198 of 1472) (group difference, −3.9 percentage point; 95% confidence interval (CI), −4.8 to −1.5, p = 0.165). Treatment success within the health care systems [DCA plus referral vs. UC plus referral, 1587/1739 (91.3%) vs. 1283/1472 (87.2%), group difference 4.1 percentage point, 95% CI, 3.7 to 4.1, p = 0.160)] was better in DCA. One child each in UC of both urban and rural sites died within day 6 after admission. Average cost of treatment per child was US$94.2 (95% CI, 92.2 to 96.3) and US$184.8 (95% CI, 178.6 to 190.9) for DCA and UC, respectively.

Interpretation In our population of children with severe pneumonia with or without malnutrition, >90% were successfully treated at Day care Clinics at 50% lower cost. A modest investment to upgrade Day care facilities may provide a cost-effective, accessible alternative to hospital management.

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*Corresponding author. 68 Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka, 1212, Bangladesh.
E-mail address: nhalam@icddrb.org (N.H. Alam).
[n]Contributed equally as senior authors.

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Research in context

Evidence before this study

We systematically reviewed the scientific literature to identify studies published before January 31, 2023, reporting the DCA for the treatment of severe pneumonia in children with or without co-morbidities. We searched Pubmed and Google Scholar to identify all published trials in English using combinations of the following search items: Day Care clinics, Day care approach, Day care, severe pneumonia, very severe pneumonia, Children, paediatric. We have also tried to identify any study by personal communication. We did not find any single study except one observational study report and three reports of clinical trials using DCA of treatment of childhood severe pneumonia published by our study group. Initial observational study carried out in children with severe pneumonia who were refused inpatient admission due to lack of paediatric beds. Subsequently, three randomised controlled trials of day care versus hospital care of children with severe pneumonia were successfully completed. All trials reported that 85%–95% children with severe pneumonia with comorbidities could be treated effectively and safely by DCA.

Added value of this study

The current study is an effectiveness trial with cluster randomised design with a larger sample size involving the primary health care settings both in urban and rural sites with community participation. The study is considered to be conducted nearer to the real world situation. Results of this study are consistent with earlier efficacy studies that support implementation of a Day care approach in the health systems of low-and middle-income countries (LMICs) including Bangladesh and that may also be incorporated in the IMCI programme.

Implications of all the available evidence

In the context of inadequate paediatric hospitals/beds and other constraints in LMICs, the evidence described above indicates potential for the Day care approach to be an effective, safe, and less costly alternative to hospital treatment of severe pneumonia in children with or without malnutrition and other co-morbidities.

Introduction

Pneumonia remains the leading cause of death in children under-five years of age, globally.[1] In 2017, more than 800, 000 under 5 children died from pneumonia worldwide; most of these deaths occurred in low-and middle-income countries (LMICs), often in the setting of underlying malnutrition, which is a major mortality risk factor.[2–6] WHO recommends that severe childhood pneumonia be treated in the hospital for supportive care including oxygen therapy for hypoxaemia, airway suctioning, antibiotics, and close monitoring. In contrast, non-severe childhood pneumonia can usually be treated at home. In LMICs, the number of children admitted to hospital due to pneumonia increased by 187%, from 5.7 million in 2000 to 16.4 million in 2015. Overall, hospital admissions for child pneumonia increased by 2.9 times during the 15-year period.[1] Unfortunately, most LMICs do not have enough hospitals (0.2 per 100,000 population in Bangladesh) or inpatient hospital beds (3 beds in Bangladesh vs. 63 in the Europe per 10,000 population).[7,8]

In the largest paediatric hospital in Bangladesh, one in four children who required hospitalisation was unable to access inpatient care due to lack of beds; children with pneumonia constituted the largest group (22%) denied admission.[9] Systems to track children denied hospitalisation are lacking but such children and especially those with malnutrition likely experience poor outcomes.

Additionally, many mothers of ill children have other child care and household responsibilities that constrain their ability to stay with the child during hospitalisation, which is often mandatory. Transportation costs, long distances between home to hospital, lack of adequate child-care at home, and/or cultural perceptions are significant additional limitations to hospitalisation. A series of efficacy trials[10–13] of a day-care treatment approach (DCA) in children with severe pneumonia with or without co-morbidities such as malnutrition, diarrhoea etc. were treated safely and effectively at a Day care clinic as an alternative to inpatient hospital care. However, demonstration of effectiveness under "real-life" conditions within the Bangladesh health system is imperative before programmatic implementation and nationwide scale-up in Bangladesh and other LMICs. This study aimed to determine if the DCA is effective, safe, and affordable for health systems as well as for households as an alternative to the usual hospital-based treatment.

Methods

Study design

This was a cluster randomised controlled clinical trial to compare DCA with usual hospitalised care (UC)

management of severe childhood pneumonia with or without malnutrition within Bangladesh health systems. The study was conducted between November 1, 2015, and March 23 2019 in urban Dhaka and rural regions of Bangladesh which have distinct demography and health systems.

Urban Dhaka settings

Two Zones of 8 Wards (clusters) each, using primary health care clinics run by NGOs, four for DCA and four for UC (hospital) were selected randomly. Primary health care of each ward (administrative unit of about 200,000 population) is provided by Smiling Sun (SH, Shurjer Hashi) Franchise clinics in collaboration with the Dhaka City Corporation. One SH clinic in each zone was selected for four intervention wards as a day-care clinic.

Rural setting

The study was implemented in Union (cluster) Health and Family Welfare Centres (HFWCs) where services are provided by the Ministry of Health and Family Welfare, Government of Bangladesh. Eight unions of about 200,000 population were selected from each Upazilla (each sub-district consists of 12–14 unions). A total of 16 unions from two Upazilas based on the availability of necessary infrastructure (e.g., space, electricity, water supply) were randomly assigned as intervention or control clusters. After study year one, two additional sub-districts with 16 clusters (8 for intervention and 8 for controls) were added to accelerate patient enrolment (protocol amendment was approved by icddr,b's institutional review board). In both urban and rural intervention sites, existing health facilities were modestly upgraded to DCA clinics as done in earlier studies[10–12] to treat childhood severe pneumonia. The randomisation was by a statistician not involved in the study. The procedure of the study sites selection and randomisation are illustrated in Fig. 1.

Inclusion criteria

Children of either sex aged 2–59 months with severe pneumonia (on the day of presentation) with or without moderate acute malnutrition (MAM), severe underweight, diarrhoea with no or some dehydration were included after written informed consent from parents/caregivers. Severe pneumonia per 2013 WHO criteria[14] was defined as cough or difficulty in breathing with at least one of the following danger signs: central cyanosis or oxygen saturation <90% by pulse oximetry, severe respiratory distress (e.g., grunting, very severe chest indrawing), inability to breastfeed or drink, or lethargy. Children were weighed without clothes (Seca weighing scale, Germany), and recumbent length/standing height was measured to the nearest one mm with a locally made length board. Nutritional status was defined per WHO criteria: MAM is weight-for-height/length Z-score > −3 and ≤−2 or MUAC ≥ 115 mm and <125 mm; severe underweight was defined as a weight for age <−3.0.

