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Keywords: Pneumonia; Amoxicillin; Randomized Trial; Antimicrobial-Resistance.



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Article

Clinical Effectiveness of Oral Amoxicillin for Treatment of Child-hood Non-Severe Pneumonia at Primary Health Centers, Sana'a Governorate Yemen – 2021: A Randomized Controlled Trail

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Abstract: Pneumonia kills over two million children under-age of five every year. Oral amoxicillin was recommended by WHO as the first drug of choice for treatment of non-severe pneumonia. The study aimed to determine the clinical failure rate of amoxycillin for the treatment of childhood non-severe pneumonia at Primary Health Care Centers (PHCCs). A randomized controlled multicenter-trial study was conducted in Sana'a. IMCI strategy was used to enrollments the cases where randomly allocated to receive amoxicillin or co-trimoxazole orally for five days. Multivariate logistic regression was used for identified risk factors associated with clinical failure. A total of 254 children were enrolled, of whom 128 cases were treated with amoxicillin while 126 with co-trimoxazole. The clinical failure for amoxicillin was significantly more than co-trimoxazole (30% vs 10%) p value > 0.001. the most risk factor which significantly associated to amoxicillin failure were pre-infection in the last 6 months, while abnormal CBC and literate mothers were associated with clinical failure of co-trimoxazole (p value > 0.05). The use of co-trimoxazole as an alternative to amoxicillin for the treatment of non-severe pneumonia in the PHCCs and conducting further studies to determine the appropriate antibiotic as the first line of defense are recommended.

Keywords: pneumonia; amoxicillin; randomized trial; antimicrobial-resistance

1. Introduction

Pneumonia is one of the largest killer of children under the age of five worldwide which kills over two million children under the age of five every year [1,2]. WHO developed standard guidelines in 2011 for management of patients to reduce the number of people dying from pneumonia [3].

The guidelines have been used widely in several less-developed countries for many years and recommend five days of oral amoxicillin for treatment of non-severe pneumonia [4]. In additional, transport to a distant facility can entail serious delays in effective treatment. Many children with severe pneumonia referred for admission to a hospital could die in transit or reach too sick to be saved [5].

Antimicrobial resistance rate is growing health problem and concern widely, studies that were conducted in different countries addressed such barriers to the recommended treatment of severe pneumonia. [6].

Furthermore, the study revealed whether oral antibiotics are equivalent to injectable antibiotics when both are given in the hospital. This was an open label equivalency study called Amoxicillin Penicillin Pneumonia International Study (APPIS), which was a large multicenter randomized controlled trial comparing injectable penicillin versus oral amoxicillin given for 7 days to children in the hospital [7].

In addition, New Outpatient Short-Course Home Oral Therapy for Severe Pneumonia Study (NOSHOTS) was a randomized, open-label equivalency trial done at seven study sites in Pakistan

and compared initial hospitalization and parenteral ampicillin for 48 h followed by 3 days of oral amoxicillin at home, to 5 days of home-based treatment with oral amoxicillin [8]. NOSHOTS showed home treatment with high dose oral amoxicillin is equivalent to hospital-based treatment with parenteral ampicillin in selected children aged 3–59 months with WHO defined severe pneumonia [8].

Later, another study called Multicenter Amoxicillin Severe Pneumonia Study (MASS) showed that clinical treatment failure and adverse event rates among children with severe pneumonia treated at home with oral amoxicillin did not substantially differ across geographic areas (Bangladesh, Ghana, Vietnam, and Egypt) and hence home-based therapy of severe pneumonia could possibly be applied to a wide variety of settings [9].

The Lancet Series on Childhood Pneumonia and Diarrhea has reported that case management is one of the three most effective interventions to reduce pneumonia deaths in children but also noted that the cost effectiveness of these interventions in national health systems needs urgent assessment [10].

The conflict in Yemen has devastated the health system, with only 51% of health facilities classified as fully functional and 19.7 million people lacking access to health care. To address the urgent need for primary health care services in rural communities, [11] This lead to increase the acute respiratory infections (ARI) which is a leading cause of mortality and morbidity among children under 5 of age in Yemen. In a recent epidemiological survey, 49% of this age group had cough and 25% had cough with difficult breathing during the 2 weeks prior to the survey. [11,12].

Therefore, our study hypothesis (null) was the clinical failure rate with Amoxycillin as the first line based on the Integrated Management Childhood Illness (IMCI) strategy or Co-trimoxazole antibiotic treatment would be similar in children with non-severe pneumonia.

General objective:

To assess the IMCI strategy in the primary health care centers (PHCCs) is beneficial for use of amoxicillin in treatment of childhood non-sever pneumonia.

Specific objectives:

1. To determine the effectiveness of antibiotic amoxicillin for treatment of childhood non-severe pneumonia.
2. To identify the risk factors associated with clinical failure.
3. Provide policy makers with evidence to make a decision.

2. Materials and Methods

2.1. Study design

A randomized controlled trail was conducted from August to October 2021.

2.2. Study setting and population.

This study was conducted at PHCCs in Sana'a governorate, which supported by World Bank. All children with age group of 2 months to 5 years, who attending the PHCCs for non-severe pneumonia as IMCI classify strategy were included in the study.

