

Project title

Effectiveness trial of day-care (DCA) versus usual care management of severe pneumonia with or without malnutrition in children using the existing health system of bangladesh (Phase I: january 2015 to december 2017; Expansion or phase II : 1.7.2017 to 31.1.2019)

Expansion phase II: Start: 1.7.2017

(EAGLE supported) Start of patient enrolment in new study sites: 1.11.2017

Project report II to EAGLE Foundation period 1.7.2018 till 31.12.2018

Date: 15.1.2019

Place of performance

07 study sites in Dhaka city and in rural areas northwest and northeast of Dhaka and Centre for Health and Population Research (icddr), Dhaka, Bangladesh in cooperation with university of Basel, Switzerland and University of Kentucky, Lexington USA.

Investigators

Nur H Alam, Abu SG Faruque, Jubair Chisti, Shahjahan Ali, Tahmeed Ahmed, Shahnawaz Ahmed, George Fuchs, Trevor Duke, Niklaus Gyr

Project brief

Principal Investigator	Dr. Nur Haque Alam, icddr Email: nhalam@icddr.org
Original project duration	January 2015 to January 2019 Expansion phase: July 1st 2017 until January 31st 2019
Donor	UNICEF Switzerland, Botnar Foundation & UBS Optimus Foundation, Switzerland , EAGLE Foundation Switzerland
Implementing Partners	icddr, MoHFW, UNICEF, Pathfinder, PSTC and CWFD
Implementation Location- 7 sites	Urban – Tikatuli, Circular road and Dhalpur Rural – Dhamrai, Karimganj, Pakundia, and Kishoregonj Sadar
Original Target	3500 children to be treated for severe pneumonia through Day care approach and referral system and existing treatment
Achievement till 31 December 2018	3134 children with severe pneumonia have been enrolled (intervention + control) for treatment under this study protocol
Budget of expansion phase	USD 1 856 282, not including USD 136 815 for the 2 international cooperators and experts G.Fuchs USA and N.Gyr Basel, now partly supported by EAGLE and UNICEF special grant

EAGLE Foundation Grant

USD 25 414 for travel, administrative and office expenses of Prof. N.Gyr (no honorarium)

Background of the project

Successful management of children with severe pneumonia (WHO 2013) requires hospitalization for antibiotic and supportive treatment such as pulse oximetry, oxygen

therapy, nebulization, nasopharyngeal clearance and monitoring etc. Most, if not all, developing countries including Bangladesh do not have enough paediatric hospital beds to accommodate the demand for admission of all children with severe pneumonia with or without malnutrition and other co-morbidities. It is therefore important to provide some other form of institutional care for those children suffering from severe pneumonia and malnutrition who cannot be hospitalized, but are too sick to be managed in the community.

The project team developed an **innovative and unique model** of Day Care Approach (DCA) as a safe and less expensive alternative to hospital management of severe childhood pneumonia and malnutrition. The new management approach has proven to be efficacious and cost-efficient (>33% less expensive) in several efficacy studies in urban Mirpur, Dhaka, under optimal test conditions (EAGLE study Pediatrics 2010)

Purpose of the study

The aim of the present trial is to prove the safety, efficacy and effectiveness of DCA within the Bangladeshi health system in a large effectiveness trial- on a quasi strategic level

Study design and study locations

The project has been designed as cluster randomized controlled trial involving Primary Health Care Facilities in urban and rural areas under the health system of Bangladesh. The locations are:

Urban location (Wards)	Rural location (Unions)
Intervention and Day Care Clinic	
Tikatuli, Dayaganj, Wari, Jatrabari, Bashabo, Dhalpur, Shantinagar and Circular Road involving the Surjer Hashi Clinics	Dhamrai - Kushura , Sanora , Shombhag , Kulla Karimganj - Baroghoria, Joyka, Niamatpur, Gundhor Pakundia – Patuabhanga, Hosendi, Narandi, Sukhia Kishorgonj Sadar –Baulai, Jasodal, Danaptali, Majikhpan involving the Health and Family welfare Clinics (HFWCs) under the Ministry of MoHFW
Control clinics (existing treatment protocol)	
Gandaria, Begumganj, Muradpur, Lalbagh, Aftabnagar, Maniknagar, Taltola and Badda involving the Surjer Hashi Clinics .	Balia, Jadabpur , Baishakanda , Nannar, Jafrabad, Kadirjongal , Noabad , Dahunda Jangalia, Barudia, Egarasindur, Charfaradi Binnati, Maria, Koshakariail, Chauddasata involving HFWCs under the MoHFW

Case Management of Pneumonia

- Children with pneumonia with/without malnutrition will be identified or those who are self-referred will be treated at home with oral antibiotic for 5 days.
- Those children with pneumonia (i.e., not severe pneumonia) who will fail after two days of oral antibiotic therapy will be referred to hospital/DCA treatment if they fulfill the criteria of **severe** pneumonia.
- Children with **severe** pneumonia are referred directly to the hospitals/Day care clinics.

