

# Cost and Clinical-Effectiveness of Implementing Integrated Services for Children with Epilepsy in Primary Care in an Outreach District in Pakistan

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## Abstract

**Background:** In order to tackle the considerable treatment gap for childhood epilepsy in many low- and middle-income countries (LMICs), a task sharing model is recommended whereby care is integrated into primary health services in outreach financially constrained districts. However, there are limited data on implementation and impact of such services in poor settings. Our study aimed to explore the perspectives of service users on the clinical-effectiveness and cost-effectiveness of childhood epilepsy treatment received in a task-shared model in an outreach-financially constrained district Bhakhar-Pakistan.

**Methods:** A qualitative interventional case control study was carried out using the center records and interviews with 240 children with epilepsy (160 being followed at the community childhood epilepsy center and 80 (control) receiving care as usual). Most of the care received was focused on medication provision with limited information provided on how to manage their illness and its effects.

**Results:** Among the children getting free AEDs and monthly pediatric neurology consultations, AEDs adherence of 85% and treatment gap of 20% was documented. In comparison the children receiving epilepsy treatment care as usual (control), had AEDs adherence 38% and childhood treatment gap was 82.5%. Childhood epilepsy treatment from local community center was 202 times cost-effective as compared to such treatment from Lahore. By integration and implementation of childhood epilepsy center in primary health financial constraints and issue of childhood epilepsy treatment could be easily sorted out.

**Conclusion:** Task-sharing improved the overall care of childhood epilepsy. Nonetheless, promotion of community involvement and family engagement were highlighted as areas requiring further improvement. Future work on implementing epilepsy care model in primary care in LMIC contexts is warranted.

**Keywords:** Epilepsy; Implementation; Task-sharing; Primary health services; Community health care; Bhakhar; Pakistan

## Introduction

The most contributing factors to the epilepsy treatment gap are the following:

- Inadequate skilled healthcare manpower.
- High treatment costs.
- Limited or no antiepileptic drug access.
- Unfavorable cultural beliefs.

These factors jointly play a role in most regions of low-middle-income-countries (LMICs), where the treatment gap is over 75% [1]. A potential strategy to reduce this treatment gap is the detection, monitoring, and treatment of epilepsy with community-based rehabilitation (CBR). Offering diagnosis, monitoring, and treatment is only one aspect of the CBR strategy. Recent studies have shown that up to 70-80% of newly diagnosed epilepsy patients can be treated successfully by low-cost community-based strategy using anti-epileptic drugs (AEDs) [2-4]. Acknowledging epilepsy as a neglected condition by the World Health Organization (WHO) in 2004 has led to increased emphasis on the development of adequate treatment strategies in LMICs [5,6].

Although cost-effective epilepsy treatments are available and accurate diagnosis can be made without technological equipment, a vast majority of individuals with epilepsy in many resource poor regions do not receive treatment (i.e. have high treatment gap) [7-9]. Treatment of childhood epilepsy in low-income countries is a challenge considering the lack of trained medical personals, priority, financial resources, availability of antiepileptic drugs, and cultural beliefs. Prior anecdotal and descriptive estimates suggest a treatment gap of more than 80% in many low-income countries [10-12]. In agreement in 2014, we documented by snap-shot study that 58% children with epilepsy (CWE) were non-adherent to the prescribed AEDs and 92% had childhood epilepsy treatment gap (CETG) [13,14]. Large community-based trials in Brazil and China have demonstrated that epilepsy can be treated with inexpensive and effective drugs at the community level by primary health professionals with basic training [15]. The Demonstration Projects have been successful in implementing treatment and management of convulsive forms of epilepsy in rural areas of the LMICs.

Physicians with basic training are shown to be able to treat people with epilepsy. This cost-effective approach was successful in reducing the epilepsy treatment gap [9].

In these lines we hypothesized that establishment of primary health multicomponent intervention childhood epilepsy center (PHMCICEC) in Bhakhar, an outreach financially constrained district in Punjab-Pakistan would improve AEDs adherence and would bridge the huge treatment gap among children with epilepsy. After 4 years of monthly free childhood epilepsy camps, telepediatricneurology support and after two years of integration and implementation of childhood epilepsy (CE) into already existing primary health care center, this study will therefore evaluate the feasibility and (cost-)effectiveness of PHMCICEC, in comparison with care as usual (CAU). As the success of any intervention is a consequence of it being sustainable in the long term, this report also presents the lessons derived for the development of an effective and sustainable framework for epilepsy care and scale-up to improve care of CWE in outreach financially constrained district in Pakistan

## Methods

This study will consist of two parts, each with its own research questions:

### Economic evaluation

What are the cost-effectiveness and the cost-utility of the PHMCICEC in comparison with CAU from a societal perspective?

### Clinical effectiveness

Is multi-component intervention childhood epilepsy center (MCICEC), through integration of childhood epilepsy care in primary health care (PHC), empowering it through combination of free consultations, antiepileptic drugs (AEDs), monthly pediatric neurology camps (management/education program) with e-Health interventions were assessed for effectiveness in anti-epileptic drugs (AEDs) adherence, bridging the treatment gap (TG) and improving epilepsy seizure control in comparison with care as usual (CAU) in an outreach financially-constrained district.

