

MANAGEMENT OF CHEST INDRAWING PNEUMONIA IN CHILDREN UNDER FIVE YEARS AT THE  
OUTPATIENT HEALTH FACILITIES IN NIGERIA: AN ECONOMIC EVALUATION

Charles E. Okafor<sup>1,2\*</sup> (M. Pharm)

<sup>1</sup>*Centre for Applied Health Economics, School of Medicine, Griffith University Queensland*

<sup>2</sup>*Menzies Health Institute, Queensland*

Correspondence:

Charles Ebuka Okafor

Centre for Applied Health Economics, School of Medicine

Griffith University

170 Kessels Road, Nathan, Queensland, 4111

Australia

Email: [charles.okafor@griffithuni.edu.au](mailto:charles.okafor@griffithuni.edu.au)

Mobile Phone Number: +61415431234

**Word count:** 3855

**Key Words:**

Pneumonia, Amoxicillin dispersible tablets, Costs, Chest indrawing, Benefits, Nigeria.

**Short title:** Economic Evaluation of Managing Chest Indrawing Pneumonia in Nigeria.

## Abstract

### Background

The recommendation of the World Health Organization (WHO) for the management of children aged < 5 years with chest indrawing pneumonia with oral amoxicillin dispersible tablets (DT) at the outpatient health facilities is imperative especially in high pneumonia mortality and low-resource setting like Nigeria. However, this recommendation has not been widely adopted in Nigeria due to poor access to healthcare and sub-optimal outpatient management and follow-up system to ensure patients' safety and management effectiveness. This study aimed to evaluate the cost effectiveness and the cost benefit of the WHO recommendation relative to usual practices in Nigeria. The outcome of this study will provide supporting evidence to healthcare providers and inform their decisions in the management.

### Methods

A cost-effectiveness and cost-benefit analyses of this study used a Markov cohort model from the healthcare provider perspective for a time horizon of five years. Three approaches were compared: a conventional approach (base-comparator); the amoxicillin DT (WHO) approach; and a parenteral approach. Bottom-up costing method was used. Health outcome was expressed as disability-adjusted life years averted and converted to monetary terms (benefit).

### Results

The incremental cost-effectiveness ratio (ICER) and the benefit-cost ratio (BCR) of the amoxicillin DT approach dominate the conventional approach. The parenteral approach was more effective and more beneficial than the amoxicillin DT approach but the ICER and BCR were \$75,655/DALY averted and 0.035 respectively.

### Conclusions

The use of amoxicillin DT proves to be the optimal choice with high benefit and low cost. The opportunity cost of not adopting an approach more effective than amoxicillin DT will be offset by the cost saved. Its use in chest indrawing pneumonia management needs to be scaled up.

**Key points for decision makers**

- Promoting the use of amoxicillin dispersible tablets in chest indrawing pneumonia management at the healthcare facilities will save healthcare cost and improve health outcome.
- Antibiotic stewardship should be promoted to mitigate the growing antibiotic resistance in the country.
- The outpatient healthcare system needs to be revamped for effective adoption of the recommendation.

## 1. Introduction

Pneumonia is the second most common disease with high burden for children after neonatal disorders [1] and is the largest infectious cause of death worldwide for children aged < 5 years [2]. Pneumonia was responsible for over 800,000 deaths in 2017 with the greatest death proportion in low- and middle-income countries [2]. Nigeria alone accounts for an incidence of over 8 million cases of pneumonia for in under-5-year-olds [3] and about 162,000 pneumonia deaths, which positions Nigeria as the country with the highest mortality rate globally [4,5]. Major reasons for high pneumonia burden and mortality include low health care-seeking, poverty and poor access to healthcare [6,7] .

In response to this health problem the World Health Organization (WHO) issued a treatment guideline for the management of pneumonia for under-5-year-olds [8]. This guideline was aimed to increase access to healthcare, improve health outcome and ensure affordability of treatments. The previous WHO pneumonia classification labelled chest indrawing pneumonia as severe pneumonia and recommended first dose antibiotic followed by referral to a health facility for injectable antibiotic and supportive therapy [8]. Based on new evidence [9], the WHO recently revised and classified chest indrawing as moderate pneumonia and recommend the use of oral amoxicillin dispersible tablets (DT) as the first-line agent in its management at the outpatient health facilities in children under five years in settings with low human immunodeficiency viruses (HIV) prevalence or in patients without general danger signs who are HIV-negative [8]. Although the new evidence found that in some regions of the world, community health workers (CHW) can effectively manage chest indrawing, it has not been generalized. So, the current recommendation is to manage chest indrawing as outpatient cases. Further details of this recommendation were described elsewhere [8].

This revised WHO recommendation is important especially in high pneumonia mortality and low-resource setting like Nigeria. The new treatment guideline for chest indrawing pneumonia had demonstrated that outpatient treatments with amoxicillin DT cost less than inpatient or outpatient treatments with injectable antibiotics. It is more convenient to dose compared to injectable antibiotics and it is also very effective. It will also increase the number of children receiving care and improve treatment outcome [8].

Despite the WHO evidence-based recommendation, outpatient management of chest indrawing pneumonia with amoxicillin DT has not been widely adopted in Nigeria. The plausible reasons include the sub-optimal outpatient management and follow-up system to ensure that patients' safety and effectiveness of management are guaranteed, physicians poor awareness of new recommendations [10] and poor access of patients to

healthcare due to financial and geographical limitations. For the pneumonia cases that report to health facilities, the majority are not severe cases and do not need admission but are being managed partly or fully as inpatients on a case-by-case basis [10,11]. These non-severe cases could be either fast breathing or chest indrawing pneumonia. The patients could be hospitalized for 2 – 3 days with intravenous medications followed by a 3- to 7-day course of oral medications as outpatients or be hospitalized for the full treatment course [10]. The more conventional practice is the partial hospitalization with intravenous medications for 2 – 3 days followed by outpatient oral medications for 3 – 7 days.