2.3. Definitions and selection criteria:

- Exposed arm: All cases with non-sever pneumonia who were treat with Oral Amoxicillin.
- Non-exposed arm: All cases with non-sever pneumonia who were treat with oral co-trimoxazole instead of amoxicillin.
- The clinical cure was defined as respiratory rate of less than 50/minute between 2 months to 12 months of age and less than 40/minute between 1 year to 5 years of age and absence of any of clinical signs of treatment failure.
- The treatment failure was defined as occurrence of any signs of WHO defined of severe pneumonia, increase respiratory rate of more than or equal 50/minute between 2 months to 12 months of age and more than or equal 40/minute between 1 year to 5 years of age. [13]

- **Inclusion Criteria:** based on IMCI strategy, any cases of non-sever pneumonia, who is attending to PHCCs and will receive oral amoxicillin or any other antibiotics.
- **Exclusion Criteria:** The cases were excluded if they have WHO signs of severe pneumonia, history of having received antibiotics for any illness anywhere 48 hours before coming to the PHCCs, previous history of wheezing including asthma or children who have been prescribed corticosteroids along with bronchodilators, children with congenital heart disease, immunodeficiency (congenital or acquired) including suspected or confirmed HIV infection, any chronic illness including chronic infections like tuberculosis, malignancy, acute/chronic organ disorder, known allergy/hypersensitivity to penicillin. [14]
- **Follow-up of cases:**
The physicians assessed every child in first day of visiting, primary follow up will be after 2 days of starting treatment, while the final follow up will be after 5 days of treatment, treatment was stopped after 5 days if respiratory rate had returned to normal.
(Figure 1).

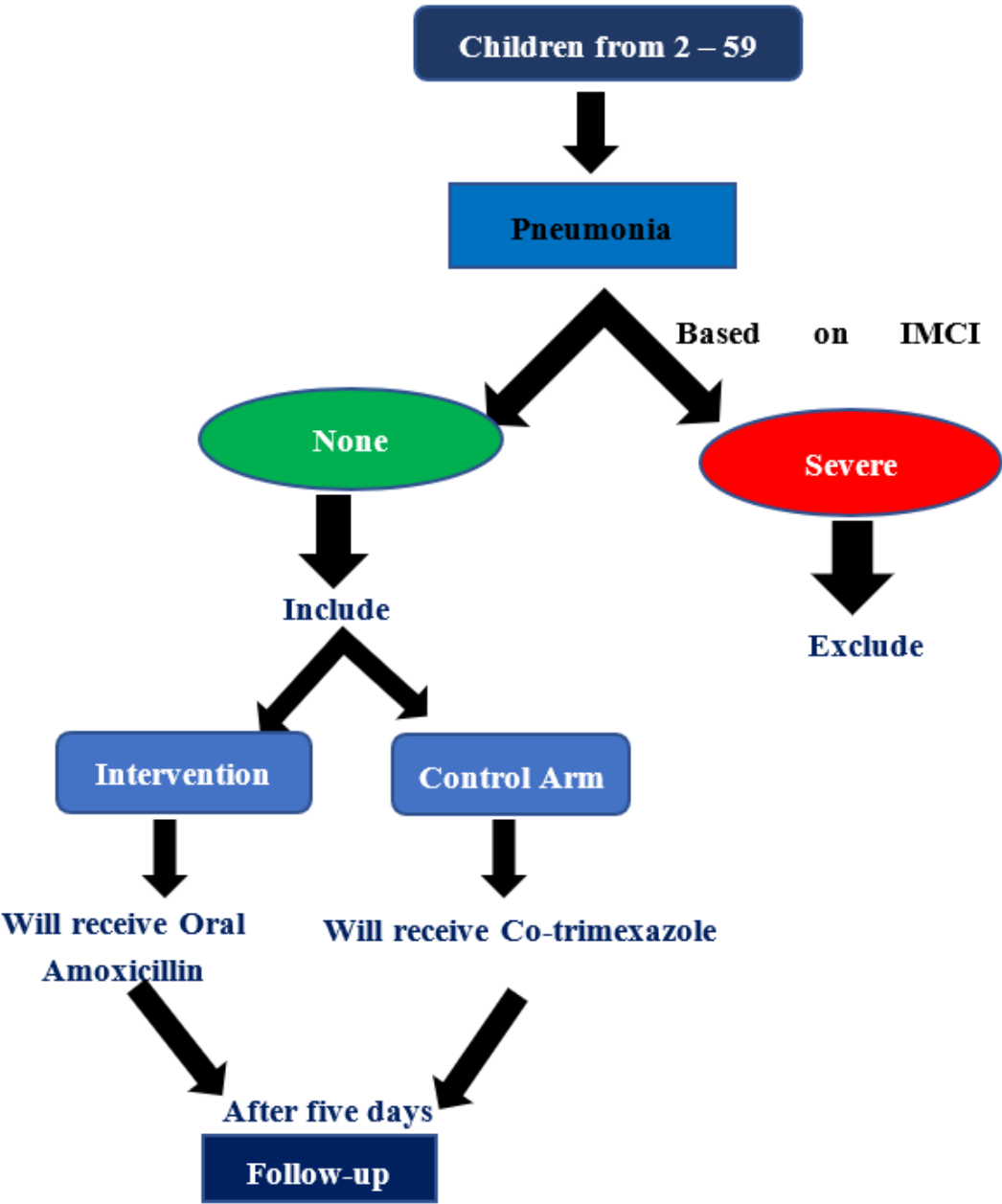


Figure 1. Flowchart of the study.

2.4. Sample size:

The sample size calculated using open Epi program with based on alpha of 0.05, Confidence Interval (CI) of 95%, power of 80%, old ratio 2.5 and assuming a treatment failure rate of expose and non-expose group according to previous studies (7). The sample size comes to 228. we increased the sample by 10% to be 254 to overcome refusal or loss to follow-up.

2.5. Sampling procedures:

The sample was selected from 30 % of districts in Sana'a governorate through choosing the main PHCCs in each district, who applied the IMCI strategy, the sampling interval will be calculated from the main HFs. Randomization of the intervention and control arms for each targeted health facility by Proportion Probability Size (PPS) which is depending on the average of the last three months reports of the non-severe pneumonia cases, the randomization selection generated by the Open Epi Random Program Version 3 which available at: www.openepi.com (Annex I).