### Design

A randomized case controlled trial (RCT) with two parallel groups of CWE:1) children diagnosed, commenced AED (s) and being followed at MCICEC and 2, children getting care as usual (control), as naturally as possible was conducted to compare the efficacy of MCICEC with CAU in CWE. The AED (s) were commenced at least 3 months prior to the study, among the intervention group and the control group. After documentation for the study, patients in the control group (CAU) had the opportunity to receive care from the MCICEC. The study has been approved by the Ethics Committee of the Brain Associates Lahore.

## Participants and recruitment procedure

Children diagnosed with epilepsy, commenced AEDs at least  $\geq 3$  months back and being followed at TDBUCEC Bhakhar, along with a primary caregiver (s), were approached for study participation from the free pediatric neurology camp held at two noncontiguous community centers. Participants were  $\leq 18$  years of age, diagnosed with epilepsy and prescribed at least one AED. To complete questionnaires and assent/consent forms, families had to read/speak Suraikee (local language), which was later translated into English. Exclusion criteria included diagnosis of epilepsy less than three months back or who were not being followed in primary health multicomponent childhood epilepsy center (PHMCICEC), or the family living  $>100$  miles away from Bhakhar City. In collaboration with the childhood epilepsy team working at PHMCICEC, potential participants and their caregivers meeting eligibility criteria were identified by the trained research assistants with significant experience recruiting families with children with epilepsy. Recruitment occurred during free childhood epilepsy camp visits. The trained research assistant approached families, provided a thorough overview of the study, including study procedures, benefits, and risks, along with answering any questions. Caregiver/guardian participants provided verbal consent, and verbal assent was obtained from older children. Once consent/assent was obtained, caregivers completed baseline assessment questionnaires. Caregivers also completed several questionnaires, which were used to measure feasibility and acceptability, psychosocial outcomes (e.g., quality of life) and financial constraints. With the exception of feasibility and clinical effectiveness, these questionnaires were not analyzed for purposes of the current study. This study was divided into two phases; 1) Assessment of MCICEC integration into primary health care centre and its sustainability and 2) clinical effectiveness of PHMCICEC in improving AEDs adherence and decreasing the childhood epilepsy treatment gap (CETG).

## Setting and recruitment

The settings for the implementation of the PHMCICEC care plan in Pakistan was Bhakhar district, located 420 km south of the capital city Lahore of Punjab province. This city has district headquarter hospital and paediatric department headed by a qualified paediatrician but no paediatric neurologist is available in the city. There are many private hospitals and clinics providing all sorts of paediatric services. Also, there are traditional healers, who are thought to possess medicinal antidotes to the occurrence of epilepsy and other neurological diseases in the children. This study is collaboration between Top-Down-Bottom-Up-Childhood-Epilepsy-Program under the auspices of the Brain Associates Lahore and the PHMCICEC Bhakhar city on 7th and 8th December 2018. The study is conducted in PHMCICEC and children attending free pediatric neurology camps at two non-contiguous community centers in Bhakhar city.

The following issues were considered before and while implementing the model: initiating public education and advocacy activities, estimating the size of the problem, providing professional education including development of training materials, developing a referral system, choosing a suitable drug, ensuring a regular drug supply, encouraging stakeholder

participation, providing continued monitoring and providing supportive legislation. While all of the above considerations were taken into account in the design of this childhood epilepsy care programme, the local issues were not discounted. Implementation of PHMCICEC in Pakistan commenced in March of 2014 when this strategy was launched voluntarily by Prof. Malik (1st author), with aim to improve the quality of childhood epilepsy care through the integration and implementation childhood epilepsy in primary health care. However, two years back (December 2016) PHMCICEC was integrated and implemented into charity primary care center in this city.

The patients willing to participate had a face-to-face interview with all possible available records with one of the researchers (local or visiting), in which patients had the opportunity to ask questions and in which inclusion and exclusion criteria was checked either by the researchers during the meeting or afterwards in consultation with clinicians. During the meeting, patients were informed about the study and that they will be randomly assigned either to the intervention or control group. During the two days of attending outpatient camps, an informed verbal consent was sought from the CWE/parents. The researcher and patients were allocated randomly to either the intervention or control group.

### Primary Care Multi-Component Intervention Childhood Epilepsy Center (PCMCICEC) Bhakhar

The TDBUCEP is actively involved in outreach and education for the community and healthcare professionals. Our goal is to help the public understand epilepsy, which in turn will make life a bit easier for CWE and their family members. Our complimentary programs and services include:

- Integration and implementation of childhood epilepsy in local community charity primary health care centers (PHMCICEC).
- Skype/mobile tele-pediatricneurology consultations and supporting PHMCICEC.
- Special events like one whole day free pediatric neurology camps in different outreach, financially- constrained communities.