Exclusion criteria

Children with non-severe pneumonia, hospital-acquired pneumonia, severe acute malnutrition, or bronchiolitis (by single-dose bronchodilator challenge test) were excluded. Children with bronchial asthma, suspected sepsis, meningitis, convulsion, congenital heart disease, severe dehydration, or other life-threatening illness, and those who received parental antibiotics for the current illness were also excluded.

Case management

Intervention cluster (DCA)

Children with pneumonia/severe pneumonia with or without malnutrition/other co-morbidities were referred to the urban SH clinics or the rural HFWCs by community health workers or self-referred by parents/caregivers (Supplementary Figs. S1 and S2). A screening evaluation was done by study physicians in the urban area or Sub Assistant Community Medical Officer followed by a study physician in rural HFWCs. Per current practice, children with pneumonia or acute lower respiratory infection without any emergency signs such as central cyanosis, hypoxaemia, grunting respiration, inability to breastfeed or drink, lethargy or reduced level of consciousness, and convulsion were treated at home with oral amoxicillin syrup 80 mg/kg/day in two divided doses for 5 days. Those who deteriorated after two days or who presented initially with severe pneumonia were enrolled in DCA. Day Care Clinics were open in urban and rural sites from 8:30 am to 4 pm and 8:30 am to 3.00 pm, respectively every day of the week including weekends and public holidays. At the end of each day, DCA children who met predetermined criteria (fully alert and absence of emergency signs) went home with mothers who continued breastfeeding (breastfed infants) and/or prescribed nutritional feeding as needed. Children returned to the DCA the following morning. DCA children were examined by study physicians at least twice and by the nurses three times daily in both urban and rural field sites and weighed daily.

Oxygen was administered to children if hypoxaemic (SpO_2 <90%) by pulse oximetry. Children received once-daily intramuscular injection of ceftriaxone 75–100 mg/kg for 5 days, the only deviation from the WHO protocol to enhance compliance by avoiding four injections of ampicillin/penicillin per day. Other supporting resources at DCA included suction machine, nebuliser, glucometer, and thermometer.

Children >6 months of age were offered therapeutic diets of milk-suji (boiled milk and rice powder of 281 KJ and 1.4 g of protein per 100 ml at 10 ml/kg/feeding every two hours including night hours. Mothers were encouraged to continue breastfeeding for breastfed children. Infants 2–6 months of age not being breastfed

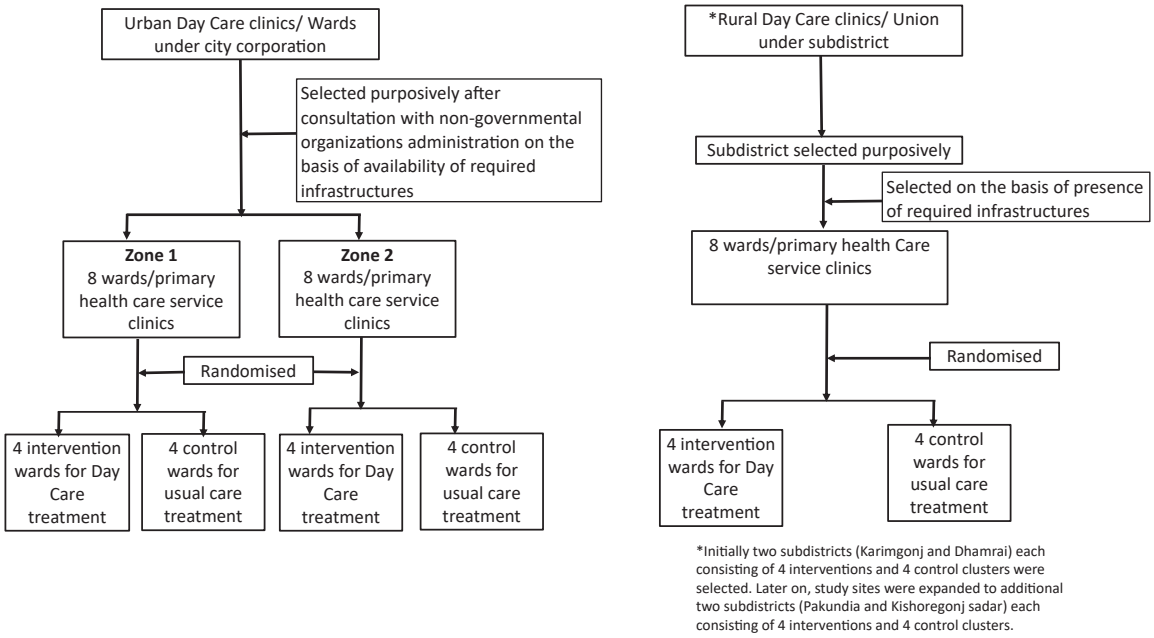

Fig. 1: Procedure of the study sites selection and randomisation.

were given infant formula (286 KJ and 1.5 g of protein per 100 ml). Mothers were provided 3–4 feeds of milk suji in a hot pot or infant formula to continue feeding during night hours.

Malnourished children were provided with vitamin A, multivitamins, folic acid, zinc, potassium, and anti-helminthic drug. Children with diarrhoea received WHO oral rehydration solution and oral zinc 20 mg elemental daily for 10 days. Caregivers received education on home management of medicines, supportive care, referral, and preparation of diets. Children attended the DCA clinic each morning for assessment and ceftriaxone injection (days 1–5) and, if stable, went home after a few hours.

DCA management was continued until the child met the following criteria for at least five days: no fever, no fast breathing, no lower chest wall in-drawing, no danger signs, and no hypoxaemia. Children with hypoxaemia by end of clinic hours or needing oxygen therapy for more than 6 hours met DCA treatment failure definition and were referred for higher-level care to a local hospital (urban sites) or sub-district or district hospital (rural sites) for continuous oxygen therapy and other needed treatment.