How Day care management works

Day Care treatment facility is a modified outpatient clinic with facilities similar to a hospital and equipped with trained physicians and nurses, 2-3 pediatric beds, availability of oxygen therapy with pulse oxymetry for measurement of oxygen saturation, long acting injectable antibiotics, nasophayngeal suction, nebulization facilities and calorie dense diet for the children. The facility operates daily during office hours from 8:30 AM to ~4 PM.

Children stay during this period. If not stabilized within this period then the children are referred to the referral hospitals. Cell phone networking is maintained during night hours to guide or refer children to appropriate facilities. There is a regular follow up.

Development of the study.

As experienced in the day-care follow-up trial of the original EAGLE study we were and are observing a similar delay of patient enrolment in the present effectiveness trial. It has most likely to do with a lower than predicted incidence of severe pneumonia which may be attributed to the introduction of the anti-pneumococcal and anti-H.influenza vaccination into the EPI (Vaccination programme). To reach the statistically required enrolment numbers we therefore decided in 2017 to have an **expansion phase** extending the trial in time by at least one year (till January 31st 2019) and to increase the number of study sites by three resulting in totally seven .The extension and expansion phase would hopefully allow us to reach the target number of 3500 children and thus to present convincing data to the health authorities.

Development 2nd half 2018 and situation of the trial per Dec 2018

Meeting of UNICEF, BOTNAR and UBSOF representatives with Prof. G. Fuchs and Niklaus Gyr in Zürich , June 28/ 29th 2018 and consecutive work.

Conclusions: the general progress and quality of the study were recognized and well accepted. Some budget issues have to be cleared with icddr and UNICEF Dhaka. It became obvious that a no cost extension will have to be granted to finish the project. Whether one could reduce the number of patients to be enrolled will have to be discussed with the statisticians as it ensues a reduction of the statistical power. There was also one sponsor who might grant additional support in case the budget would not be sufficient.

Enrolment (tables 1): Since start of the expansion phase in July 2017 1586 additional patients with severe pneumonia have been enrolled in the 18 months period resulting in a total of 3134 patients on December 31st 2018. There is still a gap of 366 patients to the original target envisaged. Again enrolment was lower than anticipated even after opening of the new study sites. We therefore decided in November 2018 after consultation with statisticians to reduce the statistical power from 0.85 to 0.80 which would allow us to reduce the enrolment target number to 3000 patients plus 2 to 300 patients for compensation of drop outs. The statistical power of 0.80 is well accepted by high ranked journals like NEJM or The Lancet and thus will yield a valid result. In addition an extension of the recruitment period up to February or March 2019 had to be planned which would allow us to finish the project in November/December 2019.

Quality of study: Clinical care, data entry and work off have been checked by the project team and Prof. G.Fuchs during his visit in June 2018 and November 2018 and appeared well performed promising convincing results.

Clinical outcome: As predicted based on the previous studies the success rates appear to be equal for DCA and control patients, amounting to about 90% in the rural study area and 80% in urban trial sites.

Economic outcome, preliminary :

Table: Comparison of household cost: DCA vs. ET (US\$)

Cost indicators	DCA	ET	Times higher
	n=1242	n=1247	
Total direct cost	5.49	50.2	9.14
Total indirect cost	21.34	74.11	3.47

Total cost	26.83	124.31	4.63
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Household cost of severe pneumonia was around 5 times higher for standard care than with DCA.

DCA in total appears to cost at least a third less than standard care.

Dissemination: Dr. Khalida Islam, Director of Primary Health and IMCI, was very favorably impressed with the study objectives and its implementation: She is interested having daycare management of pneumonia and malnutrition scaled up throughout the Bangladesh health care system. This view also was shared by the president of the Bangladesh Pediatric Society. The interest of these 2 key persons has recently been confirmed again.

Trial budget : At the end of September 2018 USD approx. 541 290 were left to finish the trial. The extension to end of 2019 as well as the planned dissemination activities with final symposium and workshop in fall 2019 will likely result in a financial gap of about USD 142 00. Submission for support will follow soon to one of our main Sponsors (January 17th 2019).

Activities of N.Gyr during the period covered by this report

N.Gyr was very much involved in the budgeting process and thereafter in budget control for the UNICEF,BOTNAR-EAGLE expansion phase grant as well as in budget development of the final extension. He was also involved in follow up of study results. The international communication was maintained with regular skype conferences,direct phone calls as well as e-mails and visits with sponsors in Switzerland.

Last visit of Dhaka in November 2017. Visit of UNICEF, Switzerland in January 2018 and June 2018. For health reasons N.Gyr was unable to visit Bangladesh in 2018.