Our center seeks not only to enhance the general awareness of epilepsy, but also to educate the public on first-aid procedures to follow if they see or experience a seizure. For the patient management to be optimised in the patient's own community, we began to explore collaboration with local non-specialist hospitals, community health centers and primary health centers to provide an outreach service in an identical manner like other developments of adequate treatment strategies in low- and middle-income countries (LMICs) [5,6], thus avoiding expensive travelling to the specialist hospitals/clinics in metropolitan cities.

We used Rukhsana Memorial Primary Health Care building, a community-based charity primary health center (CBCPHC) for the detection, monitoring, and treatment of childhood epilepsy (MCICEC). After the struggle of 2 years, we were able to convince this charity organization to integrate childhood epilepsy center into this CBCPHC, just 500 meters from District

Headquarter Hospital in Bhakhar city, 3 stories very specious multipurpose built building on the main road in more than one-acre compound.

We travel monthly from Lahore to Bhakhar the night before the camp as a team (pediatric neurologists, fellows of pediatric neurology and EEG technologists) to have one whole day camp in noncontiguous localities for pediatric neurology problems with special emphasis on childhood epilepsy (i.e., multi component interventional project; Top-Down: outreach clinics, Bottom-UP empowerment of local community, camps in different noncontiguous localities: mobile epilepsy services to remind, education, awareness and Skype/mobile consultations: Telepaedsneurology services). We provide ongoing personnel and volunteer training at all levels to ensure consistency in service delivery. We have trained pediatrician, nurses, medical and paramedical staff already working in this PHMCICEC that is now fully computerized, including its pharmacy and basic laboratory. A local network of community volunteers has been trained with ongoing training to provide education, good quality antiepileptic drugs, and to motivate the CWE/care takers for clinical follow-up. So, we have only invested in training, education and motivation of local workforce, along with our volunteer initiative. This was largely due to an increase in the number of donations and legacies of the local community leaders. In addition to our monthly one whole day of training and consultations of children with neurological disorders, we provide Video-EEG (VEEG) interpretation support, Skype call support and mobile phone advice as and when required.

Financial records were reviewed to establish expenditures on medical supplies, program support costs and staff emoluments for next six months and further donors were sought in the community to assess the sustainability of the programme dependent the on-community participation and making it to be societal as well as integrated into primary health care through periodical evaluation. Antiepileptic drugs are provided free of charge, Moreover, drug supplied are stored for each next six months, so the patients who had been started AEDs may not face an increased risk of seizures/status epilepticus. The MCICEC and primary health care in this center share resources and work very closely together, providing a continuum of care for childhood epilepsy and primary health care in the community to adults and children. This center had been redesignated by consensus as the additional paediatric epilepsy centre because of its performance, personnel, purpose-built infrastructure with geographic integrity, and its highly developed complementary services. Patients and caregivers had the opportunity to discuss their experiences related to the clinical-effectiveness in terms of adherence to AED (s) and bridging the CETG along with cost-effectiveness of the interventions by PHMCICEC. The idea is finding ways to work together to strengthen existing programs and identifying innovative approaches to coordinate use of resources which are critical in responding to childhood epilepsy care in financially constrained community.

### Control group

These are CWE, who visited the free community pediatric neurology camps but without any intervention by PHMCICEC.

After study enrolment, they were offered to get free CE care from the PHMCICEC, without any prejudice.

### Cost-effectiveness

To assess the cost-effectiveness of the PHMCICEC, outcome assessments were done for the both groups: Being followed at PHMCICEC and getting care as usual (CAU). The cost would include direct and indirect cost expenses by the parents of CWE seeking their treatment from Lahore and the cost bearded by the community center in provision of free AEDs and free pediatric neurology consultations.

### Clinical-effectiveness

The following outcomes are defined:

1. **Adherence to AED (s):** Adherence is the primary determinant of the effectiveness and defined as “the extent to which an individual's behavior regarding taking medications and performing lifestyle changes follows agreed recommendations from a health-care provider”[16] The cutoff of 85% for adherence to AEDs by self-report was based on a study by Lisk et al. [17].

2. **Bridging the childhood epilepsy treatment gap (CETG):** The CETG is defined as the number of people with active epilepsy not on treatment (diagnostic and therapeutic) or on inadequate treatment according to ILAE, expressed as a percentage of the total number with active epilepsy [18].

### Economic evaluation

This evaluation primarily adopted a healthcare perspective with the cost of providing care for participants in the two treatment groups over follow-up being compared. We examined such an intervention's clinical- and cost-effectiveness. The study evaluated patients that were offered a comprehensive care package, which included:

- Clinical assessment and commencement of AEDs by primary health care (PHC) workers following the modified mhGAP Intervention Guide (after receiving a 10-day training).
- Education and therapeutic support through individual or family counseling and patient support groups (PSGs) by community counselors (after receiving a 21-day training, in addition to a base training in counseling).
- Arranging face to face monthly consultations for complicated cases with monthly visiting pediatric neurology teams from Lahore, ensuring optimal follow-up care.