In a cost-conscious environment like Nigeria, the cost of treatment is becoming as important as its effectiveness. This study, therefore, evaluated the cost effectiveness and the cost benefit of the WHO recommendation for the management of under-five chest indrawing pneumonia relative to usual practices in Nigeria. The outcome of this study will provide supporting evidence to healthcare providers and inform their decisions in the management of chest indrawing pneumonia, which will in turn save cost and reduce the disease burden in the country.

## **2. Materials and methods**

### **2.1 Study setting and sample size**

This study was performed using a Markov cohort model. Based on pneumonia health care-seeking of 40% in Nigeria [6], the population used in the study was an estimated 13.9 million under-5-year-old Nigerian children, from the 2018 population report [12]. This population was used as the starting population in the model and they are at risk of having chest indrawing pneumonia.

### **2.2 Study perspective**

The study used retrospective data for Nigeria to estimate the costs, effectiveness and benefits of managing chest indrawing pneumonia. The costs were estimated from the healthcare provider perspective. Nigeria operates on a Universal Health Coverage (UHC) system where residents can choose from a pool of insurance companies to pay for their healthcare. All the health maintenance organizations and participating healthcare providers are regulated by the National Health Insurance Scheme (NHIS). The poor health insurance coverage of less than 10%, led to the amendment of the 'NHIS Act 35 of 1999' to encourage participation [13]. Currently, most of the

patients receiving healthcare pay directly to the healthcare providers which explains why this perspective was elected for the analyses [13].

### 2.3 Interventions

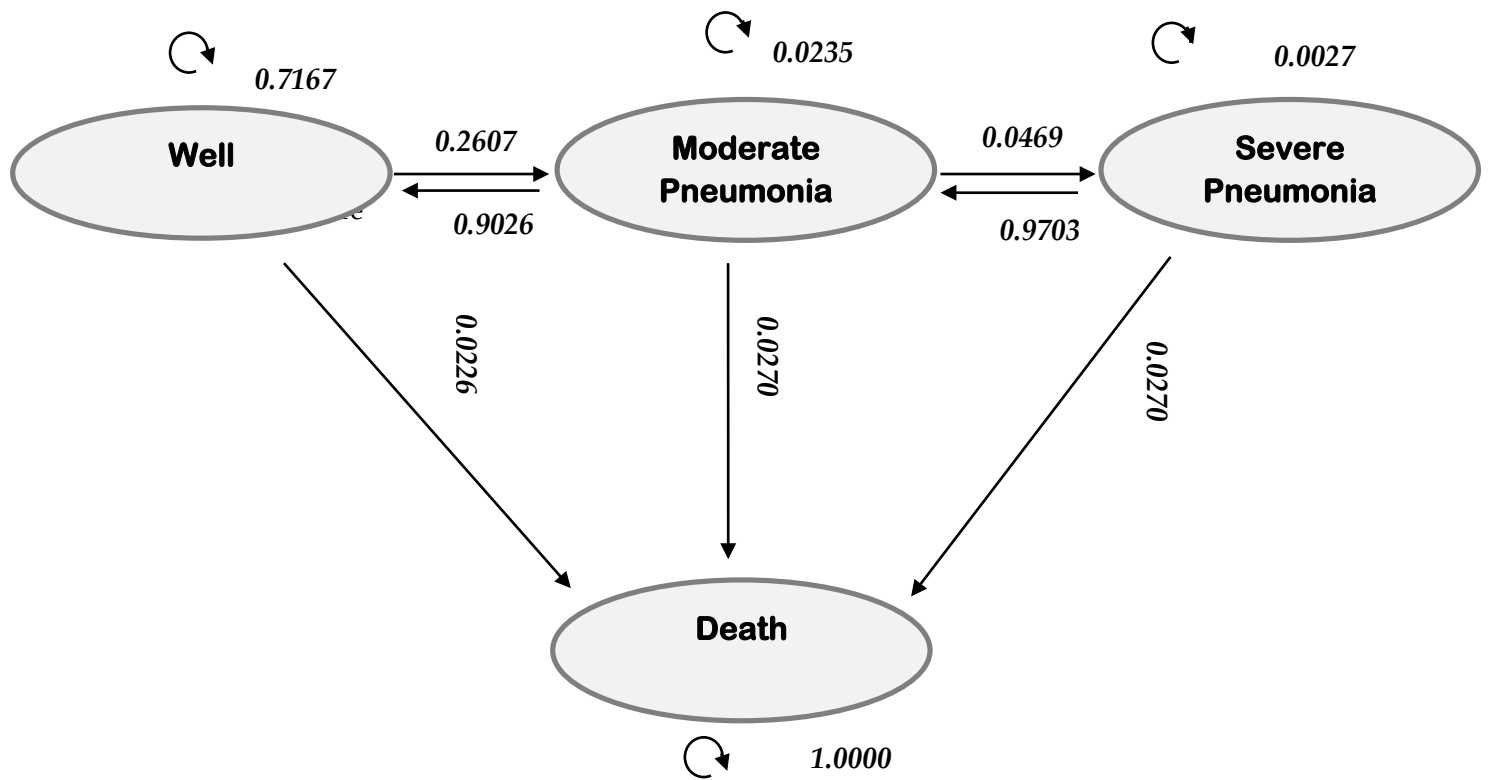
The interventions compared in this study were three evidence-based interventions used in practice.

- A. Conventional approach: In this approach patients with chest indrawing pneumonia were hospitalized for 2 days and received a 2-day course of intravenous (IV) ampicillin at 50mg/kg every 6 hours followed by an outpatient 3-day course of amoxicillin oral suspension at 90mg/kg/day in three divided doses. This was used as the base-case comparator.
- B. Amoxicillin DT (WHO) approach: In this approach, the WHO treatment guideline for chest indrawing pneumonia was used where amoxicillin DT 90mg/kg/day in two divided doses for 5 days was given to the patients at outpatient health facilities [9,14]. The patients were reviewed on day 2 and day 6.
- C. Parenteral approach: In this approach, the patients were hospitalized and received IV ampicillin 50mg/kg every 6 hours for 5 days.