2.6. Data Collection:

Data were collected through face-to-face interview with parents of the children using IMCI registration form and a predesigned questionnaire. The questionnaire that includes closed and open questions which cover demographic, socioeconomic characteristics, and clinical features with follow up.

One data collector (doctor) that will administer the questionnaire and one sample collector (lab technician) to collect blood sample will be chosen from the staff at each center. Those will be trained on data and sample collection under direct supervision of the principal investigator. All cases were reviewed after 2 days and then five days after starting treatment.

The effectiveness and therapy failure were decided based on clinical, radiological, and complete blood count results.

2.7. Variables

The following variables will be gathered for the study:

- Demographical data such as name, sex, age, place of birth, residency, ...etc.
- Clinical data such as symptoms, signs ...etc.
- Dates such as date of diagnosis, date of start onset, date of follow-up, ...etc.
- Investigation such as CBC, Nasopharyngeal swab, and chest X-ray result.
- Outcome such as clinically cured, failure of treatment.

2.8. Laboratory testing and procedures:

Three ml whole blood sample was collected twice before treatment and after 5 days of treatment from each case in a labeled plain tube with the unique identifier number. Only CBC will be measured. Regarding the failure of treatment, a nasopharyngeal swab will be taken from the cases after three days from stopping the antibiotics (Amoxicillin or Co-trimoxazole) then send the swab to the national laboratories to do culture and sensitivities test.

2.9. Analysis and data management:

Data were entered and analyzed using Epi info 7.2 version. The Chi-squared test will be used for categorical variables and T-test for continuous one. For comparing clinical failure in two interventions, Kaplan Meier survival curve analyses were employed by comparing the means and probability of survival for the two arms (groups) of cases to find any difference in response due to antibiotics therapy, P value <0.05 is considered a statistically significant cut off point.

2.10. Quality assurance and control:

The quality assurance was secured during data collection through proper training of study members on the objectives of the study and how to collect the data through the questionnaire and ensure proper case definition using during samples collection. After collection of data, the investigator will follow up the cases in a daily basis. After collections of the questionnaires, the investigator will check data for completeness and accuracy to make sure that data are correctly taken. After completing data entry, cleaning will be taken by checking frequencies for each variable looking for inconsistencies and out-of-range values.

2.11. Ethical considerations:

Study was submitted to the and approved by the Institutional Review Board of the National Committee for Health and Medical Research at the ministry of Public Health and Population (protocol code 103 and date of approval 13/8/2021). Permission from IMCI will be secured and written consent will be taken from parents of children. Privacy will be maintained during interviews, questionnaires kept in a lockable cabinet and data entered in the computer was password protected.

3. Results

3.1. Cases characteristics (Descriptive Analysis)

A total of 269 children were randomly enrolled to study, 262 cases of them were well-matched to inclusion and exclusion criteria of this study, 97% of them (254 cases) were followed up and committed until the end of the study, of whom 128 cases were treated with five days amoxicillin while 126 cases in the five days co-trimoxazole. as clarified in the trail profile ((Figure 2).

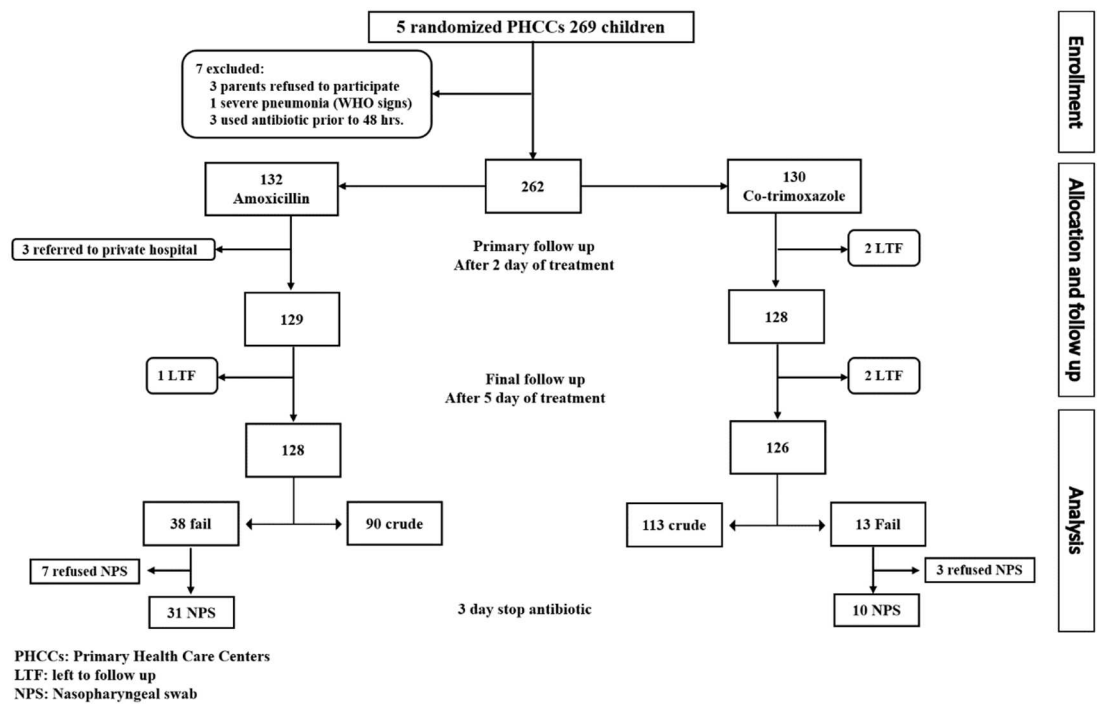


Figure 2. Trail profile.