Control cluster (UC)

Children with severe pneumonia were directly admitted to the hospital by self-referral or referred by study personnel or any physician/health workers and received usual treatment according to the respective hospital treatment protocol. The logistic characteristics of Day care clinics and hospital inpatient wards are similar with a minor difference (Table 1). In urban sites, children from the control clusters received treatment from one of several public or private hospitals. In the rural sites, children received treatment mostly from the District hospitals under the Ministry of Health and Family Welfare (MoHFW). All hospitals have medical officers and paediatric consultants. Number of paediatric beds (general) varied from 20 to 70 per hospital with a nurse to patient ratio of one per 10 to 20 patients. The hospitals are equipped with pulse oximeter, oxygen supply, suction machine, etc. Children were treated with antibiotics either Injection ampicillin plus gentamicin or injection ceftriaxone. Study personnel were responsible only to obtain caregiver's consent and data collection during hospitalisation and from households.

Follow up

Children who recovered from pneumonia by day six were considered as treatment success and discharged with instruction to return on day 14 and monthly for three consecutive months to assess for potential relapse (cough, fever, rhinorrhoea, difficulty in breathing, chest in-drawing, rales on auscultation) and specific morbidities including diarrhoeal disease since the prior visit. Nutritional status by anthropometry was characterised and unscheduled visits, readmission to hospitals, and deaths were recorded.

Outcome

Primary outcomes were treatment failure by day 6 and treatment success within the Health System (DCA plus referral or UC plus referral). Secondary outcomes were

referral to hospitals/higher facilities, relapse (recurrence of symptoms) between days 7–14 in children previously well on day 6, and death.

Economic evaluation

A within-trial economic evaluation was conducted by adopting a societal perspective. A micro-costing bottom-up approach was applied to collect and analyse economic data.[15,16] Average cost of patient was determined through estimating direct medical, direct non-medical and indirect cost.[16] An incremental cost-effectiveness ratio (ICER) was calculated by dividing the mean cost difference of DCA and UC with the mean difference of the outcome. The alternative was considered as "dominant" i.e., cost-saving alternative with a lower cost and higher outcome producing a negative ICER.[15]

Ethical review

The study was approved by the Research Review and the Ethical Review Committees of icddr,b and registered at www.ClinicalTrials.gov (Identifier: NCT02669654). The manuscript was prepared according to the CONSORT checklists (Supplementary Table S3).

Statistical analysis

Sample size was based on a cluster-randomised design for dichotomous outcomes with an equivalency expectation that results of primary outcomes would fall within the 95% confidence intervals (CIs). Sample size per cluster needed was calculated by the method of Hayes and Bennett[17] which estimated that 16 clusters were needed in each study arm. Therefore, we selected 16 control clusters (UC) and 16 intervention clusters (DCA) per year for the entire study period (3 years and 2 months). Assuming treatment failure of 10% in children in the DCA and 15% in the UC by day 6, a power of 80%, 5% level of significance and 10% dropout, we considered enrolling 40 children with severe pneumonia with or without malnutrition per cluster per year, for an estimated 1600 patients in each study arm and a total of 3200 children needed for this study. We performed both intention-to-treat and per-protocol analysis for treatment failure at day 6. The Chi-square test for categorical and Mann–Whitney test for skewed continuous variables were applied to examine the difference of socioeconomic and clinical characteristics between intervention and control groups. To choose the distributional assumptions such as to test the normality of the data, we plotted a histogram with a normal density plot. When we found symmetric curve, we opted for a parametric test and present the estimates as mean and SD.

Also, we tested skewness and kurtosis test. If both skewness and kurtosis resulted in insignificant p-values, then we opted for a parametric test. Otherwise, we performed non-parametric tests. The adjusted Wald test for testing the equality of two proportions was used to compare primary and secondary outcome variables between intervention and control groups. In regression analysis, the generalised estimating equation model was applied only for children with complete data to explore predictive factors of clinical treatment failure at day 6. However, the incomplete data were missing in random. The adjusted risk ratios, 95% CIs, and p-values were generated from log-binomial regression models using GEE. When the models were not converged, we used log-Poisson regression models using GEE. In the regression models, we omitted the secondary outcomes including death, referral, lost to follow-up because the prevalence or the number of observations of these indicators were scanty. In the cost-effective analyses, descriptive statistics were used to summarise all costs and to estimate mean cost per patient with 95% CI and to determine cost difference between groups. All costs were inflation adjusted, converted to USD in 2019 price year (1 USD = 84.5 BDT). Bootstrapping (10,000 simulations) was used to calculate point estimate of ICER and to generate 95% CIs. Data were entered and verified with statistical software SPSS version 20. The statistical software package Stata SE (version 15) and R version 4.2.2 were used for data analyses. The study protocol is provided as a Supplementary file.

Characteristics	Day care clinics	Hospital inpatient ward (control)
Number of paediatric beds	2–3 per DC Clinic	20–60 per hospital
Nurse to patient ratio	One per 2–3 patients	One per 10–20 patients
Medial officer	Present	Present
Consultant	None	Present
Antibiotic use	100%	100%
Pulse Oxymeter availability	Yes	Yes
Oxygen delivery facility availability	Yes	Yes
Number of clinical round for patients	Two times	Two times
Nutritional support given	Yes	Advised only

Table 1: **Comparison of some characteristics of the Day care clinics and hospitals (inpatient ward) for usual care (control).**

Role of the funding source

The funders (UNICEF, Botnar Foundation, UBS Optimus Foundation, and EAGLE Foundation, Switzerland) of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and had final responsibility to submit the manuscript for publication.

Results

Patient characteristics

In the Day care clinics (both urban and rural) 3423 children were screened for their eligibility (trial profile Fig. 2). Of them 1684 were excluded for various reasons, 1739 were enrolled for participation, and 1718 had

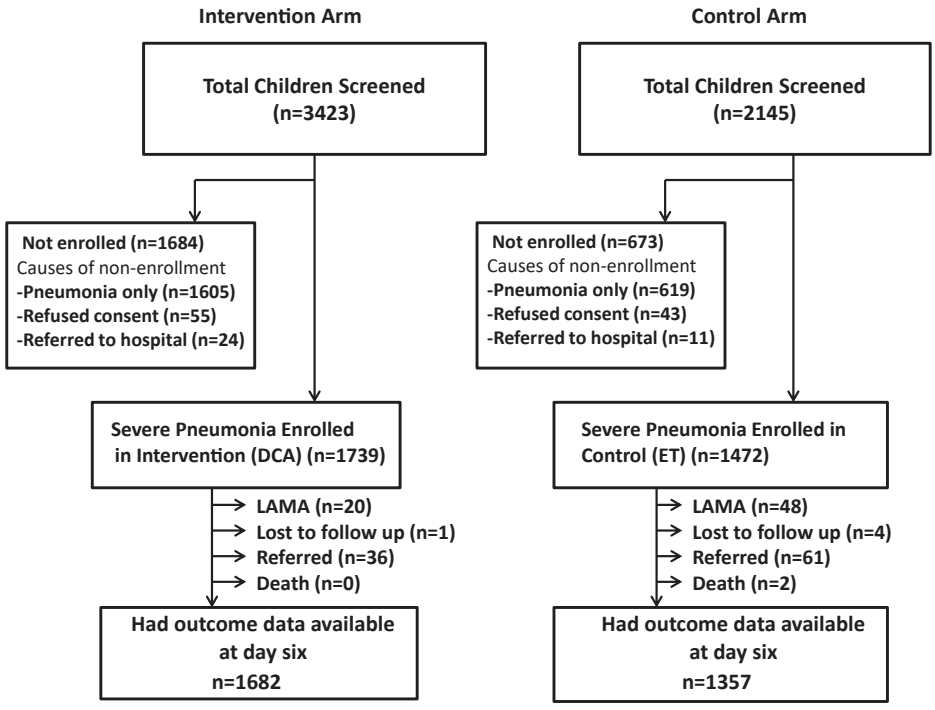

Fig. 2: Trial profile of combined sample (urban plus rural).