These interventions were considered for assessment because the effectiveness and relative risk data from clinical trials in developing countries are available where the effect of a 5-day course of oral amoxicillin was compared to the other approaches for chest indrawing pneumonia [15,16].

### 2.4 Choice of model and assumptions

A Markov cohort model with a yearly cycle for 5 years was used in the analyses. The states in the model were: 'well' state, moderate (clinical) pneumonia, severe pneumonia and death [3,17]. The starting age in the model was under-one. Children were modelled to start from the 'well' state. They can move to any of the health states or die as shown in Figure 1. The transition probabilities of moving to the different health states were estimated from a recent national estimate from a global systematic review and a population-based prospective study [3,9,18]. The yearly incidence rates were converted to yearly probabilities using the formula,  $P = 1 - e^{(-rt)}$  where P = probability, r = rate and t = time (year). The mortality rate from pneumonia and all-cause of disease were obtained from the 2017 global burden of disease (GBD) study [1].



**Fig 1** Model figure

## 2.5 Time horizon and discount rate

The model simulated costs and outcome for 5 years for a population of 13.9 million children at risk of having chest indrawing pneumonia. The costs and outcome were discounted at a rate of 5% [19].

## 2.6 The measure of effectiveness (as relative risk ratio)

The relative risk of treatment failure with the amoxicillin DT approach compared to the conventional approach and to the parenteral approach were obtained from clinical trials conducted in developing countries [15,16]. One of the trials compared the effectiveness of a 5-day course of oral amoxicillin to a 5-day course of IV ampicillin whilst the other trial compared a 5-day course of oral amoxicillin to a 2-day course of IV ampicillin followed by a 3-day course of oral amoxicillin. Details of the parameters in the model are shown in Table 1.

Table 1: Parameters input and distribution in the Markov model

Variable	Mean	Distribution (95% CI)	Source
<b><i>Transition probabilities</i></b>			
Well to moderate pneumonia	0.2607	Beta (0.1479 – 0.4161)	[3,9]
Moderate pneumonia to severe pneumonia	0.0469	Beta (0.0178 – 0.1068)	[3,9]
Recurrent moderate pneumonia	0.0235	Beta (0.0133 – 0.0375)	[3,9,18]
Recurrent severe pneumonia	0.0027	Beta (0.0010 – 0.0061)	[3,9,18]
Moderate pneumonia to well	0.9026	Beta (0.8106 – 0.9456)	[3,9,18]
Severe pneumonia to moderate pneumonia	0.9703	Beta (0.9598 – 0.9752)	[3,9,18]
Remaining well	0.7167	Beta (0.6878 – 0.8792)	[3,9,18]
All-cause mortality	0.0226	Beta (0.0186 – 0.0275)	[1]
Pneumonia to death	0.0270	Beta (0.0219 – 0.0314)	[1]
<b><i>Relative risk to conventional approach</i></b>			
Amoxicillin DT (WHO) approach	0.872	Log-normal (0.711 – 1.210)	[15]
Parenteral approach	0.854	Log-normal (0.835 – 0.991)	[16]
<b><i>Cost of treatment per patient (\$)</i></b>			
Amoxicillin DT (WHO) approach	15.10	Gamma (7.70 – 22.50)	[20,21]
Conventional approach	30.65	Gamma (15.34 – 45.96)	[20,21]
Parenteral approach	71.28	Gamma (36.22 – 106.34)	[20,21]
<b><i>Disability weights</i></b>			
Moderate (clinical) pneumonia	0.051	Beta (0.032 – 0.074)	[1]
Severe pneumonia	0.133	Beta (0.088 – 0.190)	[1]
<b><i>Discount rate</i></b>			
Cost	5%	N/A (min 0%, max 10%)	[19]
Utility	5%	N/A (min 0%, max 10%)	[19]

DT: dispersible tablets; WHO: World Health Organization

## 2.7 Health outcome

The effectiveness of the interventions was measured as disability-adjusted life years (DALY) averted. The DALY calculation was based on 2017 GBD study and recently updated disability weights for moderate and severe pneumonia were used [1]. The DALY lost was calculated as the sum of the years of life lived with disability (YLD) from morbidity and the years of life lost (YLL) from mortality.  $YLD = \text{Number of cases} \times \text{duration until remission or death} \times \text{disability weight}$  [22,23].  $YLL = \text{Number of deaths due to pneumonia} \times \text{life expectancy at the age of death}$  [23]. The standard life expectancies of < 1 year (54.7) and 1 to < 5 years (57.9) were obtained from the Nigerian life table [1]. The DALY averted was calculated as the difference in the DALY lost between two intervention arms. The relative benefit of each intervention was estimated by calculating the monetary value of the DALY averted using the Harvard-led guideline for conducting a benefit-cost analysis



project [24]. The valuation was based on ‘value of statistical life year’ (VSLY) with one DALY averted valued at 1.3 times the gross national income (GNI) per capita of a country in sub-Saharan Africa [24].

## 2.8 Determination of costs

The costs were estimated from the healthcare provider perspective. The cost components for the amoxicillin DT approach were amoxicillin DT 250mg (10 tablets) for children  $\leq 1$  (2 – 12 months) and 20 tablets (for children  $\geq 1 \leq 3$  years) and 30 tablets (for children  $\geq 3 \leq 5$  years). The hospital pack size of 100 tablets was used in the analyses. In addition to amoxicillin DT, the cost in this scenario also includes initial consultancy of the physician and reviews on day 2 and day 6. In the conventional approach, cost components include a 2-day cost of IV ampicillin, physician consultancy and reviews, nursing fees and bed stay and cost of 100ml amoxicillin oral suspension. In the parenteral approach cost components include a 5-day cost of IV ampicillin, physician consultancy and reviews, nursing fees and bed stay. The cost of amoxicillin DT, amoxicillin oral suspension and IV ampicillin were obtained from the international drug price indicator guide [20]. The cost of physician initial consultancy, physician review, nursing review and bed stay were obtained from the Nigerian NHIS price list [21]. The costs from the international drug price indicator guide were in the year 2015 international dollars, so were converted to 2015 USD using the 2015 price level ratio of Naira to USD (0.4496) and then inflated to 2019 USD using a web-based tool developed by the Campbell and Cochrane Economics Methods Group (CCEGM) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) [25]. The costs from the Nigerian NHIS price list were in 2011 Naira, so were converted to 2011 USD at an official exchange rate of 153.86 Naira to a USD which was inflated to 2019 USD using the web-based tool [25,26]. The final costs were expressed in 2019 USD. Gamma distribution was used to capture the uncertainty inherent in the cost parameters. Details of the costs are shown in Table 1 and the supplementary data.