We used clinical effectiveness in improving AED (s) adherence and bridging the treatment gap of childhood epilepsy. Process evaluation was performed to assess whether the PHMCICEC has delivered according to protocol and has met its objectives.

The economic evaluation was performed from a societal perspective and was consisting of a cost-effectiveness analysis (CEA) and a cost-minimization analysis (CMA). We distinguish four cost categories: Intervention costs, healthcare sector costs, costs for the patient and family, and productivity costs.

Intervention costs will be defined as all costs related to the PHMCICEC including travel costs, personal costs, material costs, e-Health tools (i.e. Skype/mobile phones) costs and housing costs. Healthcare and patient costs will be estimated using a questionnaire regarding healthcare resource utilization and productivity losses. A comparison between PHMCICEC and CAU will be made in terms of incremental costs and incremental effects in addition to the single consultation for a child with epilepsy/neurology problem from Lahore, a cosmopolitan city 420 Km. from Bhakhar city. To measure the use of health care resources at PHMCICEC including all activities related to childhood epilepsy, we gather data from PHMCICEC and for each patient at two free pediatric neurology camps.

### Statistical analysis

Descriptive statistics describe the characteristics of those recruited into the treatment groups, those retained at follow-up and the epilepsy care they received. Logistic regression tested for the significance of any differences between the groups. Odds-ratios (OR) and 95% confidence intervals (CI) are presented. A p-value of <0.05 was considered statistically significant.

## Results

### Recruitment and treatment groups' equivalence at baseline

Two hundred and eighty eligible CWE were identified and 240 agreed to participate. One hundred and 160 (66.6%) patients were randomized from those being intervened at PHMCICEC, which included diagnosis, commencement of AEDs and monthly follow-up for free consultations and provision of AEDs. Eighty (33.4%) CWE were randomized to care as usual (control) without any PHMCICEC intervention.

The average survey duration for each patient was 15 to 20 minutes (standard deviation: 8.4), and this analysis was of adherence/non-adherence to AEDs and factors associated with promoting drug adherence and treatment gap of childhood epilepsy according to ILAE. The age range of the patients was 4 months to 18 years (mean: 10+3.4 years). There was a male preponderance (134, 58%) with a male: female ratio of 1.26:1. Additional patient demographic information is presented in **Table 1**. The co-primary outcomes were the differences between the intervention and control for:

- Treatment cost.
- Adherence to AEDs.
- Treatment gap.

### Treatment coverage and cost-effectiveness of MCICEC

The registry record of PHMCICEC showed that 2500 CWE are registered with this center integrated in Rukhsana Shafqat Memorial Primary Health Care Center Bhakhar (RSMPHCB) and

on the average 700 CWE get free consultations and AEDs monthly from this center.

**Table 1** Demographic information of study cohorts of children with epilepsy by age and gender in Bhakhar-Pakistan (N=240).

Children with epilepsy following at PHMCICEC (n=160, 100%).				Children with epilepsy not following at PHMCICEC (n=160, 100%).		
Age	Male	Female	Total (%)	Total (%)	Female	Male
4 Mon-2 yrs	18	15	33 (20.65%)	16 (20%)	6	10
>2 yrs-5 yrs	22	10	32 (20%)	18 (22.5%)	8	10
>5 yrs-10 yrs	34	24	58 (36.25%)	26 (32.5%)	12	14
>10 yrs-15 yrs	10	15	25 (15.6%)	14 (17.5%)	4	10
>15 yrs-18 yrs	04	08	12 (7.5%)	06 (7.5%)	4	2
Total: 160 (100%)	88 (55%)	72 (45%)	160 (100%)	80 (100%)	34 (42.5%)	46 (57.5%)

As can be seen in **Table 2**, the geographic and population sizes of the catchment area in Bhakhar district is very large. Yet, the number of CWE receiving care from the PHMCICEC under the auspices of TDBUCEP, are reaching only small fraction of those in need of care. Assuming that about 1% of a given population  $\leq 18$  years of age will be suffering from childhood epilepsy (CE) at any given time [18], one can estimate that about 7,000 CWE are in need of CE service, in addition there will be some CWE from the contiguous districts. Together, these data suggest that, according to the face-to-face interview among the 80 CWE attending free pediatric neurology camps but not being followed at PHMCICEC Bhakhar were seeking treatment: 65 (81.25%) from Lahore, 10 (12.5%) from Multan and 5 (6.25%) from Bhakhar or no treatment. The expenses for each consultation from Lahore and Multan (another cosmopolitan city) were equal, but no trained medical personal for CWE was available in Bhakhar other than the PHMCICEC.