outcome data available at day 6. In the control sites (UC) 2145 children who attended the hospitals were screened for enrolment. Among them, 1472 were enrolled, and 1420 had outcome data available at day 6. Median age of all children (DCA and UC) was 9.0 months with those in the DCA older than in UC (median 10 months vs. 8.2 months, p = 0.323) (Table 2). Data were similar in urban and rural sites. Infants aged 2–11 months comprised the majority in both treatment arms (urban or rural) and >60% were male. Most children were currently breastfed and half had a history of exclusively breastfeeding. Almost (99%) children had cough, fast breathing, and chest in-drawing on admission irrespective of treatment arm or study site (urban or rural). The proportion with hypoxaemia was similar in both treatment groups. Considerably more children were unable to drink or breastfeed in DCA than UC with the difference largely attributable to the urban sites. In DCA and UC groups, 60.3% and 64.2% of children, respectively had grunting with the difference largely attributable to urban sites.

Clinical outcomes

Primary outcome

In the intention-to-treat (ITT) analysis of combined data (Urban plus Rural), the proportion of children with Day 6 treatment failure was less in DCA than UC group [between group difference –3.9 percentage point, 95% CI, –4.8 to –1.5, p = 0.165]. However, the treatment failure rate in urban sites was greater in DCA than UC (between-group difference 4.8 percentage points, 95% CI, 2.9 to 7.1, p = 0.019) while in rural sites, it was greater in the UC than DCA (between-group difference –10.5, 95% CI –18.8 to –5.4, p = 0.016) (Table 3). Integrating the results of the health system (DCA or UC plus outcome of the referred cases), 89.4% (2870 of 3211) children were successfully treated within the health system. But more children were successfully treated under DCA (91.3% vs. 87.2% in DCA plus referral vs. UC plus referral, respectively; 95% CI 3.7 to 4.1, p = 0.160) (data not shown in the table). In the per-protocol analysis of combined data, we found similar results as ITT analysis of Day 6 treatment failure between DCA than UC group (Supplementary Table S1). We also performed sub-group analysis by age (2–11 months vs. 12–59 months) and malnourishment (stunted (HAZ < –2) vs. non-stunted and wasted (WLZ/WHZ < –2) vs. non-wasted). We found more treatment failure among children of 2–11 months age group (13.1% vs. 8.8%; p = 0.014) and wasted children (15.9% vs. 10.8% p = 0.091) (Supplementary Table S2).

Secondary outcomes

There were also significant differences in case of referral to hospital/higher level facility due to treatment failure between two groups of urban (DCA vs. UC, 4.2%, 31 of 739 vs. 1.1%, 10 of 954, group difference 3.2, 95% CI, 2.6 to 3.4, p < 0.001) and rural (DCA vs. UC, 0.5%, 5 of 1000 vs. 9.9%, 51 of 518, group difference –9.4, 95%