## 2.9 Data analyses

The costs data, transition probabilities, relative risk and utilities were made probabilistic using the appropriate distributions as shown in Table 1. Half cycle correction using the life table method was employed in the model [27]. The DALY lost and the cost of treatment was calculated for each cycle and accumulated over the time horizon of five years and averaged to obtain the probabilistic DALY lost per child and the cost of treatment per child respectively in the cohort in each intervention arm. The probabilistic DALY lost per child and the cost of

treatment per child in each intervention arm were used in the probabilistic sensitivity analysis (PSA). The PSA was used to assess simultaneous uncertainty in the variables. This approach expresses overall parameters uncertainty [28]. To assess how simultaneous change of several variables affects the costs and outcomes, a Monte-Carlo simulation (a type of multivariate sensitivity analysis) was performed using 1000 iterations [28]. Univariate sensitivity analysis was also performed to assess the extent to which each key variable can affect the results.

Summary of the cost-effectiveness analysis result was expressed as an incremental cost-effectiveness ratio (ICER) while the cost-benefit analysis result was expressed as a benefit-cost ratio (BCR). The ICER threshold used was '3 times the Gross Domestic Product (GDP) per capita' of Nigeria in 2019 [29,30], whilst the threshold for the BCR was 1. Data were analysed using Microsoft Excel 365.

### **3. Results**

From the analyses, the mean cost per child in the cohort in the conventional, the amoxicillin DT and the parenteral intervention arms were \$5.85 (SD: \$2.03), \$2.88 (SD: \$0.99) and \$13.48 (SD: \$4.40) respectively, whilst the DALY lost per child in the cohort in the conventional, amoxicillin DT and the parenteral intervention arms were 0.146947 (SD: 0.040176), 0.146049 (SD: 0.039969), and 0.145834 (SD: 0.039878) respectively.

The incremental cost of the amoxicillin DT approach relative to the conventional approach was 'cost-saving' with a positive DALY averted (incremental effectiveness). This presents amoxicillin DT ICER in the south-east quadrant of the cost-effectiveness plane, indicating that amoxicillin DT dominates the conventional approach. The incremental cost and effectiveness of the parenteral approach relative to the conventional approach showed that the ICER was \$6,858.67/DALY averted which is higher than the cost-effectiveness threshold of '3 times the GDP per capita' (\$6,690/DALY averted). This indicates that switching from the conventional to parenteral approach will not be a worthwhile decision. The incremental cost and effectiveness of the parenteral approach relative to the amoxicillin DT approach showed that the ICER was \$75,654.93/DALY averted which is 11 times higher than the ICER threshold. Details of the ICER results are shown in Table 2, Figure 2 and Figure 3 and the supplementary data. Figure 4 shows the cost-effectiveness acceptability curve.

Estimates of the monetary value of the DALY averted (benefit), showed that the benefit per child in the cohort of the amoxicillin DT approach relative to the conventional approach was \$2.58. The benefit of the parenteral

approach relative to the conventional approach was \$2.94 per child, whilst the benefit of the parenteral approach relative to the amoxicillin DT approach was \$0.37 per child. With the incremental cost for each switch, the BCR result showed that the amoxicillin DT approach dominates the conventional approach. The BCR of the parenteral approach relative to the conventional approach was 0.385, whilst the BCR of the parenteral approach relative to the amoxicillin DT approach was 0.035. Based on the BCR threshold of 1, switch from conventional to parenteral or adopting parenteral over the amoxicillin DT approach would not be worthwhile. Details of the BCR analysis are shown in Table 2 and the supplementary data.

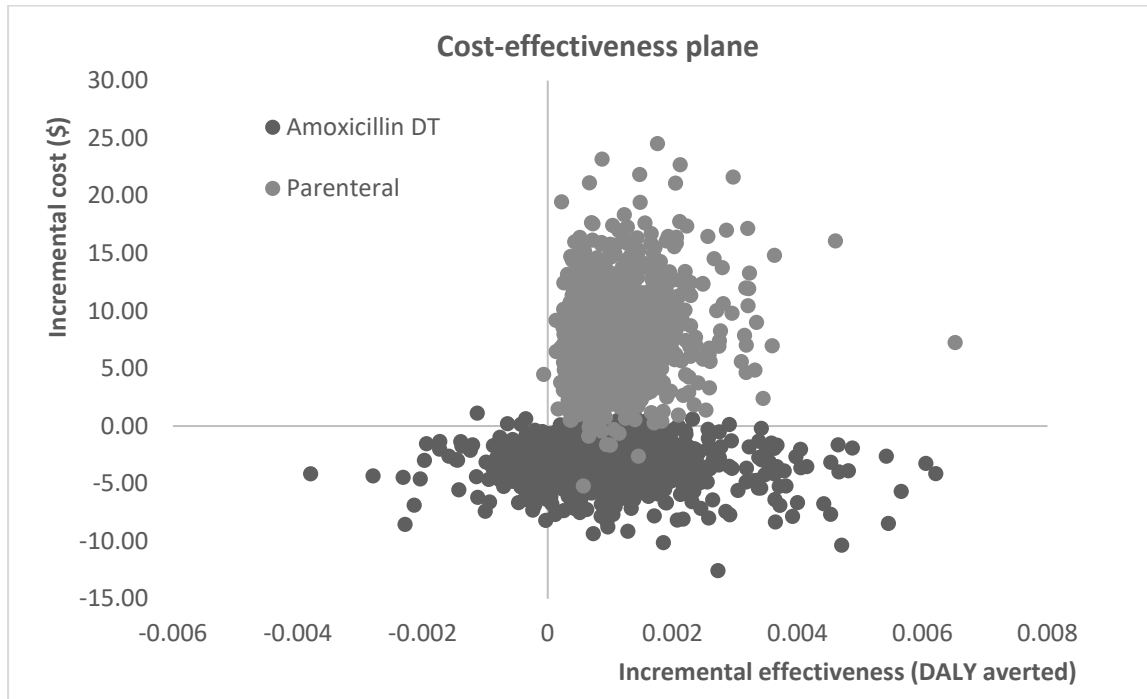
The results show that amoxicillin DT is the most optimal choice with strong dominance. Although the parenteral approach was more effective than amoxicillin DT, it was much more expensive. The opportunity cost (benefit of \$0.37 per child) for adopting the amoxicillin DT approach instead of the parenteral approach will be offset by the cost saved (\$10.74), which is the incremental cost averted.

