

## Research Article

# Pneumonia Prevalence and Associated Risk Factors among under-Five Children in Goncha Siso Enesie District, Northwest Ethiopia

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Received 24 December 2021; Revised 15 July 2022; Accepted 18 July 2022; Published 4 August 2022

Academic Editor: Daniel Diaz

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**Background.** Pneumonia is one of the leading causes of morbidity and mortality among under-five children in various localities of Ethiopia. This study was aimed to assess the prevalence of pneumonia and its associated factors among under-five children who were visiting Ginde Woyin health center, Goncha Siso Enesie District, Northwest Ethiopia. **Methods.** A health center-based cross-sectional study was conducted among 403 participants by a systematic random sampling technique. Data were collected using questionnaires and sputum diagnosis. Data were analyzed using Statistical Package for Social Science (SPSS) version 26.0. Binary and multivariable logistic regressions were used to analyze the risk variables, and  $P$  values  $< 0.05$  were considered statistically significant. **Results.** The overall prevalence of pneumonia among under-five children was 24.3% (95% CI: 20.1, 28.3). The significant predictors for under-five pneumonia identified were the use of wood as a source of fuel for cooking (AOR = 2.769;  $P = 0.049$ ), starting complementary food before six months of age (AOR = 2.080;  $P = 0.033$ ), and mixed breastfeeding conditions (AOR = 5.229;  $P = 0.001$ ). The highest under-five pneumonia was observed among children of age below one year (33.6%), rural dwellers (30.4%), family sizes above five (31.8%), children from families with a monthly income of less than 1000 Ethiopian Birr (<19.03 USD) (27.8%), whose mothers were students (61.5%), houses where cooking took place in the living room (37.8%), homes that lacked windows in the kitchens (28.4%), homes that lacked windows (41.5%), and mixed breastfeeders (44.1%). **Conclusion.** The prevalence of under-five pneumonia in the present study was relatively high. The findings in the present study will help policy makers and program officers to design pneumonia-preventive interventions.

## 1. Background

Pneumonia is a disease of the lung or inflammation of the parenchyma of the lungs, such as the alveoli and bronchioles [1]. It results in the mortality of many under-five children in many countries. In 2018 alone, it resulted in 802,000 under-five mortalities. The annual global cases of pneumonia reach 1,400 cases per 100,000 children, or one case per seventy-one children [2]. Globally, more than 802,000 under-five children were affected by pneumonia in 2018, resulting in 2,200 mortalities per day. Also, there are over 1,400 cases of pneumonia per 100,000 Children, or one case per 71 children every year, with the highest incidence occurring in

South Asia (2,500 cases per 100,000 children) and West and Central Africa (1,620 cases per 100,000 children) [3].

Among African countries, this ranged from 11,000 in Sudan to 162,000 in Nigeria and 32,000 in Ethiopia [4]. Around 153,000 (19%) of the under-five children died within their first month of age (close to 2,200 under-five mortalities per day and one child every 39 seconds) [4].

In Ethiopia, 44,000 under-five children encounter pneumonia annually, which contributes to 20% of all the causes of death every year and is a leading cause of death during the postnatal period [5]. The associated risk factors of pneumonia were sociodemographic status (educational status, occupation, monthly income, family size), living

condition factors (housing condition, toilet facility, water facility, cooking area, and rooms in the main house), and comorbid diseases (diarrhea, upper respiratory tract infections (URTI), and asthma) [6–12].

According to Ginde Woyin (Goncha Siso Enesie District) health center clinical reports, under-five pneumonia was the first of the top ten diseases in 2020. Therefore, the present study was undertaken to assess the prevalence and the associated risk factors of pneumonia among under-five children who were attending Ginde Woyin health center, Goncha Siso Enesie District, Northwest Ethiopia.

## 2. Materials and Methods

**2.1. Study Area, Study Population, and Study Design.** Goncha Siso Enesie is located 335 km northwest of Addis Ababa (the capital city of Ethiopia). The district is located at the geographical location of 10°8'00" to 11°09'00" North latitude and between 37°9'00" to 39°00'00" East longitude. The average temperature of the district is about 18.5°C, and the average annual rainfall ranges from 762 to 1825 mm. According to the Ethiopian Census 2021 current year projection, the total population of the district was 192,628 [94,613(49.12%) males and 95,015 (50.88%) females]. The rural population was 183,948 (95.49%), and the urban population was 8680 (4.51%)[13].