**Table 2** Census of Pakistan 2017 population of Bhakhar district of Punjab.

Variables	Rural	Urban	Total
Population	1390404	260114	1650518
Male	710842	133405	844247
Female	699552	126683	806235
Children $\leq 18$ yrs	557262	105145	662407

On the average cost of the single consultation from the cosmopolitan cities is 16000 PRS (**Table 3**), in addition to costly undue private investigations and newer AEDs. Whereas by integration and implementing PHMCICEC in RSMPCB the additional monthly cost to the dedication of the visiting and local teams are: one additional nurse, PRS 25000, one additional computer operator 20000 PRS, solely for taking care of CWE. Addition of this staff along with training of the already working pediatrician, physician, medical and paramedical staff has improved the overall functioning of RSMPCB. The voluntary cost of the monthly visiting team is 15000 PRS supported by The Brain Associates Lahore; cost of monthly provision of free AEDs

is 500 PRS (from local donations): making total additional cost of 25000+15000+15000+500 (55500 PRS). The average monthly cost of the locally treated 700 CWE from Lahore or Multan would be 11,200,000 PRS (PHMCICEC is 202 time's cost-effectiveness).

### Effect of PHMCICEC intervention on AEDs adherence

Primary outcomes were daily "taking adherence" (proportion of prescribed doses taken) and "timing adherence" (proportion of prescribed doses taken within 1 hour before to 2 hours after the prescribed dosing time), as measured by self-reporting method. We examined three main types of interventions by MCICEC:

- Education and counseling of participants about topics such as epilepsy and medication used to control epilepsy.
- Behavioral interventions such as asking epileptic patients to link the intention of taking their medication with a particular time, place and other routine activity.
- The use of more than one intervention (monthly free pediatric neurology consultations and provision of free AEDs). Such interventions were not reported among the control group.

The study enrolled 240 children and of these 95 (39.6%) CWE were  $\leq 05$  years of age. Among the total children and adolescents with epilepsy who were interviewed, 160 (66.6%) reported seeking treatment from MCIUCEC and 80 (33.4%) were diagnosed commenced on AED (s) from different sources including faith healers, physicians, and government health facilities. The average survey duration for each patient was 15 to 20 minutes (standard deviation: 8.4), and this analysis was of adherence/non-adherence to AEDs and factors associated with promoting drug adherence. The age range of the patients was 4 months to 18 years (mean: 10+3.4years). There was a male preponderance (134, 58%) with a male: female ratio of 1.26:1. Of the total 240 patients, 82 (34%), were nonadherent and 158 (66%) were adherent to the prescribed AEDs for different reasons. Among the 160 CWE commenced AED (s) and being followed at PHMCICEC, 136 (85%) were adherent, while 24 (15%) were nonadherent to the prescribed drugs. While among the 80 CWE not being treated and followed at the center, 50

(62.5%) were nonadherent and only 30 (27.5%) were adherent to the prescribed AED (s). Additional patient demographic information is presented in **Table 4**.

**Table 3** Economic costs due to childhood epilepsy treatment Lahore/Multan (Average travelling persons-4 (Father, Mother, Patient and Siblings).

No	Cost Reason	Cost in Pak Rupees
1	Travel Cost	10000
2	Boarding and Lodging	2000
3	Consultants Fees	2000
4	Off Work	2000
Total		16000

### Factors associated with adherence/nonadherence to AEDs

Factors that were found to be significantly associated with medication adherence in the univariate analysis are costs of AEDs, no response to AEDs, counseling by local faith healers, side –effects of AEDs, Poor/no counseling by the treating physician (s) and Non availability of AED (s). Among the 50 CWE not being treated and followed at TDBUCEC, 28 (56%) reported

the cost of their treatment causing nonadherence to their prescribed AEDs, whereas only 2 (08.3%) reported this cause of their nonadherence among CWE being intervened by MCICEC. Uncontrolled seizures were reported associated with 31.5% of the patients being followed at the center as compared with 12% nonadherent patients among the control cohort. Misleading and false counseling of local faith healers was significantly associated with nonadherence, more prevalence among the CWE being followed at MCICEC (25%), as compared with those affording their own treatment (12%). Additional significant factors Associated with AEDs- adherence/nonadherence are shown in **Table 4**.

### Effect of MCICEC intervention on bridging treatment gap

At both camps a total of 240 children were diagnosed with epilepsy at least ≥3months prior to study date. Of the total 160 (66.6%) were taking treatment from PHMCICEC and 80 (33.4%) had sought care as usual (control) at the time of the study. At baseline, the two cohorts had similar social demographic and clinical characteristics. All CWE included in the study were suffering from active convulsive epilepsy with either primary or secondary generalization. Demographic and clinical characteristics of these groups along source of seeking medical treatment are summarised in **Tables 5 and 6**.

**Table 4** Distribution of children with epilepsy and nonadherence to AEDs by age and gender in Bhakhar-Pakistan (N=240).