The univariate sensitivity analysis showed that the variation of each key parameter did not affect the results. It showed that amoxicillin DT approach dominates the conventional approach. However, at high relative risk values of amoxicillin DT to the conventional approach, the ICER of the amoxicillin DT approach relative to the conventional will increase up to \$1698.57/DALY averted but this value still presents amoxicillin DT approach as the optimal choice. The result of the univariate sensitivity analysis for the optimal choice was not presented in a Tornado diagram since the base ICER was dominant and over 95% of the key parameters univariates showed dominance of the amoxicillin DT approach. 93.2% of the multivariate simulations for the optimal choice were below the cost-effectiveness threshold. The results are deemed robust as the multivariate and the univariate sensitivity analyses performed showed that the results were insensitive to the parameters. Details of the univariate sensitivity analysis are shown in the supplementary data.

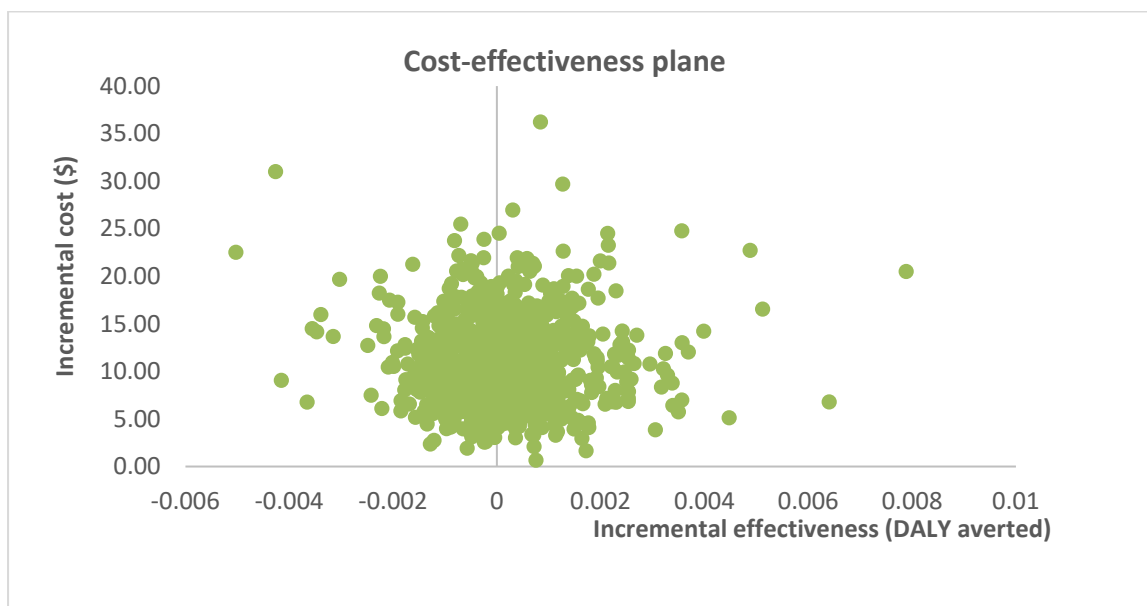
Table 2: Incremental costs, effectiveness and benefits of the interventions from the probabilistic sensitivity analysis

	Conventional to amoxicillin DT	Conventional to parenteral	Amoxicillin DT to parenteral
Incremental cost (\$) [SD]	-3.11[1.81] †	7.63[4.00]	10.74[4.55]
DALY averted	0.0009792	0.0011125	0.0001420
Incremental cost-effectiveness ratio (\$/DALY averted)	Dominates §	6,858.67	75,654.93
Incremental benefit (\$)	2.58	2.94	0.37
Incremental benefit-cost ratio	Dominates §	0.385	0.035