There are eight health centers and 43 health posts in the district. Ginde Woyin health center is among the eight health centers. It gives service to 35,813 people. Under this health center, six rural and two urban health posts are assigned to implement the health extension program. We chose Ginde Woyin health center because under-five pneumonia was the first of the top 10 diseases in the 2020 clinical report (Goncha Siso Enesie Health Office Annual Report, 2020). A health center-based cross-sectional study was conducted on under-five children who attended Ginde Woyin health center from February 3, 2021, to April 10, 2021.

**2.2. Sample Size Determination.** There was no similar study previously conducted in the area; a 50% prevalence rate of under-five pneumonia was taken, assuming that pneumonia is significantly prevalent among under-five children attending Ginde Woyin health center. Accordingly, the minimum number of sample size ( $n$ ) required was determined using a single population proportion formula for cross-sectional surveys [14], i.e.,  $n = Z^2 p(1-p) / d^2 = 1.96^2 \times 0.50 \times 0.50 / .05^2 = 384$  students. To compensate for the nonrespondents and to minimize errors probably arising from the likelihood of noncompliance, a 5% contingency was added, giving a final sample size of 403 study participants.

### 2.3. Variables of the Study

- (i) Dependent variable- the prevalence of under-five pneumonia
- (ii) Independent variables- environmental factors (air pollution, use of firewood for cooking, tobacco

smoke exposure, sanitation, lack of windows in the kitchen, lack of windows in the living room, lack of a separate kitchen, and overcrowding); health facility and child care factors (availability/distance/cost of health facility, immunization/vaccination, and comorbidity); and sociodemographic characteristics (age, sex, parental occupation, parental education level, and family size)

### 2.4. Eligibility Criteria

**2.4.1. Inclusion Criteria.** Under-five children who did not take antipneumonia drugs and those whose parents/primary guardians were voluntary to sign consent were included.

**2.4.2. Exclusion Criteria.** Under-five children who took antipneumonia drugs, those children and parents/guardians who have hearing impairments, and those whose parents or guardians did not sign consent were excluded.

**2.5. Sample Collection and Processing.** Structured questionnaires comprising the known risk factors were developed in English and translated into Amharic (local language). The authors interviewed the participants and the parents of younger children to obtain the socio-demographic characteristics and the related risk factors for pneumonia. The language was translated back into English. The questionnaires were pretested on a nonstudy sample population.

Fresh sputum samples were collected in clean, labeled cups [15]. The authors recorded the date, name, age, and sex of each participant during the sputum collection. The sputum samples were smeared on slides, air-dried, and fixed by heating [16]. Following fixation, the slides were treated with carbon fusion and heat. Five minutes after fusion, the slides were washed with water and 3% acidic alcohol. After three minutes, they were again washed with water. Then, they were stained with methylene blue for one minute, washed with water, and dried in the air. Finally, we observed the sputum slides under a microscope for examination. A change in the color of the sputum to dark green indicates a positive for pneumonia. Generally, Ginde Woyin health center lacks an X-ray machine to confirm under-five pneumonia. Therefore, physicians in the health center used the symptoms such as cough; difficulty breathing; thick yellow, green, brown, or blood-stained mucus (phlegm); rapid heartbeat; high temperature; sweating and shivering; loss of appetite, and chest pain as confirmations of pneumonia. Consequently, the researchers of the present study confirmed pneumonia in the same way [17].

**2.6. Data Analysis.** We analyzed the data using the Statistical Package for Social Sciences (SPSS) version 26.0. We used descriptive statistics to show the prevalence of pneumonia among the different sociodemographic groups of under-five children. Associations between the risk

factors and under-five pneumonia were determined using univariable logistic regression. We used multivariable logistic regression to test the strength of the associations. *P* values below 0.05 were considered significant.

### 3. Results

**3.1. Sociodemographic Characteristics of the Respondents.** The present study included 403 under-five children with a response rate of 100% of their parents/guardians (49.4% males and 50.6% females). Age-wise, the respondents were 1 to 3 (49.9%), less than one (36.2%), and 4 to 5 (13.9%). The majority of the study participants (60.8%) were rural dwellers. Two hundred and nine (51.9%) were from four up to five, 31% from above five, and 17.1% from below three family sizes.