Variable	Urban				Rural				Combined			
	Total n = 1693	DCA n = 739	UC n = 954	p-value	Total n = 1518	DCA n = 1000	UC n = 518	p-value	Total n = 3211	DCA n = 1739	UC n = 1472	p-value
Age (months), (median, IQR)[a]	9.1 (5.1, 16.3)	10.0 (5.1, 18.2)	8.3 (5.1, 16.0)	0.317	9 (5, 17)	10 (5, 19)	8 (4, 15)	0.140	9.02 (5.0, 17.0)	10.0 (5.0, 18.3)	8.2 (5.0, 15.0)	0.323
Infant 2–11 months	1039 (61.4%)	417 (56.4%)	622 (65.2%)	0.041	904 (59.6%)	572 (57.2%)	332 (64.1%)	0.066	1943 (60.5%)	989 (56.9%)	954 (64.8%)	0.009
Male	1066 (63.0%)	449 (60.8%)	617 (64.7%)	0.230	962 (63.4%)	632 (63.2%)	330 (63.7%)	0.856	2028 (63.2%)	1081 (62.2%)	947 (64.3%)	0.290
Currently breastfed	1512/1659 (91.1%)	643/726 (88.6)	869/933 (93.1%)	0.099	1197/1432 (83.6%)	765/937 (81.6%)	432/495 (87.3%)	0.219	2709/3091 (87.6%)	1408/1663 (84.7%)	1301/1428 (91.1%)	0.021
Exclusive breastfed	305/597 (51.1%)	133/262 (50.8%)	172/335 (51.3%)	0.918	259/559 (46.3)	153/341 (44.9%)	106/218 (48.6%)	0.647	564/1156 (48.8%)	286/603 (47.4%)	278/553 (50.3%)	0.578
Household income, Median (IQR)[a]	19,000 (14,000, 30,000)	17,000 (12,000, 25,000)	20,000 (15,000, 30,000)	<0.001	15,000 (10,000, 22,000)	15,000 (10,000, 25,000)	13,000 (9000, 20,000)	0.0006	16,000 (11,000, 25,000)	15,000 (10,000, 25,000)	18,000 (12,000, 30,000)	<0.001
Stunted (HAZ < −2), (%)	615/1691 (36.4%)	277/739 (37.5%)	338/952 (35.5%)	0.750	374/1514 (24.7%)	240/999 (24.0%)	134/515 (26.0%)	0.545	989/3205 (30.9%)	517/1738 (29.8%)	472/1467 (32.2%)	0.632
Wasted (WLZ/WHZ < −2)	167/1691 (9.9%)	70/739 (9.5%)	97/952 (10.2%)	0.651	179/1514 (11.8%)	117/999 (11.7%)	62/515 (12.0%)	0.906	346/3205 (10.8%)	187/1738 (10.8%)	159/1467 (10.8%)	0.961
Underweight (WAZ ≤ −2)	447/1691 (26.4%)	223/739 (30.2%)	224/952 (23.5%)	0.053	348/1514 (23.0%)	216/999 (21.6%)	132/515 (25.6%)	0.324	795/3205 (24.8%)	439/1738 (25.3%)	356/1467 (24.3%)	0.744
Cough	1693 (100%)	739 (100%)	954 (100%)	–	1514 (99.7%)	999 (99.9%)	515 (99.4%)	–	3207 (99.9%)	1738 (99.9%)	1469 (99.8%)	0.297
Duration of cough, Median (IQR)	5 (3, 7)	5 (4, 7)	5 (3, 7)	0.317	3 (3, 5)	3 (3, 5)	3 (2, 4)	0.037	4 (3, 6)	4 (3, 6)	4 (3, 6)	0.532
Fever	1436 (84.8%)	527 (71.3)	909 (95.3%)	<0.001	1015 (66.9%)	688 (68.8%)	327 (63.1%)	0.082	2451 (76.3%)	1215 (69.9%)	1236 (84.0%)	0.321
Duration of fever, Median (IQR)[b]	3 (2, 5)	3 (2, 4)	3 (2, 5)	–	3 (2, 4)	3 (2, 3)	3 (2, 4)	–	3 (2, 4)	3 (2, 4)	3 (2, 5)	0.427
Temperature ≥ 38 °C	701 (41.4%)	170 (23.0%)	531 (55.7%)	0.001	505 (33.3%)	327 (32.7%)	178 (34.4%)	0.685	1206 (37.6%)	497 (28.6%)	709 (48.2%)	0.004
Chest-in-drawing	1651 (97.5%)	716 (96.9%)	935 (98.0%)	0.179	1429 (94.1%)	930 (93.0%)	499 (96.3%)	0.019	3080 (95.9%)	1646 (94.7%)	1434 (97.4%)	0.010
Rapid breathing	1682 (99.4%)	735 (99.5%)	947 (99.3%)	0.687	1515 (99.8%)	998 (99.8%)	517 (99.8%)	0.975	3197 (99.6%)	1733 (99.7%)	1464 (99.5%)	0.461
Vomiting	472 (27.9%)	281 (38.0%)	191 (20.0%)	0.066	29 (1.9%)	1 (0.1%)	0 (0%)	–	473 (14.7%)	282 (16.2%)	191 (13.0%)	0.711
Oxygen saturation <90%	179/1639 (10.9%)	64/738 (8.7%)	115/901 (12.8%)	0.454	167/1452 (11.5%)	123/999 (12.3%)	44/453 (9.7%)	0.360	346/3091 (11.2%)	187/1737 (10.8%)	159/1354 (11.7%)	0.774
Cyanosis	19 (1.1%)	5 (0.7%)	14 (1.5%)	0.365	1 (0.1%)	1 (0.1%)	0 (0%)	–	20 (0.6%)	6 (0.4%)	14 (1.0%)	0.262
Unable to drink or breastfeed	804 (47.5%)	456 (61.7%)	348 (36.5%)	0.090	478 (31.5%)	325 (32.5%)	153 (29.5%)	0.484	1282 (39.9%)	781 (44.9%)	501 (34.0%)	0.264
Grunting	601 (35.5%)	143 (19.4%)	458 (48.0%)	0.115	1393 (91.8%)	906 (90.6%)	487 (94.0%)	0.104	1994 (62.1%)	1049 (60.3%)	945 (64.2%)	0.799
Drooping or Lethargy	445 (26.3%)	172 (23.3%)	273 (28.6%)	0.347	263 (17.3%)	157 (15.7%)	106 (20.5%)	0.325	708 (22.1%)	329 (18.9%)	379 (25.8%)	0.082
Diarrhoea	745 (44.0%)	359 (48.6%)	386 (40.5%)	0.301	390 (25.7%)	267 (26.7%)	123 (23.8%)	0.345	1135 (35.4%)	626 (36.0%)	509 (34.6%)	0.827

Data presented as n (%) unless otherwise stated. HAZ, height-for-age z-score; WLZ, weight-for-length z-score; WHZ, weight-for-height z-score; WAZ, weight-for-age z-score; IQR, Interquartile range. [a]p-values were generated from Mann Whitney test otherwise Chi-square test for adjusting clusters. [b]p-values for the urban and rural sites were not generated due to a single observation in a cluster.

***Table 2*: Baseline characteristics of the study participants across urban and rural and combined sample.**

Variable	Urban Site					Rural Site					Combined				
	Total n = 1693	DCA n = 739	UC n = 954	Diff (95% CI)[b]	p-value[a]	Total n = 1518	DCA n = 1000	UC n = 518	Diff (95%CI)[b]	p-value[a]	Total n = 3211	DCA n = 1739	UC n = 1472	Diff (95% CI)[b]	p-value[a]
Primary outcome															
Treatment failure up to/on day six[c]	259/1693 (15.3%)	133/739 (18.0%)	126/954 (13.2%)	4.8 (2.9–7.1)	0.019	106/1518 (7.0%)	34/1000 (3.4%)	72/518 (13.9%)	−10.5 (−18.8 to −5.4)	0.016	365/3211 (11.4%)	167/1739 (9.6%)	198/1472 (13.5%)	−3.9 (−4.8 to −1.5)	0.165
Secondary outcomes															
Referred to hospital/ higher level facility due to treatment failure	41/1693 (2.4%)	31/739 (4.2%)	10/954 (1.1%)	3.2 (2.6–3.4)	<0.001	56/1518 (3.7%)	5/1000 (0.5%)	51/518 (9.9%)	−9.4 (−17.7 to −4.3)	0.018	97/3211 (3.0%)	36/1739 (2.1%)	61/1472 (4.1%)	−2.1 (−6.4 to −0.5)	0.299
Relapse between day 7–14 who are well at day 6	54/1595 (3.5%)	42/673 (6.2%)	12/876 (1.4%)	4.9 (3.3–7.0)	0.001	15/1404 (1.1%)	3/960 (0.3%)	12/444 (2.7%)	−2.4 (−3.8 to −1.6)	0.003	69/2953 (2.3%)	45/1633 (2.8%)	24/1320 (1.5%)	0.9 (0.2–2.4)	0.299
Death	1/1693 (0.1%)	0/739 (0%)	1/954 (0.1%)	−0.1 (−1.1 to −0.01)	0.390	1/1518 (0.1%)	0/1000 (0%)	1/518 (0.2%)	−0.2 (−0.5 to −0.02)	0.328	2/3211 (0.1%)	0/1739 (0%)	2/1472 (0.1%)	−0.1 (−0.6 to −0.03)	0.199
Lost to follow-up[d]	66/1693 (3.9%)	16/739 (2.2%)	50/954 (5.2%)	−3.1 (−4.8 to −1.9)	0.084	7/1518 (0.5%)	5/1000 (0.5%)	2/518 (0.4%)	0.1 (0.07–0.11)	0.737	73/3211 (2.3%)	21/1739 (1.2%)	52/1472 (3.5%)	−2.3 (−4.7 to −1.1)	0.080

Data are presented as number (%). [a]P-values were generated from the Adjusted Wald test (difference of proportions between daycare vs. usual care adjusted for clusters). [b]The difference in percentage points between daycare and usual care. [c]Included referral and death as failure. [d]Lost to follow-up includes leave against medical advice (LAMA) plus drop-out children.