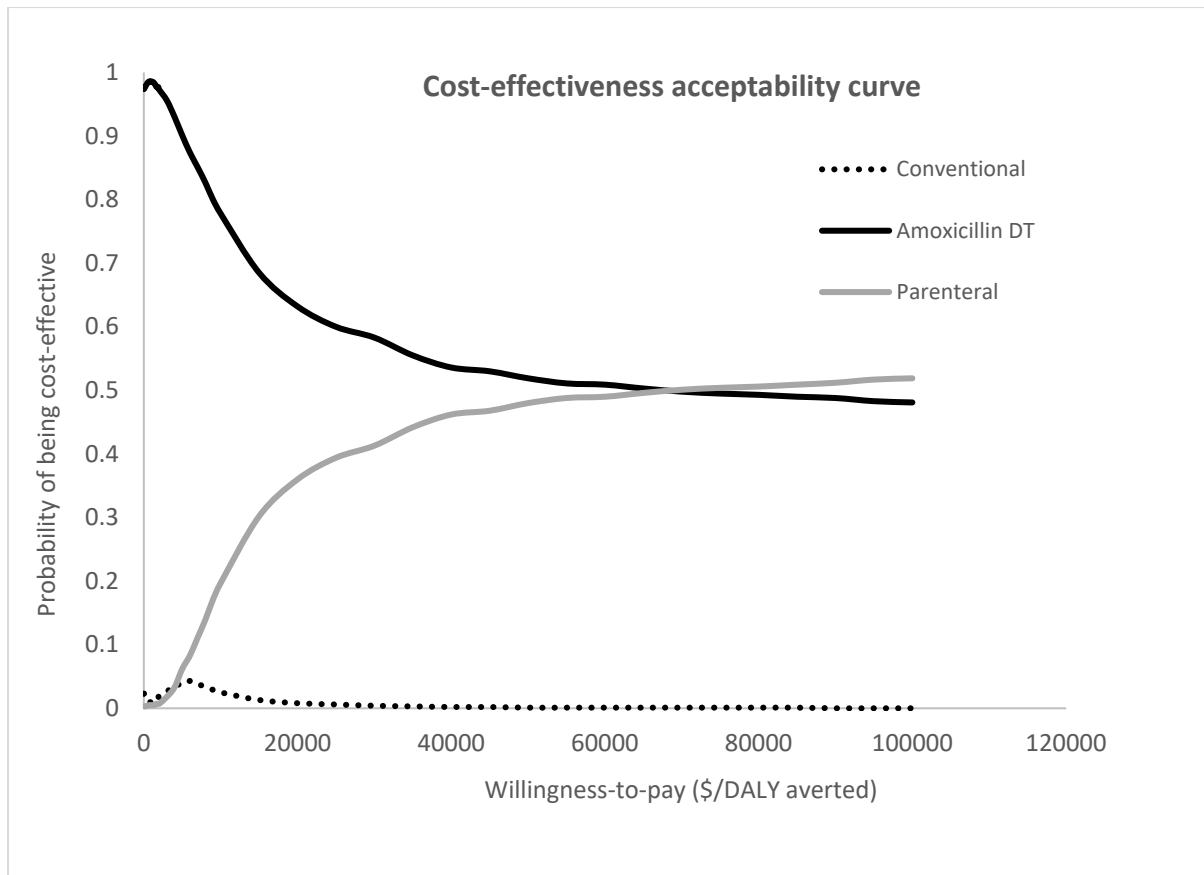
2019 gross national income per capita = \$2030; 1 DALY averted = \$2639 benefit; DALY: disability-adjusted life years; DT: dispersible tablets; †: Cost-saving; §: Amoxicillin DT approach dominates the conventional approach.



**Fig 2** Cost-effectiveness plane for the amoxicillin dispersible tablets approach and the parenteral approach relative to the conventional approach.



**Fig 3** Cost-effectiveness plane for the parenteral approach relative to the amoxicillin dispersible tablets approach.



**Fig 4** Cost-effectiveness acceptability curve of the conventional, amoxicillin DT and the parenteral approaches.

#### 4. Discussion

Whilst evidence-based recommendation for the management of chest indrawing pneumonia was made by the WHO, the uptake remains poor in Nigeria. This study provides cost-effectiveness and cost-benefit estimates and implications that will inform healthcare providers decisions in the management of chest indrawing pneumonia in Nigeria.

Amoxicillin DT is not the most effective drug in the management of chest indrawing pneumonia in children but studies (including this study) have shown that it is relatively cheaper, more convenient and the relative efficacy to more effective drugs in the management is approximately same [8,15,16]. The result of this study showed that the amoxicillin DT approach was cost-saving and had a significant benefit compared to the conventional approach. Although the parenteral approach was more effective than the amoxicillin DT approach, its cost is > 26 times higher. Besides, very limited Nigerians can afford to pay the \$71 to manage chest indrawing

pneumonia by the parenteral approach [7]. This provides further evidence on the need to widely adopt the new WHO recommendation.

In a low-resource and high pneumonia mortality setting like Nigeria, adopting the amoxicillin DT approach needs to be scaled-up [2]. Low health care-seeking and poor access to care are two major drawbacks [6,7]. The financial instability of many households and the geographical locations of health facilities relative to residents' home have contributed to the poor uptake of this new recommendation [6,7]. Initiatives to improve patients' health care-seeking and access to healthcare through the CHW are ongoing in Nigeria [31,32]. The limited evidence on the safety of managing chest indrawing by CHW [8] has led to the ongoing clinical trials in Nigeria to determine the feasibility, effectiveness and safety of CHW in managing chest indrawing pneumonia [31,32]. Another major limitation to scaling up treatment for chest indrawing pneumonia is the poor outpatient management system in Nigeria which needs major reforming to ensure patients' safety and effectiveness in the management. Unless this system is proactive in implementing the new recommendation on the 40% of pneumonia cases that visit health facilities [6], healthcare will remain sub-optimal in Nigeria as most health facilities will continue to use the conventional approach or a parenteral approach due to uncertainty of complications or losing a patient to death if managed as an outpatient with amoxicillin DT. The sub-optimal outpatient management system has also led to increasing antibiotics resistance including amoxicillin. Effort should be made to promote antibiotic stewardship which will ensure right diagnoses, dosing of antibiotics and patient counselling on medication adherence and drug abuse. Furthermore, the awareness of the new recommendation needs to be promoted as many healthcare professionals are not aware of new management recommendations [10]. Also, caregivers of children need to be aware of or educated on major signs of pneumonia to ensure early diagnosis, referral and treatment. Whilst the aforementioned challenges need to be considered, there is also need to strengthen the national supply chain system to ensure availability of amoxicillin DT in all paediatric health facilities, especially in remote regions of the country.