Epileptic Patients Following at Top-Down-Bottom-Up Center (n=160, 100%)					Epileptic Patients Not Following at Top-Down-Bottom-Up Center (N=80, 100%)			
Age	Male	Female	Total (%)	Nonad (%)	Nonad (%)	Total (%)	Female	Male
6 Mon-2 yrs	18	15	33 (20.65%)	06 (3.50%)	10 (12.5%)	16 (20%)	6	10
>2 yrs-5 yrs	22	10	32 (20%)	04 (2.50%)	12 (15%)	18 (22.5%)	8	10
>5 yrs-10 yrs	34	24	58 (36.25%)	08 (5%)	16 (20%)	26 (32.5%)	12	14
>10 yrs-15 yrs	10	15	25 (15.6%)	04 (2.50%)	10 (12.5%)	14 (17.5%)	4	10
>15 yrs-18 yrs	04	08	12 (7.5%)	02 (2.50%)	02 (2.5%)	06 (7.5%)	4	2
Total: 160 (100%)	88 (55%)	72 (45%)	160 (100%)	24 (15%)	50 (62.5%)	80 (100%)	34 (42.5%)	46 (57.5%)

A total of 160 CWE being treated and followed at MCICEC 32 (20%) had previously sought medical treatment that was not according to the guidelines of ILAE [19]. In comparison of the 80 CWE, seeking their care as usual (control), 66 (82.5%) were not being treated properly due to various reasons: this means that that CWE being intervened through PHMCICEC had CETG of 20%, as compared to 82.5% of such CETG among patients not being intervened through MCICEC and seeking care as usual. Higher percentage of CETG was documented among the children ≤ 5 years of age (**Table 6**). Attributed causes of the TG were multiple and overlapping in most of the cases, however individual predominant causes of CETG are shown in **Table 7**. These causes were also similar for rural and urban regions. The

highest median (25%) for each was associated with inadequate skilled manpower and uncontrolled seizures among CWE being intervened through MCICEC. In comparison, poverty (42.40%) and inadequate skilled manpower (24.25%) were the predominant cause among the control group.

### Discussion

For many reasons including resource restrictions, simply adopting healthcare guidelines created for higher-resourced areas and using these in resource-limited settings is neither appropriate nor feasible [20]. We propose a package of care, a combination of interventions aimed at improving the

recognition and management of conditions to achieve optimal outcomes for childhood epilepsy in 2014 [13,14]. Limitations in the availability, number, and geographic distribution of specialists trained in the care of childhood epilepsy are a major cause of the delays in accessing care. Several studies have reported that over 90% of people with epilepsy (PWE) in developing countries do not receive appropriate treatment for their condition, a phenomenon known as the treatment gap (TG) [21]. Similarly, in 2014 we documented TGSE of 92% among

children ≤ 18 years of age in Bhakhar: an outreach financially constrained district in Punjab-Pakistan [14]. The most contributing factors to the epilepsy treatment gap are the following:

- Inadequate skilled healthcare manpower.
- High treatment costs.
- Limited or no antiepileptic drug access.
- Unfavorable cultural beliefs [22].

**Table 5** Reasons for nonadherence to AEDS (s) among children with epilepsy in Bhakhar-Pakistan (N=74).

Patients Non-adherent to AED (s) Following at Top-Down-Bottom-Up Center (n=24, 100%)				Patients Non-adherent to AED (s) Not Following at Top-Down-Bottom-Up Center (n=50, 100%)	
No	Reasons for non-adherence to AED (s)	No	Percentage	Percentage	No
1	Cost of AED (s)	02	08.3	56	28
2	No response to AED (s)	08	33.3	12	06
3	Counseling by local faith healers	06	25.0	12	06
4	Side –effects of AEDs	04	16.8		02
5	Poor/no counseling by the treating physician (s)	02	08.3	10	05
6	Non availability of AED (s)	02	08.3	10	03
Total		24	100	100	50

**Table 6** Distribution of epileptic children with treatment gap (TG) by age group and gender in Bhakhar District- Pakistan (n=240).

Epileptic Patients Following at Top-Down-Bottom-Up Center (n=160, 100%)					Epileptic Patients Not Following at Top-Down-Bottom-Up Center (n=80, 100%)			
Age group	Male	Female	Total (%)	TG (%)	TG (%)	Total (%)	Female	Male
2 Mon-2 yrs	18	15	33 (20.65%)	8/35=23%	15/16=94%	16 (20%)	6	10
>2 yrs-5 yrs	22	10	32 (20%)	6/26=23%	16/18=89%	18 (22.5%)	8	10
>5 yrs-10 yrs	34	24	58 (36.25%)	10/61=16.4%	22/26=85%	26 (32.5%)	12	14
>10 yrs-15 yrs	10	15	25 (15.6%)	4/25=16%	10/14=71%	14 (17.5%)	4	10
>15 yrs-18 yrs	4	8	12 (7.5%)	4/13=15%	3/6=50%	06 (7.5%)	4	2
Total:	88 (55%)	72 (45%)	160 (100%)	32/160=20%	66/80=82.5%	80 (100%)	34 (42.5%)	46 (57.5%)
160 (100%)								

The Global Campaign Against Epilepsy, a partnership between the World Health Organization (WHO), International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) was launched in 1997 to bring epilepsy “out of the shadows” by addressing some of the factors outlined above [12,23].

In 2002, several demonstration projects were set up in various countries, to reduce the TG and the physical, economic and social burden of epilepsy through community-level interventions

[23]. Despite this concerted effort by different stakeholders in different countries, there was no such service for CWE in Bhakhar district. We started top-down-bottom-up-childhood-epilepsy-program [TDBUCEP], which is a multi-component strategy for CWE in outreach financially constrained district. After two years of awareness, educational and treatment free pediatric neurology camps, two years prior to study, we integrated and implemented this program into primary health [24].