One hundred and seventy-one (42.4%) of the respondents came from families with monthly income ranging from 1000–2500 birr (19.03–47.57 USD), 37.5% from families with income less than 1000 birr (19.03 USD), and 20.1% from families with income greater than 2500 birr (47.57 USD). One hundred and ninety-three (47.9%) of the mothers and 44.7% of the fathers were illiterate. Sixty-two (15.4%) of the mothers and 60 (14.9%) of the fathers had an educational level of diploma or above. More than half of the mothers (63%) were housewives, while 3.2% were students. The highest proportion of the fathers ( $n = 227$ , 56.3%) were farmers, followed by daily laborers ( $n = 44$ , 10.9%), and 20 (5%) of them were civil servants (Table 1).

**3.2. Prevalence of under-Five Pneumonia.** The overall prevalence of pneumonia among under-five children is presented in Table 2. Out of the 403 examined under-five children, pneumonia cases were 98 (24.3%). The gender distribution of under-five pneumonia was 46 (23.1%) among males and 52 (25.5%) among females. The pneumonia cases were higher in male children in the below one year age group (27%) and female children in one up to three age groups (24.8%).

**3.3. Risk Factors Associated with Pneumonia.** The univariate logistic regression analysis showed that children who were breastfed for less than two years were 1.75 times at higher risk of pneumonia (COR = 1.752; 95% CI: 1.009–3.041;  $P = 0.046$ ) compared to children who were breastfed for more than two years. Cooking in the living room was 2.5 times riskier than cooking in the kitchen (COR = 2.483; 95% CI: 1.121, 5.502;  $P = 0.025$ ) (Table 3).

In the multivariable logistic regression, children from families who used wood for cooking were 3.5 times more likely to be infected by pneumonia (AOR = 3.535; 95% CI: 0.829–9.724;  $P = 0.047$ ) than electricity users. When compared to exclusive breastfeeders, children who received mixed breastfeeding were 5.2 times at higher risk of pneumonia (AOR = 5.229; 95% CI: 3.025–9.041;  $P = 0.001$ ). Children who started complementary food before six months of age were 2 times at higher risk of pneumonia

(AOR = 2.080; 95% CI: 1.061–4.076;  $P = 0.033$ ) than those who started after six months (Table 3).

### 4. Discussion

The overall prevalence of pneumonia (24.3%) was in line with the findings from Tanzania (22%) [18], in the Sheka zone of SNNPR (Ethiopia) (23.8%) [19], and in Gondar city (Ethiopia) (26.3%) [20]. It was higher than that of studies in Debre Birhan (Ethiopia) (5.5%) [7], Mali (6.7%) [21], Uganda (6.9%) [22], and Kenya (6.9%) [23]. However, it was lower than the findings in Nigeria (31.6%) [24], Sudan (65%) [11], Kenya (74%) [25], Uganda (56%) [26], and the Sidama Zone, Wondo Genet district (Ethiopia) (33.5%) [10]. The difference in the prevalence could be due to sociodemographic differences, seasonal variation, socioeconomic differences, environmental change [8], and immunization inaccessibility or provision [27]. It is because Africa is a continent characterized by marked ethnic, sociodemographic, and economic diversity [28]. Sociodemographic factors such as age, gender, socioeconomic status (SES), race/ethnicity, and immigration status may in turn affect the status of vaccination [29]. Furthermore, geographical inequality contributes to child mortalities and morbidities [30].

Children who were from families that used wood for cooking were 2.77 times more likely to be infected by pneumonia (AOR = 2.769; 95% CI: 0.488, 15.727;  $P = 0.049$ ) than electricity users. This result was in line with studies in Gondar city (Northwest Ethiopia) [20], the Sheka Zone (Southwest Ethiopia) [19], and the Jimma zone (Southwest Ethiopia) [31]. The possible reason behind this might be that firewood smoke contains indoor air pollutants, which adversely affect the defenses of the respiratory tract against pathogens [32]. Wood smoke can irritate the lungs, cause inflammation, suppress the immune system, and make the lungs more susceptible to infections [33]. Reports also show that reducing exposure to smoke from open fires and wood-burning cook stoves significantly reduces the incidence of pneumonia, the leading cause of death for children five and under in developing countries [34].

Children who started complementary food before six months of age were 2 times (AOR = 2.08; 95% CI: 1.061–4.076;  $P = 0.033$ ) more infected by pneumonia than those who started complementary food after six months of age. This finding agreed with studies conducted in Ethiopia [35]. The possible reason might be that starting complementary food early in childhood may reduce breast milk intake and make the children susceptible to different infections [36]. Similarly, being partially breastfed or not breastfed at all increases the risk of mortality due to various infections [37], as does pneumonia.