Table 1 shows the demographic characteristics of childhood non-severe pneumonia cases. Male (64%), farmer jobs of the fathers (61%), children aged less than 12 months (53%), and the primary or secondary education level of fathers (50%) formed the majority of cases. The overall median age of children was 12 months (rang: 2.5 - 59), the overall median wight of children was 8 kilograms (range: 4 - 17.5), and the overall mean monthly income was 30,830 YER ($\pm 12,637$).

100 % of cases were their mothers' housewife, 35 % of cases enrolled from Bani matter district and 94 % of cases were their own houses. This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

Table 1. Socio-demographic characteristics of the childhood non-severe pneumonia cases, at PHCCs, Sana'a Governorate, 2021 (N = 254).

Characteristics	Overall total (N=254)	Amoxicillin (N=128)	Co-trimoxazole (N=126)	P value
Gender				
Male	163 (64%)	81 (50 %)	82 (50 %)	0.866
Female	91 (36%)	47 (52%)	44 (48%)	
Age group				
Infants (2 – 11) months	135 (53%)	71 (53 %)	64 (47%)	0.442
Children (12 – 23) months	56 (22%)	24 (43%)	32 (57%)	
Children (24 – 59) months	63 (25%)	33 (52%)	30 (48%)	
Districts name				
Arhab district	26 (10%)	19 (73%)	7 (27%)	0.075
Bani Matar district	88 (35%)	39 (44%)	49 (56%)	
Hamdan district	70 (27%)	31 (44%)	39 (56%)	
Sanhan district	38 (15%)	21 (55%)	17 (45%)	
Belad Al-Rous district	32 (13%)	18 (56%)	14 (44%)	
Father education				
Illiterate	30 (12%)	17 (57%)	13 (43%)	0.680
Read & write	57 (22%)	25 (44%)	32 (56%)	
Primary or Secondary	128 (50%)	66 (52%)	62 (48%)	
University	39 (15%)	20 (50%)	19 (50%)	
Mother education				
Illiterate	100 (39%)	50 (50%)	50 (50%)	0.947
Read & write	54 (21)	28 (52%)	26 (48%)	
Primary or Secondary	86 (34%)	44 (51%)	42 (49%)	
University	14 (6%)	6 (43%)	8 (57%)	
Father job				
Casual labor	50 (20 %)	20 (40%)	30 (60%)	0.100
Employer	31 (12%)	12 (39%)	19 (61%)	
Farmer	156 (61%)	85 (54%)	71 (46%)	
Jobless	17 (17%)	11 (65%)	6 (35%)	
Home type				
Own house	238 (94%)	123 (52%)	115 (48%)	0.100
Rent house	13 (5%)	3 (23%)	10 (77%)	
Other	3 (1%)	2 (67%)	1 (33%)	

Table 2 show the last 6 months medical characteristics of childhood non-severe pneumonia cases, 122 cases (48%) had a previous history of pneumonia infection during the last 6 months, most of them 85% used antibiotics, 60% of them were syrup in type, the final outcome was cured and represented 89%.

Table 2. Previous medical history of the childhood non-severe pneumonia cases, at PHCC, Sana'a Governorate, 2021 (N = 254).

Characteristics	Overall total	Amoxicillin (N=128)	Co-trimoxazole (N=126)	P value
Previous attack in the last 6 months (N=254)				

Yes	122 (48%)	66 (54 %)	56 (46 %)	0.312
No	132 (52%)	62 (47%)	70 (53%)	
Pre-used of antibiotic (N=122)				
Yes	104 (85%)	51 (49 %)	53 (51%)	0.014
No	18 (15%)	15 (83%)	3 (17%)	
Type of the previous antibiotic (N=104)				
Drop	2 (2%)	1 (50%)	1 (50%)	0.001
Syrup	62 (60%)	22 (43%)	40 (75%)	
Vial	40 (38%)	28 (55%)	12 (23%)	
Where was the previous treatment (N=122)				
At home	6 (5%)	3 (50%)	3 (50%)	0.006
In the pharmacy	45 (36%)	19 (43%)	25 (57%)	
At private HF's	33 (27%)	25 (79%)	7 (21%)	
At public HF's	39 (32%)	18 (46%)	21 (54%)	
Previous outcome (N=122)				
Cured	108 (89%)	58 (54%)	50 (46%)	0.680
Failure	14 (11%)	8 (57%)	6 (43%)	

Table 3: shows the clinical presentation, signs, laboratory finding of childhood non-severe pneumonia cases, the mean of temperature, respiratory rate, and T.WBC 37.7, 51.7, and 11.2, respectively. The common symptoms of cases were cough, difficulty of breath and fever 99 %, 97 % and 82 %, respectively. In addition, the common measured signs were tachypnea 100%, fever (axillary 37.2<) 70%, chest indrawing 41%, and under wight (Z score > -2) 40%. The lab findings show abnormal deferential blood count (CBC) which represent 61%, out of 51 failure of treatment cases, 80% conduct nasopharyngeal swab, 49% of them were Staph. aureus while 7% no growth, nasopharyngeal sensitivity significantly show resistance for amoxicillin vs co-trimoxazole (91% vs 9%). However, there were statistically significant differences between two arms in the diarrhea, malnutrition, otitis media, CBC, and nasopharyngeal sensitivity.

Table 3. The clinical presentation, signs, and lab findings of the non-severe pneumonia cases, PHCC, Sana'a Governorate, 2021 (N = 254).