Table 3: **Primary and secondary outcomes between Day care (DCA) and Usual care (UC).**

CI, −17.7 to −4.3, p = 0.018) sites. The difference in relapse within days 7–14 among those previously well on day 6 was comparable between all DCA and UC children, relapse was greater in DCA than UC (p = 0.001) and UC than DCA (p = 0.003) in urban and rural sites, respectively. One child each in UC of both urban and rural sites died within day 6 after admission (Table 3). In regression analysis, underweight children, younger children (<2 years), higher pulse rate (>160/min.) crepitation, and oxygen saturation <90% had a greater risk of treatment failure on or before day 6 (Table 4).

Economic outcome

Overall, the mean soceital cost per patient was estimated to US$94.2 and US$184.8 for DCA and UC, respectively (Table 5). The average cost was highest at urban sites of usual care (US$221.7) which was mainly driven by indirect costs (caregiver's productivity loss, US$110.3). Hence, the cost difference was mainly driven by caregivers' time cost (mean difference US$−69.8; [95% CI: −73.5 to −66.2]) which was about three times higher for children who received UC. The mean cost difference was US$-90.6 (95% CI: US$-96.7 to US$-84.5) and the outcome difference was 0.04 (95% CI: 0.02 to 0.06). This produced an ICER of US$-2288 (dominant) which means DCA is a cost-saving intervention (lower cost with a higher outcome). Considering study areas, the mean cost and outcome difference was US$-117.9 (95% CI: US$-127.6 to US$-108.2) and −0.04 (95% CI: −0.08 to −0.01); and US$-29.0 (95% CI: US$-34.1 to US$-23.9) and 0.10 (95% CI: 0.07 to 0.14) for urban and rural, respectively. Given the greater effectiveness at a lower cost, the DCA is cost-saving (ICER US$-273). However, for urban, DCA was less costly as well as less effective (ICER US$6121) which reveals DCA intervention required US$6121 per additional success over UC (economic analysis details to be published elsewhere).

Discussion

Significant constraints exist in LMICs that limit access to care of children 2–59 months of age with severe pneumonia with or without malnutrition. Our earlier efficacy studies showed the DCA to treat severe childhood pneumonia to be safe and less costly than UC.[10–13] The current study in a more "real world" context demonstrated superior day six treatment success in the DCA compared with UC in rural areas while better rates were observed with UC than DCA in the urban setting. Importantly, treatment failure/success within the health system in its entirety was equivalent between the two treatment approaches, i.e., with the inclusion of children who failed treatment at the DCA and UC levels and who were referred to and received higher-level care.

Variables	Urban			Rural			Combined data		
	Adjusted Risk Ratio[a]	95% CI	p-value	Adjusted Risk Ratio[b]	95% CI	p-value	Adjusted Risk Ratio[b]	95% CI	p-value
Wealth index									
Poorest	1.18	0.66, 2.1	0.583	3.60	1.17, 11.09	0.026	1.37	0.84, 2.24	0.212
Poorer	1.19	0.73, 1.92	0.486	3.29	0.93, 11.63	0.065	1.36	0.85, 2.15	0.198
Middle	1.12	0.70, 1.81	0.627	4.20	1.53, 11.55	0.005	1.25	0.80, 1.96	0.317
Richer	1.15	0.68, 1.97	0.599	3.98	1.31, 12.1	0.015	1.37	0.85, 2.19	0.195
Richest	Ref.						Ref.		
Child's age categories									
2–5 months	2.43	1.62, 3.64	<0.001	2.59	1.07, 6.24	0.034	2.57	1.77, 3.73	<0.001
6–11 months	1.68	1.11, 2.53	0.024	1.25	0.45, 3.45	0.667	1.65	1.12, 2.44	0.012
12–23 months	2.15	1.62, 2.86	<0.001	1.41	0.54, 3.72	0.485	1.93	1.46, 2.54	<0.001
24–59 months	Ref.			Ref.			Ref.		
Father's education									
Illiterate	0.61	0.37, 1.01	0.056	5.46	0.51, 58.75	0.161	0.85	0.52, 1.38	0.512
Primary	0.70	0.52, 0.96	0.026	4.87	0.44, 54.01	0.198	0.88	0.61, 1.27	0.354
Secondary	0.79	0.54, 1.13	0.195	2.28	0.29, 18.26	0.436	0.86	0.59, 1.27	0.452
Higher	Ref.			Ref.			Ref.		
Father's occupation									
Skilled worker, office executive office non-executive	1.01	0.68, 1.51	0.941	0.82	0.40, 1.67	0.587	1.00	0.70, 1.41	0.984
Businessman/rickshaw	1.03	0.79, 1.34	0.816	0.77	0.47, 1.27	0.306	1.00	0.78, 1.28	0.975
Other/day labor, Garment/Industry worker	Ref.			Ref.			Ref.		
Mother's education									
Illiterate	1.20	0.77, 1.88	0.426	0.21	0.05, 0.91	0.037	0.91	0.57, 1.45	0.678
Primary	0.95	0.55, 1.63	0.844	0.33	0.07, 1.62	0.173	0.82	0.47, 1.42	0.471
Secondary	1.01	0.66, 1.56	0.954	0.40	0.09, 1.72	0.218	0.91	0.57, 1.44	0.684
Higher	Ref.			Ref.			Ref.		
Mother's occupation									
Housewife	1.05	0.78, 1.42	0.725	0.32	0.14, 0.76	0.01	0.99	0.73, 1.36	0.962
Others	Ref.			Ref.			Ref.		
Child's sex									
Male	0.96	0.78, 1.18	0.693	0.84	0.48, 1.46	0.536	0.95	0.77, 1.16	0.587
Female	Ref.			Ref.			Ref.		
Child underweight (WAZ < −2)									
Yes	1.53	1.22, 1.92	<0.001	1.38	0.92, 2.06	0.116	1.54	1.29, 1.84	<0.001
No	Ref.			Ref.			Ref.		
Rapid breathing (Res. Rate/min)									
<50/min	Ref.			Ref.			Ref.		
50–59/min	1.52	0.84, 2.74	0.164	0.35	0.12, 0.98	0.046	1.11	0.66, 1.86	0.687
≥60/min	1.98	1.15, 3.43	0.014	0.50	0.16, 1.56	0.232	1.52	0.94, 2.45	0.087
Pulse rate (/min)									
<120	Ref.			Ref.			Ref.		
120–140	1.20	0.62, 2.33	0.592	1.28	0.40, 4.1	0.681	1.31	0.73, 2.35	0.373
141–160	1.40	0.74, 2.66	0.307	1.45	0.43, 4.87	0.548	1.49	0.81, 2.76	0.201
>160	1.60	0.92, 2.80	0.099	2.20	0.52, 9.26	0.281	1.84	1.05, 3.25	0.034
Duration of cough									
1–5 days	Ref.						Ref.		
Six or more days	1.20	0.93, 1.56	0.162	2.15	1.14, 4.06	0.018	1.26	0.97, 1.65	0.089
Oxygen saturation									
≥90%	Ref.			Ref.			Ref.		
<90%	1.52	1.15, 2.03	0.004	5.87	3.39, 10.16	<0.001	2.24	1.64, 3.06	<0.001
Crepitation									
Yes	1.63	1.06, 2.51	0.027	1.85	0.38, 9.02	0.445	1.69	1.06, 2.69	0.029
No	Ref.			Ref.			Ref.		