This study has some limitations. The study only compared two approaches to the amoxicillin DT approach. More comparators could have provided higher robustness to the amoxicillin DT approach as being the optimal choice. However, two comparators were used because of the availability of comparative effectiveness data on chest indrawing pneumonia management [15,16]. Also, the two approaches compared are the most widely used in health facilities in Nigeria [10]. Secondly, the model did not capture alternate treatment cost in the case of the first-line failure. This limitation, however, did not affect the results since the effect of treatment failure was

captured in the DALY lost in each treatment approach. Thirdly, the study failed to capture the treatment approach for sickle cell patients [14] or HIV patients with chest indrawing pneumonia [8], but these will not have a significant impact on the results as the population of HIV and sickle cell under-5-year-olds is less than 2% of the cohort size. Fourthly, the actual cost of treatment may vary from the estimate used in this study due to variation in geographical and financial characteristics of different regions in Nigeria. The challenge of the supply chain in remote areas of Nigeria could make the cost more expensive in these regions. However, for generalizability, using a central cost estimate is preferred.

More importantly, the use of IV amoxicillin in the model instead of IV ampicillin would have been more suitable because IV amoxicillin is used more frequently in Nigeria than IV ampicillin [14]. However, the use of IV amoxicillin in the model will not be ideal since the relative risk of oral amoxicillin to IV amoxicillin in chest indrawing pneumonia was not available. Despite this limitation, a justification for the results can be demonstrated. Amoxicillin is highly aqueous-soluble and highly tissue-permeable and belongs to class 1 (up to 875mg dose) in the biopharmaceutics classification system (BCS) which indicates that the bioavailability of the oral dosage is high [33]. Furthermore, studies have shown that the relative bioavailability of oral amoxicillin to IV amoxicillin ranges from 76.5% to 97.0% [33,34]. This implies that IV amoxicillin is about 1.031 to 1.307 times as effective as the oral dosage form. Although their effectiveness was not demonstrated on patients with chest indrawing, empirically, the relative risk of oral amoxicillin to the IV for chest indrawing pneumonia cannot be above 1.307 based on its BCS characteristics and bioequivalence evidence. Thus, using a crude relative risk of oral amoxicillin to IV amoxicillin to be between 1.031 to 1.307 yielded ICER of \$1,229.28/DALY averted and BCR of 2.36 for the amoxicillin DT approach relative to the conventional approach, but yielded ICER of \$9,068/DALY averted and BCR of 0.371 for the parenteral approach relative to the amoxicillin DT approach.

Future studies should evaluate if the potential benefits of the WHO recommendation outweigh the cost and risk of scale-up in Nigeria. The result of the proposed future studies could further substantiate the findings of this study.

## **5. Conclusion**

The parenteral approach in under-5-year-olds with chest indrawing pneumonia was the most beneficial management, but the cost outweighs its benefit. Besides, scale-up of this approach is not feasible in Nigeria based on the high cost and poor access to healthcare. The use of amoxicillin DT proves to be the optimal choice

with high effectiveness and benefit and low cost. The opportunity cost of not adopting an approach more effective than amoxicillin DT will be offset by the cost saved. Whilst clinical trials on the feasibility, safety and effectiveness of managing chest indrawing pneumonia by CHW are ongoing in Nigeria in a bid to improve access to care, the use of amoxicillin DT for chest indrawing pneumonia management needs to be scaled up at the healthcare facilities. Improved diagnostic practises, optimal drug dosing and patient counselling on medication adherence and abuse are imperative to minimize amoxicillin resistance and ensure sustainability of the recommendation.



**Declarations****Funding**

The author received no funding for this research

**Conflict of interest**

The author declares no competing interest

**Ethics approval**

Not applicable

**Consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

The model used in this study was provided to the journal's peer reviewers for their reference when reviewing the manuscript. The data used for the study are provided as supplementary file.

**Code availability**

Not applicable

## References

1. Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: [Internet]. 2018. Available from: <http://ghdx.healthdata.org/gbd-results-tool>
2. WHO. Pneumonia: Key facts [Internet]. Geneva; 2019. Available from: <https://www.who.int/news-room/fact-sheets/detail/pneumonia>
3. Mcallister DA, Liu L, Shi T, Chu Y, Reed C, Burrows J, 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 Heal* [Internet]. 2019;7(1):e47–57. Available from: [http://dx.doi.org/10.1016/S2214-109X\(18\)30408-X](http://dx.doi.org/10.1016/S2214-109X(18)30408-X)
4. UN Inter-agency Group for Child Mortality Estimation. Nigeria Under-five Mortality Rate [Internet]. 2018. Available from: <https://childmortality.org/data/Nigeria>
5. UNICEF. Nigeria contributes highest number to global pneumonia child deaths [Internet]. 2019. Available from: <https://www.unicef.org/nigeria/press-releases/nigeria-contributes-highest-number-global-pneumonia-child-deaths>
6. Noordam AC, Carvajal-Velez L, Sharkey AB, Young M, Cals JWL. Care seeking behaviour for children with suspected pneumonia in countries in sub-Saharan Africa with high pneumonia mortality. *PLoS One* [Internet]. 2015;10(2):1–14. Available from: <https://doi.org/10.1371/journal.pone.0117919>
7. National Bureau of Statistics. Poverty Rates [Internet]. 2019. Available from: <https://nigerianstat.gov.ng/>
8. WHO. Revised WHO classification and treatment of childhood pneumonia at health facilities: implications for policy and implementation. 2014;1–4. Available from: <http://apps.who.int/iris/handle/10665/137331>
9. WHO. Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Evidence Summaries [Internet]. World Health Organization. 2014. 26 p. Available from: [https://www.who.int/maternal\\_child\\_adolescent/documents/child-pneumonia-treatment/en/](https://www.who.int/maternal_child_adolescent/documents/child-pneumonia-treatment/en/)
10. Onyedum CC, Chukwuka JC. Admission profile and management of community acquired pneumonia in Nigeria-5 year experience in a tertiary hospital. *Respir Med* [Internet]. 2011;105(2):298–302. Available from: <http://dx.doi.org/10.1016/j.rmed.2010.11.003>
11. Iliyasu G, Mohammad FD, Habib AG. Community acquired pneumococcal pneumonia in northwestern Nigeria: Epidemiology, antimicrobial resistance and outcome. *African J Infect Dis* [Internet]. 2018;12(1):15–9. Available from: <https://www.ajol.info/index.php/ajid/article/view/167143>
12. United Nations. World Population Prospects 2019 [Internet]. 2019 [cited 2020 May 5]. Available from:

<https://population.un.org/wpp/Download/Standard/Population/>

13. Awosusi A, Folaranmi T, Yates R. Nigeria's new government and public financing for universal health coverage. *Lancet Glob Heal* [Internet]. 2015;3(9):e514–5. Available from: [http://dx.doi.org/10.1016/S2214-109X\(15\)00088-1](http://dx.doi.org/10.1016/S2214-109X(15)00088-1)
14. Olowu A, Elusiyan J, Esangbedo D, Ekure E, Esezobor C, Falade A, et al. Management of community acquired pneumonia ( CAP ) in children : Clinical practice guidelines by the Paediatrics Association of Nigeria ( PAN ). 2015;42(4):283–92. Available from: <http://dx.doi.org/10.4314/njp.v42i4.1>
15. Hazir T, Fox LM, Nisar Y Bin, Fox MP, Ashraf YP, MacLeod WB, et al. Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. *Lancet* [Internet]. 2008 Jan 5;371(9606):49–56. Available from: [https://doi.org/10.1016/S0140-6736\(08\)60071-9](https://doi.org/10.1016/S0140-6736(08)60071-9)
16. Addo-Yobo E, Chisaka N, Hassan M, Hibberd P, Lozano JM, Jeena P, et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. *Lancet* [Internet]. 2004 Sep 25;364(9440):1141–8. Available from: [https://doi.org/10.1016/S0140-6736\(04\)17100-6](https://doi.org/10.1016/S0140-6736(04)17100-6)
17. Pitt C, Roberts B, Checchi F. Treating childhood pneumonia in hard-to-reach areas : A model-based comparison of mobile clinics and community-based care. *BMC Health Serv Res* [Internet]. 2012;12(1):9. Available from: <http://www.biomedcentral.com/1472-6963/12/9>
18. Dang TT, Eurich DT, Weir DL, Marrie TJ, Majumdar SR. Rates and risk factors for recurrent pneumonia in patients hospitalized with community-acquired pneumonia: Population-based prospective cohort study with 5 years of follow-up. *Clin Infect Dis* [Internet]. 2014;59(1):74–80. Available from: <https://academic.oup.com/cid/article/59/1/74/404795>
19. Haacker M, Hallett TB, Atun R. On discount rates for economic evaluations in global health. *Health Policy Plan* [Internet]. 2020;35(1):107–14. Available from: <https://academic.oup.com/heapol/article/35/1/107/5591528>
20. WHO/MSH. International Medical Products Price Guide [Internet]. 2015. Available from: <https://www.msh.org/sites/default/files/msh-2015-international-medical-products-price-guide.pdf>
21. National Assembly of the Federal Republic of Nigeria. National Health Insurance Scheme Drug Price List. 2013; Available from: <http://www.nigeria-law.org/National Health Insurance Scheme Decree.htm>
22. WHO. Disability-Adjusted Life Year (DALY): Quantifying the Burden of Disease from mortality and morbidity. [Internet]. 2012 [cited 2015 Aug 1]. Available from: [http://www.who.int/healthinfo/global\\_burden\\_disease/metrics\\_daly/en/](http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/)
23. WHO. Global Burden of Disease Concept [Internet]. 2004 [cited 2015 Aug 1]. Available from: [http://www.who.int/quantifying\\_ehimpacts/publications/en/9241546204chap3.pdf](http://www.who.int/quantifying_ehimpacts/publications/en/9241546204chap3.pdf)

24. Robinson LA, Hammitt JK, O’Keeffe L. Valuing Mortality Risk Reductions in Global Benefit-Cost Analysis. *J Benefit-Cost Anal* [Internet]. 2019;10:15–50. Available from: <https://doi.org/10.1017/bca.2018.26>
25. CCEMG and EPPI-Centre. CCEMG - EPPI-Centre Cost Converter v.1.6 [Internet]. 2019 [cited 2020 Mar 15]. Available from: <https://eppi.ioe.ac.uk/costconversion/default.aspx>
26. WorldBank. Currency Exchange Rate [Internet]. 2019. Available from: <https://unctadstat.unctad.org/wds/TableView/tableView.aspx?ReportId=117>
27. Barendregt JJ. The life table method of half cycle correction: Getting it right. *Med Decis Mak* [Internet]. 2014;34(3):283–5. Available from: <https://doi.org/10.1177/0272989X13519863>
28. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation [Internet]. New York: Oxford University Press Inc; 2006. Available from: <https://www.herc.ox.ac.uk/downloads/decision-modelling-for-health-economic-evaluation>
29. WorldBank. Gross Domestic Product per Capita [Internet]. 2019. Available from: <https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=NG>
30. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, et al. WHO CEA guidelines. 2003; Available from: [https://www.who.int/choice/publications/p\\_2003\\_generalised\\_cea.pdf?ua=1](https://www.who.int/choice/publications/p_2003_generalised_cea.pdf?ua=1)
31. Malaria Consortium. Community case management of chest indrawing pneumonia in children [Internet]. 2017. Available from: <https://www.malariaconsortium.org/what-we-do/projects/76/community-case-management-of-chest-indrawing-pneumonia>
32. Counihan H, Baba E, Oresanya O, Adesoro O, Hamzat Y, Marks S, et al. One-arm safety intervention study on community case management of chest indrawing pneumonia in children in Nigeria. *Glob Health Action* [Internet]. 2020;13(1). Available from: <https://doi.org/10.1080/16549716.2020.1775368>
33. Thambavita D, Galappaththy P, Mannapperuma U, Jayakody L, Cristofolletti R, Abrahamsson B, et al. Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Amoxicillin Trihydrate. *J Pharm Sci* [Internet]. 2017;106(10):2930–45. Available from: <http://dx.doi.org/10.1016/j.xphs.2017.04.068>
34. Arancibia A, Guttmann J, Gonzalez C. Absorption and disposition kinetics of amoxicillin in normal human subjects. *Antimicrob Agents Chemother* [Internet]. 1980;17(2):199–202. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC283758/>