Characteristics		Overall total (N=254)	Amoxicillin (N=128)	Co-trimoxazole (N=126)	P value
Temperature	mean (SD)	37.7 (± 0.8)	37.7 (± 0.8)	37.7 (± 0.7)	0.425
Respiratory rate	mean (SD)	51.7 (± 6.5)	52 (± 6.2)	51.3 (± 6.8)	0.422
T.WBC*	mean (SD)	11.2 (± 3)	11.5 (± 3.2)	10.8 (± 2.9)	0.070
Neutrophil	median (range)	70 (40 - 88)	71.5 (40 - 88)	66.7 (40 - 86)	0.009
Fever (by history)					
	Yes	209 (82%)	102 (49%)	107 (51%)	0.353
	No	45 (18%)	26 (58%)	19 (42%)	
Difficulty breath (by history)					
	Yes	245 (97%)	121 (49%)	124 (51%)	0.182
	No	9 (52%)	7 (78%)	2 (22%)	
Cough					
	Yes	251 (99%)	126 (5%)	125 (50 %)	1.000
	No	3 (1%)	2 (67%)	1 (33%)	
Runny nose					
	Yes	92 (36%)	42 (46%)	50 (54%)	0.131
	No	162 (64%)	86 (53%)	76 (47%)	
Fever (Measured)					
	Temp. (> 37.2)	178 (70%)	88 (49%)	90 (51%)	0.742
	Normal	76 (30%)	40 (53%)	36 (47%)	

Chest indrawing					
Yes	104 (41%)	50 (48%)	54 (52%)	0.626	
No	150 (59%)	78 (52%)	72 (48%)		
Wheeze					
Yes	4 (2%)	2 (50%)	2 (50%)	1.000	
No	250 (98%)	126 (50%)	124 (50%)		
Stridor					
Yes	6 (2%)	4 (67%)	2 (33%)	0.693	
No	248 (98%)	124 (50%)	124 (50%)		
Diarrhea					
Yes	50 (20%)	2 (4%)	48 (96%)	0.000	
No	204 (80%)	126 (62%)	78 (38%)		
Vomiting					
Yes	21 (8%)	7 (33%)	14 (66%)	0.160	
No	233 (92%)	121 (52%)	112 (48%)		
Sweeting					
Yes	34 (0%)	20 (59%)	14 (41%)	0.383	
No	220 (86%)	108 (84%)	112 (89%)		
General Weakness					
Yes	36 (14%)	17 (47%)	19 (53%)	0.817	
No	218 (86%)	111 (51%)	107 (49%)		
Anemia					
Yes	28 (11%)	12 (43%)	16 (57%)	0.518	
No	226 (89%)	116 (51%)	110 (49%)		
Malnutrition (History)					
Yes	22 (9%)	16 (73%)	6 (27%)	0.048	
No	233 (91%)	112 (48%)	120 (52%)		
Otitis Media					
Yes	28 (11%)	24 (86%)	4 (14%)	0.000	
No	226 (89%)	104 (46%)	122 (54%)		
Z Score (Weight for Age)					
Under weight	101 (40%)	52 (52%%)	49 (48%)	0.877	
Normal	153 (60%)	76 (50%)	70 (50%)		
Lab result (CBC)					
Abnormal	156 (61%)	93 (72%)	63 (50%)	0.000	
Normal	98 (39%)	35 (27%)	63 (50%)		
Nasopharyngeal swab (N=51)					
Yes	41 (80%)	31 (76%)	10 (24%)	1.000	
No	10 (20%)	7 (70%)	3 (30%)		
Nasopharyngeal culture (N=41)					
No growth	3 (7%)	3 (100%)	0 (0%)	0.942	
H. influenzae	4 (10%)	3 (75%)	1 (25%)		
K. pneumoniae	5 (12%)	4 (80%)	1 (20%)		
Staph. aureus	20 (49%)	15 (75%)	5 (25%)		
Streptococci sp.	9 (22%)	6 (67%)	3 (33%)		
Nasopharyngeal sensitivity (N=38)					
Sensitive	11 (28%)	4 (36%)	7 (64%)	0.002	
Moderate	4 (11%)	3 (75%)	1 (25%)		
Resistant	23 (61%)	21 (91%)	(9%)		

*T.WBC: Total White Blood Cells.

3.2. Clinical outcome:

The clinical effectiveness of two arms of antibiotics were shown in (Table 4), which was the failure of treatment for amoxicillin significantly more than co-trimoxazole based on the IMCI failure criteria (30% vs 10%, p value < 0.001).

Table 4. The failure and cured rate by antibiotics of the non-severe pneumonia cases, PHCC, Sana'a Governorate, 2021 (N = 254).

Factors	Failure	Cured	OR (CI)	P value
Amoxicillin	38 (30%)	90 (70%)	3.670	0.000
Co-trimoxazole	13 (10%)	0%	(1.84 – 7.30)	

3.3. Predictors (Risk factors) associated with clinical failure:

Risk factors associated with clinical failure bivariate analysis of two groups of antibiotics with baseline variables are given in (Table 5).

Table 5. Comparison of antibiotics with factors association in treatment failures of childhood non-severe pneumonia cases at PHCCs, Sana'a governorate, 2021.