As guidelines are being implemented, program evaluations to assess their operational performance in clinical practice and their effects on care quality should be concurrently planned and budgeted [25]. As in more medically developed countries [26], low-income countries need valid quality indicators for epilepsy care that can adequately assess the effects of guideline implementation. It may be possible to develop such quality

indicators even with basic health records in some LAMIC institutions [27]. The clinical care algorithms provided in the mhGAP were developed for use in a wide range of possible low-income and middle-income settings, and therefore must be adapted to local resources and needs, especially if the guidelines are to be used for childhood epilepsy in resource-constrained settings.

**Table 7** Reasons for Childhood Epilepsy Treatment Gap (CETG) in Bhakhar District (N=98).

Patients Being Intervened and Following at MCICEC (n=32, 100%)				Patients Being not Intervened and not Following at MCICEC (n=66, 100%)	
No	Reasons for non-adherence to AED (s)	No	Percentage	Percentage	No
1	Cost of AED (s)	02	06.25	42.40	28
2	Untrained professionals	08	25	24.25	16
2	No response to AED (s)	08	25	09.10	06
3	Counseling by local faith healers	06	18.75	09.10	06
4	Side –effects of AEDs	04	12.50	03.05	02
5	Poor/no counseling by the treating physician (s)	02	06.25	07.60	05
6	Non availability of AED (s)	02	06.25	04.50	03
Total		32	100	100	66

Almost universally, developing countries have marked inequalities in the distribution of health care resources [11]. Health care in private, settings of these countries may be relatively equivalent to first-world care, but care for the poor is virtually nonexistent. Inequities in the distribution of public services favoring urban regions are also problematic. Neurologists with local experience and knowledge of the culture, who are willing to serve as educators, policy advisors, and advocates, can make a difference. After two years of integration and implementation of this primary health multi-component interventional childhood epilepsy center (PHMCICEC) into primary health care centre, examined this model's effectiveness in terms of its impact on: 1) treatment coverage and cost-effectiveness of PHMCICEC 11) effect of PHMCICEC intervention on AEDs adherence and, 111) effect of MCICEC intervention on bridging treatment gap [24].

### Treatment coverage and cost-effectiveness of MCICEC

Of the 35 million people with epilepsy who live in developing countries, around 85% receive no treatment at all [10,28]. In many parts of Africa and Asia, notions about epilepsy are rooted not in a medical model but in a spiritual model [29]. In agreement after 4 years of awareness and teaching complains, then after 2 years of integration of childhood epilepsy in primary health care center, we have registered only 2500 CWE/recurrent seizures of the total approximate 7000 CWE in Bhakhar district. The epilepsy burden is different in Asia, Latin America, and Africa [30], and even within one area there are significant variations in the epidemiology, etiologies, and perceptions of epilepsy in different geographical regions and communities [31].

Population based neuroepidemiologic studies in different regions of India have shown that epilepsy constitutes nearly a third to a fifth of all neurological disorders, but scarce data is available on childhood epilepsy in outreach districts [32,33].

We estimated that more than 81% of the parents of CWE are seeking treatment for their children from Lahore and on the average cost for single consultation and AEDs for one month is 17000 PRS. But out of this huge amount for poor people 16000 PRS. are indirect cost. Cost-effective epilepsy treatments are available, and an accurate diagnosis can be made without technological equipment. Nonetheless, a vast majority of individuals with epilepsy in many resource-poor regions do not receive treatment due to diversities of causes [7-9]. Thus, epilepsy imposes a large economic burden on global health care systems and is a major public health problem in low- and middle-income countries (LMICs) [34]. However, only a very few studies have estimated the cost of epilepsy in these countries [35,36].

In agreement, almost free treatment through MCICEC is being offered and even when the charity money is compared with out of pocket expenses, it is 202 times cost effective. We strongly agree with others that the use of local resources potentially results in high cost-effectiveness, particularly in resource-poor settings [37].

Adherence is the degree to which patients' drug taking is consistent with instructions provided by health professionals [38]. AED effectiveness is minimized if prescribed regimens are not followed [39]. Previous studies have reported that 20–60% of adults with epilepsy are non-adherent to their prescribed AED therapy [40-42]. In children however, these rates are even lower estimated between 25-75% [43,44]. Self-report has been the



main method of assessing adherence in Low Resource Settings since its affordable and adaptable to study population. In summary, in 2014 we documented AED (s) nonadherence by self-reporting method among 58% [6] and was still 62% among CWE without local community intervention (**Table 3**). Previous studies have documented a number of factors affecting adherence to antiepileptic drugs such as duration of taking drugs, number of tablets, uncontrolled seizures, believes in faith healers, use of alternative treatment, family support and financial constraints [45-47].