Children who used mixed breastfeeding were 5.2 times at higher risk of pneumonia (AOR = 5.229; 95% CI: 3.025–9.041;  $P = 0.001$ ) than exclusive breastfeeders. This finding agreed with the studies conducted in India (AOR = 1.92; 95%CI: 0.79, 4.68) [38] and in the Jimma zone, Ethiopia (AOR = 3.3; 95%CI: 1.266, 8.3) [31]. The reason might be that breast milk contains nutrients, antioxidants,

TABLE 1: Sociodemographic characteristics of the respondents in Goncha Siso Enesie District, Northwest Ethiopia ( $n = 403$ ).

Independent variables	Coding categories	Frequency	Percent
Sex	Male	199	49.4
	Female	204	50.6
Age	<1 year	146	36.2
	1–3 year	201	49.9
	4–5 year	56	13.9
Residence	Urban	158	39.2
	Rural	245	60.8
Size of the family	≤3	69	17.1
	4–5	209	51.9
	Above 5	125	31.0
Monthly income of the family	<1000 birr (\$19.03)	151	37.5
	1000–2500 birr (\$19.03–47.57)	171	42.4
	>2500 birr (\$47.57)	81	20.1
Maternal education	Illiterate	193	47.9
	Primary (1–8)	92	22.8
	Secondary (9–12)	56	13.9
	Diploma and above	62	15.4
Paternal education	Illiterate	180	44.7
	Primary (1–8)	109	27.0
	Secondary (9–12)	54	13.4
	Diploma and above	60	14.9
Maternal occupation	Farmer	254	63.0
	Daily laborers	27	6.7
	Merchant	82	20.3
	Student	13	3.2
	Civil servant	27	6.7
Paternal occupation	Farmer	227	56.3
	Daily labor	44	10.9
	Merchant	63	15.6
	Student	49	12.2
	Civil servant	20	5.0

TABLE 2: Prevalence of pneumonia among under-five children by age and sex.

Sex and age	Total examined N (%)	Pneumonia		
		Positive, N (%)	Negative, N (%)	
Male	<1 year	63 (100)	17 (27)	46 (73)
	1–3 years	110 (100)	23 (20.9)	87 (79.1)
	4–5 years	26 (100)	6 (23.1)	20 (76.9)
	Total	199 (100%)	46 (23.1)	153 (76.9)
Female	<1 year	29 (100)	15 (51.7)	14 (48.3)
	1–3 years	129 (100)	32 (24.8)	97 (75.2)
	4–5 years	46 (100)	5 (10.9)	41 (89.1)
	Total	204 (100%)	52 (25.5)	152 (74.5)
Both sexes	<1 year	92 (100)	32 (34.8)	60 (65.2)
	1–3 years	239 (100)	55 (23)	184 (77)
	4–5 years	72 (100)	11 (15.3)	61 (84.7)
	Total	403 (100)	98 (24.3)	305 (75.7)
Overall	403 (100)	98 (24.3)	305 (75.7)	

hormones, lymphocytes, and antibodies that prevent infection [38]. Exclusive Breast Feeding (EBF) for the first six months of life prevents child mortality and morbidity [39].

Several studies reported that factors such as maternal and parental educational status, gender of the child, child age, history of past morbidity, the condition of the child's

vaccination, housing, and environmental factors are significantly associated with under-five pneumonia [7, 31, 40], but in the present finding, these factors were not associated with under-five pneumonia. It agrees with the report saying that in Africa, a one-year increase in maternal education is not associated with a significant change in pneumonia rates

TABLE 3: Univariate and multivariate logistic regression analysis of potential risk factors associated with under-five pneumonia in Goncha Siso Enesie District, Northwest Ethiopia, 2020/2021.