Factors	Amoxicillin (N=38)			Co-trimoxazole (N=13)		
	no. (%)	OD (CI)	P value	no. (%)	OD CI	P value
Gender						
Male	23 (28%)	1.14	0.879	8 (10%)	0.84	1.000
Female	15 (32)	(0.53-2.44)		5 (11%)	(0.25-2.75)	
Age group						
Infant (2-11)	19 (31%)	1.14	0.879	5 (9%)	0.73	0.822
Children (12-95)	19 (28%)	(0.53-2.44)		8 (12%)	(0.22-2.37)	
Father education						
illiterate	13 (31%)	1.09	0.989	4 (9%)	0.78	0.930
literate	25 (29%)	(0.49-2.44)		9 (11%)	(0.22-2.69)	
Mother education						
illiterate	19 (24%)	0.52	0.147	3 (4%)	0.16	0.009
literate	19 (38%)	(0.24-1.13)		10 (20%)	(0.04-0.63)	
Father Job						
Has a job	7 (23%)	0.62	0.441	2 (6%)	0.42	0.431
jobless	31 (31%)	(0.24-1.59)		11 (12%)	(0.08-2.00)	
Pre-infection in the last 6 months						
Yes	26 (39%)	2.70	0.022	6 (11%)	1.08	1.000
No	12 (19%)	(1.21-6.03)		7 (10%)	(0.34-3.41)	
Antibiotic used in the last 6 months						
Yes	21 (41%)	2.47	0.034	6 (11%)	1.20	0.984
No	17 (22%)	(1.13-5.36)		7 (10%)	(0.38-3.81)	
Type of antibiotic used in the last 6 months						
Vial	16 (57%)	4.80	0.023	5 (41%)	28.57	0.001
Syrup/Drop	5 (22%)	(1.38-16.61)		1 (2%)	(2.9-282.7)	
Where was the previous treatment						
Home / pharmacy	4 (18%)	0.22	0.025	1 (4%)	0.17	0.194
at HF's	22 (50%)	(0.06-0.76)		5 (18%)	(0.01-1.56)	
Malnutrition diagnosed by (History)						
Yes	9 (56%)	3.67	0.028	1 (14%)	1.48	1.000
No	29 (26%)	(1.25-10.77)		12 (10%)	(0.16-13.4)	
Otitis Media						

Otitis Media

Yes	10 (42%)	1.93	0.239	1 (25%)	3.05	0.884
No	28 (27%)	(0.77-4.86)		12 (10%)	(0.29-31.7)	
Anemia						
Yes	5 (42%)	1.79	0.533	1 (6%)	0.54	0.894
No	33 (29%)	(0.53-6.06)		12 (11%)	(0.06-4.49)	
First action since the illness appear						
referred latterly	9 (18%)	0.37	0.034	4 (10%)	0.91	1.000
referred directly	29 (37%)	(0.15-0.87)		9 (11%)	(0.26-3.15)	
Other medication (except antibiotic) used prior to 48 hours						
Yes	8 (20%)	0.48	0.158	3 (6%)	0.45	0.381
No	30 (34%)	(0.19-1.17)		10 (13%)	(0.11-1.73)	
Z score (weight/age)						
Underweight	13 (25%)	0.68	0.445	1 (2%)	0.11	0.032
Normal	25 (33%)	(0.30-1.49)		12 (16%)	(0.01-0.89)	
Deferential blood count CBC						
Abnormal	36 (39)	10.42	0.000	12 (19%)	14.58	0.003
Normal	2 (6%)	(2.35-46.10)		1 (2%)	(1.83-116)	
Fever (Measured)						
Temp. (> 37.2)	30 (48%)	6.47	0.000	10 (16%)	3.77	0.078
Normal	8 (12%)	(2.66-15.77)		3 (5%)	(0.98-14.4)	

The multivariate analysis was done to estimate the treatment effect after considering the imbalance in certain baseline variables. Only pre-infection in the last 6 months, malnutrition, abnormal CBC, and high-grade fever were found to be associated with clinical failure of amoxicillin even after adjustment ($p > 0.05$) while abnormal CBC and literate mothers associated with clinical failure of co-trimoxazole ($p > 0.05$) (Table 6).

Table 6. Multivariate analysis with factors association in treatment failures of childhood non-severe pneumonia cases at PHCCs, Sana'a governorate, 2021.

Factors	Amoxicillin (N=38)			Co-trimoxazole (N=13)		
	no. (%)	OD (CI)	P value	no. (%)	OD CI	P value
Pre-infection in the last 6 months						
Yes	26 (39%)	2.84	0.028	6 (11%)	1.76	0.430
No	12 (19%)	(1.11-7.23)		7 (10%)	(0.42-7.29)	
Malnutrition diagnosed by (History)						
Yes	9 (56%)	3.87	0.036	1 (14%)	2.25	0.561
No	29 (26%)	(1.08-13.77)		12 (10%)	(0.14-35.01)	
Deferential blood count CBC						
Abnormal	36 (39%)	5.91	0.024	12 (19%)	18.41	0.006
Normal	2 (6%)	(1.25-27.83)		1 (2%)	(2.22-152)	
Fever (Measured)						
Temp. (> 37.2)	30 (48%)	5.74	0.000	10 (16%)	2.53	0.220
Normal	8 (12%)	(2.16-15.25)		3 (5%)	(0.57-11.22)	
Mother education						
illiterate	19 (24%)	0.98	0.978	3 (4%)	0.12	0.004
literate	19 (38%)	(0.38-2.54)		10 (20%)	(0.03-0.52)	

There were no deaths and only 3 cases were hospitalization from amoxicillin arm, there were no serious adverse drug reactions in the amoxycillin or co-trimoxazole arm, four cases on co-trimoxazole drop out during follow up while one on amoxicillin.

4. Discussion

Globally, most deaths due to childhood pneumonia occur at the community level (1) and increasing concern over bacterial resistance to amoxicillin, which is recommended by WHO and IMCI strategy as a first-line drug for treating non-severe pneumonia, led to the suggestion that this might not be optimal therapy. (3) However, changing to alternative antimicrobial agents which is the second line drug, such as co-trimoxazole, is more effective. (4)

During the period of study, almost 53% of the cases were infants below the age of one years, and this is in concordance with other trail conduct in India that have shown maximum no. of cases in the age group below one years (9).