(Table 4 continues on next page)

Variables	Urban			Rural			Combined data		
	Adjusted Risk Ratio[a]	95% CI	p-value	Adjusted Risk Ratio[b]	95% CI	p-value	Adjusted Risk Ratio[b]	95% CI	p-value
(Continued from previous page)									
Unable to drink or breastfed									
Yes	0.92	0.74, 1.15	0.46	0.67	0.38, 1.18	0.164	0.91	0.72, 1.15	0.430
No	Ref.			Ref.			Ref.		
Grunting									
Yes	0.91	0.75, 1.09	0.284	0.45	0.24, 0.84	0.013	0.74	0.61, 0.90	0.002
No	Ref.			Ref.			Ref.		
Study arm									
Daycare	1.03	0.79, 1.33	0.847	0.49	0.26, 0.93	0.028	0.86	0.62, 1.19	0.357
Usual care	Ref.			Ref.			Ref.		
Place of residence									
Urban	n/a	n/a	n/a	n/a	n/a	n/a	Ref.		
Rural	n/a	n/a	n/a	n/a	n/a	n/a	0.48	0.31, 0.74	0.001

Ref. = Reference category; n/a = not applicable. [a]Adjusted risk ratios, 95% confidence intervals and p-values were obtained from log-binomial regression model using the generalised estimating equation. [b]Adjusted risk ratios, 95% confidence intervals and p-values were obtained from log-Poisson regression model using the generalised estimating equation since it was not converged in log-binomial regression.

Table 4: **Factors associated with failure at day six (Multiple generalised estimating equation model).**

While not different between DCA and UC when urban and rural data were combined, relapse rates were greater in the DCA than UC and UC than DCA children in the urban and rural sites, respectively. This might reflect differences in antimicrobial use in the two settings. Specifically, urban DCA antibiotics were administered for a fixed five days compared to UC in which some received antibiotics for 7–10 days; in the rural sites, DCA children received ceftriaxone while UC children received ampicillin and gentamicin. Specific antibiotic use in control UC clusters, especially in the private hospitals was to some extent more heterogeneous with children treated with the recommended treatment protocols of the respective health facilities which might have included ceftriaxone, gentamicin, and/or flucloxacillin.

DCA avoids hospitalisation and is relatively simple and less costly. The cost difference between the two care models was striking with UC cost approximately double that of DCA and which was driven primarily by greater indirect costs incurred by families in the UC group through items such as lost wages of caregivers because of the greater time demands associated with UC management. DCA was also less costly than UC to the health system but the difference was less dramatic than that among the households. The analysis, therefore, demonstrates DCA as a dominant (cost-saving) alternative and more cost-effective intervention in comparison to UC, i.e., provides an equivalent/higher effectiveness but at a lower cost. The greater financial burden on caregivers in UC compared to DCA model in indirect time costs likely contributes to hesitancy to seek expeditious care. Programmatic implementation of the DCA, therefore, has the potential to reduce healthcare inequity by facilitating access to crucial services.

Ambulatory treatment modalities have been reported from Pakistan in uncomplicated pneumonia (according to WHO classification 2013) without co-morbidities providing oral antibiotics in the community.[18–20] The DCA, unlike community-based management, addresses severe pneumonia with hypoxaemia which is a serious complication associated with significantly increased

Cost categories	Day care approach (DCA)			Usual care (UC)		
	Overall (n = 1739)	Urban (n = 742)	Rural (n = 1002)	Overall (n = 1472)	Urban (n = 957)	Rural (n = 515)
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Direct medical (e.g., medicines, physician)	59.5 (58.2, 60.7)	73.3 (71.0, 75.7)	49.2 (48.2, 50.2)	65.9 (63.4, 68.3)	85.0 (82.0, 88.1)	30.3 (28.7, 31.8)
Direct non-medical (e.g., transport, food)	1.8 (1.7, 2.0)	1.5 (1.3, 1.8)	2.1 (1.9, 2.3)	6.4 (6.0, 6.7)	7.8 (7.2, 8.3)	3.8 (3.4, 4.1)
Indirect/productivity loss (e.g., time cost)	25.8 (24.6, 27.0)	24.6 (23.0, 26.3)	26.7 (25.0, 28.3)	95.6 (91.9, 99.3)	110.3 (105.2, 115.5)	68.2 (64.6, 71.9)
Capital and recurrent cost	6.5 (6.3, 6.7)	3.5 (3.3, 3.7)	8.8 (8.5, 9.1)	10.7 (9.9, 10.2)	12.1 (11.8, 12.2)	7.3 (7.1, 7.5)
Average cost per patient (US$)	94.2 (92.2, 96.3)	103.8 (100.5, 107.1)	87.1 (84.6, 89.6)	184.8 (178.6, 190.9)	221.7 (213.5, 229.9)	116.1 (111.0, 121.2)

Table 5: **Estimated average societal costs by urban-rural cost distribution with cost differences between DCA and ET (US$2019).**

mortality. It is estimated that ≥13% of children with severe pneumonia requiring admission to health facilities have hypoxaemia.[21] Therefore, there are an estimated 1.5–2.7 million cases of hypoxaemic pneumonia[22] amongst the 11–20 million children presenting to hospitals with pneumonia, nearly all of whom have the potential to be successfully managed by DCA. We believe the DCA modality of treatment can be readily replicated within most existing urban and rural outpatient facilities of LMICs with staff training and the provision of logistic support. These results offer reassurance of the DCA as a viable effective, safe, and affordable alternative to UC, evidence needed prior to consideration by policymakers to invest limited healthcare resources into larger-scale programmatic implementation.