However, we documented in 2014 and 2018, that in financially constrained settings cost of AEDs and other medical costs are predominant causes on AED (s) nonadherence among CWE in these communities. In support of this, by provision of free AEDs and pediatric neurology consultation at door steps of 160 CWE, believes in faith healers and uncontrolled seizures after commencement of AEDs were the most important causes of nonadherence to AEDs, **Table 5**. Adherence to antiepileptic drugs in resource limited settings is not well understood. These settings are prone to frequent drug shortages and with the poverty level in these settings, patients and/or caregivers may not always afford purchasing antiepileptic drugs as prescribed. Adherence to antiepileptic drugs may be improved by using a number of interventions such as patient counseling, use of a special medication container, self-recording of medication intake and seizures, and mailed reminders to collect prescription refills and attend clinic appointments [48]. Whereas, in our study integration of childhood epilepsy in local primary health (PH) through multicomponent interventional childhood epilepsy center (MCICEC) empowering the already existing local health system is the best strategy to overall improve the CE care. This was evidenced that that CWE being followed at local PHMCICEC, being proved free pediatric neurology consultations and AEDs, had AED (s) nonadherence of 15%. As compared to 62% among the similar CWE (control) not being supported from MCICEC, **Table 4**.

Our study demonstrates that although estimates of treatment gap among resource-constrained countries are limited, the economic gradient and availability of healthcare and childhood epilepsy-specific resources matter in these countries. The treatment gap, which is defined as the difference between the number of people with active epilepsy and the number whose seizures are being appropriately treated, is high in many LMICs [1]. Overall, 56% (range 7%–98%) of PWE in LMICs remain untreated, with 73% remaining untreated in rural regions compared to 46% in urban settings [5]. The treatment gap for epilepsy in LMICs for active epilepsy ranges from 25 to 100%, compared to less than 10% in HICs. There is substantial heterogeneity across and within countries, with treatment gaps higher in rural than urban areas [1,49,50].

Similarly, in 2014 we found CETG of 92% and it was still 82.5% without local community intervention in Bhakhar- an outreach financially constrained district. Acknowledging epilepsy as a neglected condition by the World Health Organization (WHO) in 2004 has led to increased emphasis on the development of adequate treatment strategies in low- and middle-income countries [4,5,22].

Specialists not only have a role to play in managing and treating complex cases, but they are especially needed to provide education and training, and ongoing supervision and support to non-specialists working at the primary health care level, we adopted the similar principles.

After documentation of huge CETG we started monthly free educational, diagnostic and therapeutic pediatric neurology camps and after integration of CE in primary health and established PHMCICEC in December 2016. After two years of free provision of AEDs and pediatric neurology consultations, we documented CETG steeply dropped from 92% to 20%, whereas, the CETG among the control at the study time and in the same population (control) was 82.5%.

It is unlikely that AED could be provided solely by government-funded schemes alone in poor countries. Moreover, private provision of AEDs could cause significant financial hardships to already poor households. Consequently, a large number of those affected go untreated, or are inadequately treated, particularly in developing countries where an estimated 75 to 90% receive no treatment at all [51,52]. While the treatment gap is a very useful global measure for assessing epilepsy care in a given setting, it is also important to recognize its limitations, as the measure alone fails to elucidate anything about the etiology of a high treatment gap.

One of the factors contributing to the treatment gap in epilepsy in LMICs is the lack of a continuous and affordable supply of AEDs. This affirms our findings in which provision of free AEDs through MCICEC in local community improved AEDs adherence to 85% and CETG dropped steeply from 92% to 20% [53-55]. Monthly free pediatric neurology camps and telepediatricneurology support are extremely useful for community awareness, education of medical and paramedical staff and overall monitoring of the project. Evidence is accruing that epilepsy diagnosed using a phone application is possible and this can at least be used as a screening tool in remote, outreach rural communities [56,57]. Already such projects and documented the success achieved in reducing the epilepsy treatment gap in China by managing convulsive forms of epilepsy at a primary health-care level [58,59]. As the success of any intervention is a consequence of it being sustainable in the long term, this report also presents the lessons derived for the development of an effective and sustainable framework for epilepsy care and scale-up in resource-poor settings by partnership with already existing local private primary health care in Pakistan.

## Conclusion

Strengthening health system performance is a wide-ranging subject, likely to require action on many fronts and management levels. The PHMCICEC programs are effective in bridging the childhood epilepsy treatment gap in outreach financially-constrained districts and implementing the WHO mhGAP. The combined cost-effectiveness and close collaboration with the local public and private community primary health allows PHMCICEC to overcome these barriers. Our lessons learned in Bhakhar district may also be applicable to the other outreach

financially constrained district in Pakistan, where the CETG is equally high. The indirect costs of epilepsy due to disease and its complications are likely to be very high in developing countries due to the large treatment gap. The district care model can help much to lessen the expenditure for travel, food, and lodging and hence the total treatment expenditure for childhood epilepsy. Novel techniques like telemedicine can be implemented as cost-effective measure. Ideally, the delivery of these packages should be integrated into existing primary health care with the help of NGOs and other nonmedical staff involved in community-based health care provision.

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