Male preponderance was noticed in our study with male: female ratio being 1.7:1. This is like the findings of other studies (8,9,10). The higher incidence among males might be due to their increase exposure to outdoor activities which make them in a high risk to be sick with pneumonia.

Regarding clinical features, cough, fast breathing, and fever are the dominant symptoms in addition to runny nose; all of these are the most common symptoms reported throughout the literature on non-severe pneumonia and agreed with our findings. (8,9,10)

All cases were included in the study based on IMCI classification of clinical criteria of non-severe pneumonia. As tachypnea is the earliest sign of pneumonia before the laboratory evidence of pneumonia occur, is the best method with combination of high sensitivity and specificity to detect pneumonia in children below 5 years of age. (14)

However, in all cases complete blood counts (Hb, T.WBC, Neutrophil were carried out before the treatment and the abnormal cases were repeated after treatment. Our finding shows higher in abnormal findings of CBC (61%) compared to a trail conducted in India (18%). (9)

Our results shows that the clinical efficacy of the amoxicillin is a significantly higher than cotrimoxazole when given in daily basis for five days to treat children with non-severe pneumonia and this is in contrast to study conducted in India (9) but in Pakistan, there was no difference in effectiveness of treating children with non-severe pneumonia with oral co-trimoxazole for 5 days or oral amoxycillin for 3 days. (10)

Relatively high failure rate with amoxicillin in our study might be due to number of factors like the extensive use of newer generations of antibiotics, inappropriate prescribing of antibiotics and use of antibiotics without medical prescription in addition to the availability of those drugs over the count all this lead to use it without return to doctors. (15)

The cure rate among children of intervention group (amoxicillin) was 70% and in control group (co trimoxazole) 90%. Higher cure rate with co-trimoxazole in our study is in contrast to the study conducted in India which was the cure rate of amoxicillin (91%) cases and in co trimoxazole (60%). (9)

The Limitation was the difficulty of the road and the distance of the targeted health facilities from the central laboratory which led to delay to receive the NPS.

5. Conclusions and recommendation

The frequency of treatment failure was higher in Amoxicillin group than in the Co-trimoxazole group among children under 5 years with non-severe pneumonia. The pre-infection in the last 6 months, malnutrition, abnormal CBC, and high-grade fever were the most important associated factors to the failure of treatment of amoxicillin in our study.

Recommendations:

- Oral co-trimoxazole should be used instead of amoxicillin for the treatment of non-severe pneumonia in the IMCI strategy in Yemen.
- Update IMCI strategy is essential in the development of treatment management that are based on clinical outcomes.
- Increase the awareness activities and sessions about antimicrobial resistance.
- Further study to determine the suitable antibiotics instead of amoxicillin as first line for non-severe pneumonia.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.”.

Data Availability Statement: data is unavailable due to privacy or ethical restrictions.

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Appendix A





Sample Randomization (N = 250) and flow chart for the data collection

1. Al-Wagash District Hospital, Bani Matar District

Table 1. Sample Randomization for Al-Wagash DH (1 – 125) N = 88.

Intervention Arm (N = 44)					Control Arm (N = 44)				
2	31	56	78	100	3	33	58	79	103
4	34	59	81	102	6	36	61	82	104
9	37	62	83	106	11	38	63	84	107
12	39	64	85	108	13	41	65	87	110
14	42	66	88	111	16	44	67	89	113
18	45	68	90	115	19	46	69	91	116
21	48	71	92	118	23	49	73	93	120
25	51	74	94	122	27	52	75	96	124
28	53	76	97		29	55	77	99	

Week no.	Status	Sat.	Sun.	Mon.	Tue.	Wed.	Thu.	Fri.
1st week (28/08-03/09)	New cases	2 3 4	6 9 11	12 13 14	16 18 19	21 23 25	27 28 29	Off
	Follow up	-	-	-	-	2 3 4	6 9 11	Off
2nd week (04/09-10/09)	New cases	31 33 34	36 37 38	39 41 42	44 45 46	48 49 51	52 53 55	Off
	Follow up	12 13 14 16 18 19	21 23 25	27 28 29	-	31 33 34	36 37 38	Off
3rd week (11/09-17/09)	New cases	56 58 59	61 62 63	64 65 66	67 68 69	71 73 74	75 76 77	Off
	Follow up	39 41 42 44 45 46	48 49 51	52 53 55	-	56 58 59	61 62 63	Off
4th week (18/09-24/09)	New cases	78 79 81	82 83 84	85 87 88	89 90 91	92 93 94	96 97 99	Off
	Follow up	64 65 66 67 68 69	71 73 74	75 76 77	-	78 79 81	82 83 84	Off
5th week (25/09-01/10)	New cases	100 103 102	104 106 107	108 110 111	113 115 116	118 120 122	124	Off
	Follow up	85 87 88 89 90 91	92 93 94	96 97 99	-	100 103 102	104 106 107	Off
6th week (02/10-08/10)	New cases	-	-	-	-	-	-	Off
	Follow up	108 110 111 113 115 116	118 120 122	124	-	-	-	Off

 New cases
  Follow up
  Amoxicillin
  Co-trimoxazole

2. Qa'a Al-Reqah Health Center, Hamdan district

Table 3. Sample Randomization for Qa'a Al-Reqah HC (200 – 310) N = 68.