A strength of our trial is the integrated treatment of severe pneumonia together with most childhood illnesses (e.g., malnutrition, diarrhoea) except for severe disease (e.g., SAM, sepsis, diarrhoea with severe dehydration, meningitis). Moreover, the daycare facilities were in relatively close proximity to the communities where children and families resided and attractive to the parents/caretakers. We provided pulse oximeter and oxygen therapy capacity (included in the economic analyses) in the daycare clinics including in the rural areas.

Our study has certain limitations. For safety reasons, we provided trained staff (physicians and nurses) to the existing primary health centres for the DCA care of these very sick children as these primary health care centres were run mostly by paramedics. There was heterogeneity in certain baseline characteristics including child age, breastfeeding status, family income, and specific symptoms of illness as well as in certain outcomes such as relapse rates between DCA and UC groups. The UC group had significantly greater hypoxaemia, high fever, grunting and lethargy, which are the key features of 'severe pneumonia', that is, UC group may have been a sicker cohort. Differences are not unexpected in an effectiveness trial in which efficacy trial type of matching is not done, however, the extent to which these differences might have influenced study outcomes is not clear. The mortality rate in our study population was low including no death among the children treated in the DCA either in the acute or the follow-up phase, which is reassuring. We attribute this in part to the careful exclusion of children with some features (convulsion, severe sepsis, altered consciousness, severe dehydration, etc.) of severe disease not manageable in the Day care clinics described under exclusion criteria as well as referral of day six treatment failures to a higher level of care. A common barrier encountered during trial implementation was the need to upgrade the primary healthcare settings into daycare settings, equipped to provide severe pneumonia treatment in children on par with inpatient facilities but for a shorter period. There was also the need for community awareness of the availability of the daycare facility for severe pneumonia treatment. With the launching of an awareness programme in the communities involving major stakeholders along with the provision of quality care, this was successfully achieved; there was also the added benefit of the education of parents/caregivers on the danger signs of severe pneumonia and when to seek health care. The sample size of this study—both in urban and rural sites were large which we considered representative and generalisable for the Bangladeshi population. We recommend further study with a large sample size in other settings in other countries.

The current study demonstrates that 80–90% of children with severe pneumonia with or without malnutrition were successfully treated in Day care clinics within the context of the health systems and at a much lower cost than the current standard of hospital-based treatment both in rural and urban settings. A modest investment in the development and upgrading Day care facilities through capacity building of human resources and procurement of supporting equipment provides a medical and cost-effective alternative to hospital management of severe childhood pneumonia and other common co-morbidities.

Contributors

NHA, HA, NG, GJF, TD, MJC, MS, KZ, and TA conceived, designed, and developed the study protocol. NHA, ASF, MS, SA, EH, SN, SA, MT, RA, AHM, LK, MoS, WK, KI, MK, and MV supervised the data collection. NHA, ASF, MS, and MT analysed the data. NHA, ASF, NG, GF, TD, MS, SN, SA, MT, and MJC wrote the manuscript. The NHA and MT have verified the underlaying data.

Data sharing statement

Request for access to data used for analysis for this manuscript can be made by contacting the corresponding author.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102023.

References

1 McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *Lancet Glob Health*. 2019;7:e47–e57.
2 Caulfield LE, de Onis M, Blössner M, Black RE. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. *Am J Clin Nutr*. 2004;80:193–198.
3 Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008;371:243–260.

4 Save the Children. Changing lives in our lifetime. In: *Global Childhood Report*. 2019.
5 World Health Organization (WHO). Pneumonia. https://www.who.int/news-room/fact-sheets/detail/pneumonia; 2021.
6 United Nations Children's Fund. One is too many. https://www.unicef.org/reports/one-too-many; 2016.
7 World Health Organization (WHO). World health statistics. https://www.who.int/docs/default-source/gho-documents/world-health-statistic-reports/world-health-statistics-2015.pdf; 2015.
8 World Health Organization (WHO). World health statistics. https://www.who.int/publications/i/item/9789241563819; 2009.
9 Saha S, Santosham M, Hussain M, Black RE, Saha SK. Perspective piece rotavirus vaccine will improve child survival by more than just preventing diarrhea: evidence from Bangladesh. *Am J Trop Med Hyg*. 2018;98:360–363.
10 Ashraf H, Jahan SA, Alam NH, et al. Day-care management of severe and very severe pneumonia, without associated co-morbidities such as severe malnutrition, in an urban health clinic in Dhaka, Bangladesh. *Arch Dis Child*. 2008;93:490–494.
11 Ashraf H, Mahmud R, Alam NH, et al. Randomized controlled trial of day care versus hospital care of severe pneumonia in Bangladesh. *Pediatrics*. 2010;126:e807-15. https://doi.org/10.1542/peds.2009-3631.
12 Ashraf H, Alam NH, Sultana M, et al. Day clinic vs. hospital care of pneumonia and severe malnutrition in children under five: a randomised trial. *Trop Med Int Health*. 2019;24:922–931.
13 Ashraf H, Jobayer M, Haque N. Treatment of childhood pneumonia in developing countries. *Health Manag*. 2010. https://doi.org/10.5772/9887.
14 World Health Organization (WHO). Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. https://apps.who.int/iris/handle/10665/81170; 2013.
15 Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes, 2nd ed. *Am J Prev Med*. 1998;14:243.
16 Sultana M, Alam NH, Ali N, et al. Household economic burden of childhood severe pneumonia in Bangladesh: a cost-of-illness study. *Arch Dis Child*. 2021;106(6):539–546. https://doi.org/10.1136/archdischild-2020-320834.
17 Hayes R, Bennett S. Sample size calculation for cluster randomized trials. *Int J Epidemiol*. 1999;28:319–326.
18 Soofi S, Ahmed S, Fox MP, et al. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial. *Lancet*. 2012;379:729–737.
19 Bari A, Sadruddin S, Khan A, et al. Community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Haripur district, Pakistan: a cluster randomised trial. *Lancet*. 2011;378:1796–1803.
20 Hazir T, Fox LAM, Nisar YB, et al. Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. *Lancet*. 2008;371:49–56.
21 Subhi R, Adamson M, Campbell H, Martin W, Smith K, Duke T. The prevalence of hypoxaemia among ill children in developing countries: a systematic review. *Lancet Infect Dis*. 2009;9:219–227.
22 Duke T, Subhi R, Peel D, Frey B. Pulse oximetry: technology to reduce child mortality in developing countries. *Ann Trop Paediatr*. 2009;29:165–175.