Independent variables	Coding categories	Pneumonia status		Univariate logistic regression		Multivariate logistic regression	
		Positive (percent)	Negative (percent)	COR (95% CI)	P value	AOR (95% CI)	P value
Age	Below 1 year	49 (33.6)	97 (66.4)	0.598 (0.295, 1.216)	0.156	0.897 (0.317, 2.539)	0.837
	1–3 years old	36 (17.9)	165 (82.1)	1.386 (0.676, 2.840)	0.373	1.439 (0.568, 3.845)	0.443
	3–5 years old	13 (24.1)	43 (75.9)	1			
Residence	Rural	48 (30.4)	110 (69.6)	1.702 (1.074, 2.695)	0.023*	0.538 (0.303, 0.953)	0.034*
	Urban	50 (20.4)	195 (79.6)	1			
Size of the family	>5	22 (31.8)	47 (68.2)	1.450 (0.799, 2.633)	0.222	0.465 (0.200, 1.081)	0.075
	4–5	51 (24.4)	158 (75.6)	1.872 (0.958, 3.658)	0.066	0.651 (0.342, 1.238)	0.191
	≤3	25 (20)	100 (80)	1			
Monthly income of the family (birr)	<1000 birr (\$19.03)	42 (27.8)	109 (72.2)	0.590 (0.304, 1.146)	0.119	0.589 (0.262, 1.326)	0.201
	1000–2500 birr (\$19.03–47.57)	41 (23.9)	130 (76.1)	0.721 (0.372, 1.396)	0.332	0.872(0.397, 1.919)	0.734
	>2500 birr (\$47.57)	15 (18.5)	66 (81.5)	1			
Maternal occupation	House wives	51 (20.1)	203 (79.9)	1.393 (0.559, 3.474)	0.477	1.274 (0.158, 10.296)	0.820
	Daily labor	11 (40.7)	16 (59.3)	0.509 (0.161, 1.613)	0.261	0.168 (0.014, 2.061)	0.163
	Merchant	21 (25.6)	61 (74.4)	1.017 (0.377, 2.745)	0.974	0.784 (0.086, 7.114)	0.829
	Student	8 (61.5)	5 (38.5)	0.219 (0.053, 0.896)	0.035*	1.011 (0.972, 3.643)	0.061
	Civil servant	7 (25.9)	20 (74.1)	1			
Source of fuel for cooking	Wood	69 (28.9)	170 (71.1)	1.232 (0.3, 5.065)	0.773	2.769 (0.488, 15.727)	0.049*
	Charcoal	26 (16.7)	129 (83.3)	2.481 (0.583, 10.56)	0.219	1.390 (0.251, 7.697)	0.706
	Electricity	3 (33.3)	6 (66.7)	1			
Cooking area	Kitchen	59 (24.7)	180 (75.3)	1			
	Outdoor	25 (19.7)	102 (80.3)	1.857 (0.898, 3.84)	0.095	0.520 (0.205, 1.319)	0.169
	Living room	14 (37.8)	23 (62.2)	2.483 (1.121, 5.502)	0.025*	0.895 (0.481, 1.665)	0.726
Presence of windows in the kitchen	No	61 (28.4)	154 (71.6)	0.619 (0.388, 0.986)	0.043*	0.626 (0.361, 1.085)	0.045*
	Yes	37 (19.7)	151 (80.3)	1			
Number of windows in the main house	> three	21 (23.8)	67 (76.2)	1			
	Two	23 (20.9)	87 (79.1)	1.186 (0.606, 2.321)	0.619	1.503 (0.689, 3.280)	0.306
	One	27 (19.3)	113 (80.7)	1.312 (0.688, 2.501)	0.410	1.252 (0.591, 2.653)	0.557
	No window	27 (41.5)	38 (58.5)	0.441 (0.220, 0.884)	0.021*	0.598 (0.264, 1.356)	0.218
BF status of the child	Mixed BF	60 (44.1)	76 (55.9)	0.21 (0.130, 0.340)	0.001*	5.229 (3.025, 9.041)	0.001*
	Exclusive BF	38 (14.2)	229 (85.8)	1			



TABLE 3: Continued.

Independent variables	Coding categories	Pneumonia status		Univariate logistic regression		Multivariate logistic regression	
		Positive (percent)	Negative (percent)	COR (95% CI)	P value	AOR (95% CI)	P value
Years of BF	Up to 1 year	12 (29.3)	29 (70.7)	2.240 (1.109, 4.526)	0.025*	1.357 (0.509, 3.613)	0.542
	Up to 2 years	25 (19.8)	101 (80.2)	1.752 (1.009, 3.041)	0.046*	1.699 (0.179, 16.101)	0.644
	Up to date	49 (30.2)	113 (69.2)	1.048 (0.494, 2.222)	0.903	1.599 (0.729, 3.505)	0.242
	>2 years	12 (16.2)	62 (83.8)	1			
Age when complementary feed started	>6 months	29 (20.7)	111 (79.3)	1			
	<6 months	23 (14.0)	131 (86.0)	1.037 (0.593, 1.814)	0.898	2.080 (1.061, 4.076)	0.033*
	Not started	36 (36.7)	63 (63.3)	0.457 (0.256, 0.815)	0.008*	1.925 (0.961, 3.855)	0.065

ARTI = acute respiratory tract infection; BF = breastfeeding; \* statistically significant at  $P < 0.05$ .

[41], the exposure rate of under-five males and females may not be different in rural Ethiopia, the routine immunization in Ethiopia only includes preventable diseases such as measles, diphtheria, pertussis, tetanus, polio, and tuberculosis [42], and most houses and other environmental factors in rural Ethiopia may be of close status.

## 5. Conclusion

The prevalence of under-five pneumonia in the present study was relatively high. The significant predictors for under-five pneumonia identified were the use of wood as a source of fuel for cooking; starting complementary food before six months of age; and mixed breastfeeding conditions.

**5.1. Recommendations.** The authors recommend awareness-creation programs on the importance of breastfeeding in the study area, the need for kitchen windows, and using healthy fuel alternatives to firewood.

**5.2. Significance of the Study.** The findings of the present study provide information for health offices, parents, policy makers, and program officers to design pneumonia-preventive interventions.

**5.3. Limitation of the Study.** This study was limited to sputum (mucus) and blood tests with pulse oximetry. But, these tests cannot strictly identify pneumonia. In addition, the use of the chest X-ray test helps to look at the extent of the infection (prevalence) of pneumonia. However, failure to use this method in the present study may underestimate the prevalence of pneumonia among the study subjects.

### 5.4. Operational Definition of Variables

(i) **Age** refers to the participants' age measured in years between the time from birth and the date of data collection (February 3, 2021, to April 10, 2021)

- (ii) **Associated risk factors**- sociodemographic, behavioral, and environmental factors that caused or contributed to the development of pneumonia among under-five children visiting Ginde Woyin health center (February 3, 2021, to April 10, 2021)
- (iii) **Family size** refers to the number of persons in the family of under-five children visiting Ginde Woyin health center (February 3, 2021, to April 10, 2021)
- (iv) **Maternal/paternal education**- the level of the "formal" education of the mothers/fathers of under-five children visiting Ginde Woyin health center (February 3, 2021, to April 10, 2021)
- (v) **Maternal/paternal occupation**- the main sectors of employment of the mothers/fathers of under-five children visiting Ginde Woyin health center (February 3, 2021, to April 10, 2021)
- (vi) **Monthly income of the family**- the combined monthly incomes (Ethiopian Birr) of all members of the households (18 years and above) of under-five children visiting Ginde Woyin health center (February 3, 2021, to April 10, 2021)
- (vii) **Prevalence of pneumonia**- the calculated value of pneumonia cases among under-five children visiting Ginde Woyin health center (February 3, 2021, to April 10, 2021) divided by the total number in a study of under-five children multiplied by 100
- (viii) **Residence**- defined based on the dwelling of under-five children visiting Ginde Woyin health center (February 3, 2021, to April 10, 2021) by relating to the countryside or the town, the former as rural and the latter as urban residents
- (ix) **Sex** was the physical condition of being a male or female of under-five children visiting Ginde Woyin health center, Goncha Siso Enesie District, Northwest Ethiopia, February 3, 2021, to April 10, 2021
- (x) **Sputum**- a mixture of saliva and mucus coughed up from the respiratory tracts of under-five

children visiting Ginde Woyin health center (February 3, 2021, to April 10, 2021)

- (xi) **Under-five pneumonia** is an infection of the lungs caused by fungi, bacteria, or viruses with symptoms including chest pain, fever, cough, and trouble breathing

## Data Availability

All data generated or analyzed during this study are included in this article (and its supplementary information files).

## Conflicts of Interest

The authors declare no conflicts of interest.

## Acknowledgments

The authors would like to thank all the study participants who were voluntarily involved in this study. They also thank Bahir Dar University (<https://ir.bdu.edu.et/handle/123456789/12289>) and staff members of Ginde Woyin health center. Their special thanks go to sister Workinesh Yedemie (a Pediatrician) at Ginde Woyin health center.

## Supplementary Materials

S1\_ File: Supplementary material. (*Supplementary Materials*)

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