Intervention Arm (N = 34)					Control Arm (N = 34)				
201	224	248	269	291	202	225	249	270	293
203	227	251	272	294	204	229	253	273	296
206	231	254	275	297	208	233	256	277	299
210	235	257	278	300	211	236	259	279	302
213	238	260	281	303	214	239	262	283	306
216	241	264	285	307	218	242	265	287	309
220	244	266	289		222	246	268	290	

Table 4: Flow chart for the data collection for Qa'a Al-Reqah HC (N = 68)								
Week no.	Status	Sat.	Sun.	Mon.	Tue.	Wed.	Thu.	Fri.
1 st week (28/08-03/09)	New cases	201 202	203 204	206 208	210 211	213 214	216 218	Off
	Follow up	-	-	-	-	188 189	190 192	Off
2 nd week (04/09-10/09)	New cases	220 222	224 225	227 229	231 233	235 236	238 239	Off
	Follow up	206 208 210 211	213 214	216 218	-	220 222	224 225	Off
3 rd week (11/09-17/09)	New cases	241 242	244 246	248 249	251 253	254 256	257 259	Off
	Follow up	227 229 231 233	235 236	238 239	-	241 242	244 246	Off
4 th week (18/09-24/10)	New cases	260 262	264 265	266 268	269 270	272 273	275 277	Off
	Follow up	248 249 251 253	254 256	257 259	-	260 262	264 265	Off
5 th week (25/09-01/10)	New cases	278 279	281 283	285 287	289 290	291 293	294 296	Off
	Follow up	266 268 269 270	272 273	275 277	-	278 279	281 283	Off
6 th week (02/10-08/10)	New cases	297 299	300 302	303 306	307 309	-	-	
	Follow up	266 268 269 270	272 273	275 277		278 279	281 283	
7 th week (09/10-15/10)	New cases	-	-	-	-	-	-	Off
	Follow up	285 287 289 290	-	-	-	-	-	Off

New cases

Follow up

Amoxicillin

Co-trimoxazole

3. Bahran Health Center, Sanhan Wa Bni Bahlol District

Table 5. Sample Randomization for Bahran HC (310 – 370) N = 38.

Intervention Arm (N = 19)					Control Arm (N = 19)				
312	325	339	350	362	314	328	340	351	363
317	330	342	353	365	318	332	344	355	367
320	334	345	356	369	321	335	347	358	370
322	337	348	359		323	338	349	360	

Table 6: Flow chart for the data collection for Bahran HC (N = 38)								
Week no.	Status	Sat.	Sun.	Mon.	Tue.	Wed.	Thu.	Fri.
1 st week (28/08-03/09)	New cases	312	314	317	318	320	321	
	Follow up	-	-	-	-	312	314	
2 nd week (04/09-10/09)	New cases	322	323	325	328	330	332	
	Follow up	317 318	320	321	-	322	323	
3 rd week (11/09-17/09)	New cases	334	335	337	338	339	340	
	Follow up	325 328	330	332	-	334	335	
4 th week (18/09-24/09)	New cases	342	344	345	347	348	349	
	Follow up	337 338	339	340	-	342	344	
5 th week (25/09-01/10)	New cases	350	351	353	355	356	358	
	Follow up	345 347	348	349	-	350	351	
6 th week (02/10-08/10)	New cases	359	360	362	363	365	367	
	Follow up	353 355	356	358	-	359	360	
7 th week (09/10-15/10)	New cases	369	370	-	-	-	-	
	Follow up	362 363	365	367	-	369	370	

New cases Follow up Amoxicillin Co-trimoxazole





4. Al-Naqeel Health Unit, Blad Al-Rous District

Table 7. Sample Randomization for Al-Naqeel HU (400 – 450) N = 30.

Intervention arm (N = 15)					Control arm (N = 15)				
400	411	419	429	439	402	413	421	430	441
405	415	422	432	442	407	416	423	434	444
408	417	425	435	445	409	418	427	437	447

Table 8: Flow chart for the data collection for Al-Naqeel HU (N = 30)

Week no.	Status	Sat.	Sun.	Mon.	Tue.	Wed.	Thu.	Fri.
1 st week (28/08-03/09)	New cases	400	402	405	407	408	409	Off
	Follow up	-	-	-	-	400	402	Off
2 nd week (04/09-10/09)	New cases	411	413	415	416	417	418	Off
	Follow up	405 407	408	409	-	411	413	Off
3 rd week (11/09-17/09)	New cases	419	421	422	423	425	427	Off
	Follow up	415 416	417	418	-	419	421	Off
4 th week (18/09-24/09)	New cases	429	430	432	434	435	437	Off
	Follow up	422 423	425	427	-	429	430	Off
5 th week (25/09-01/10)	New cases	439	441	442	444	445	447	Off
	Follow up	432 434	435	437	-	439	441	Off
6 th week (02/10-08/10)	New cases	-	-	-	-	-	-	Off
	Follow up	442 444	445	447	-	-	-	Off

 New cases
  Follow up
  Amoxicillin
  Co-trimoxazole





5. Al-Hazm Health Center, Arhab District

Table 9. Sample Randomization for Al-Hazm HC (460 – 500) N = 26.

Intervention arm (N = 13)					Control arm (N = 13)				
462	474	482	490	499	463	475	483	492	500
464	477	484	494		466	479	485	495	
470	480	487	497		472	481	488	498	

Table 10: Flow chart for the data collection for Al-Hazm HC (N = 26)

Week no.	Status	Sat.	Sun.	Mon.	Tue.	Wed.	Thu.	Fri.
1 st week (28/08-03/09)	New cases	462	463	464	466	470	472	Off
	Follow up	-	-	-	-	462	463	Off
2 nd week (04/09-10/09)	New cases	474	475	477	479	480	481	Off
	Follow up	464 466	470	472	-	474	475	Off
3 rd week (11/09-17/09)	New cases	482	483	484	485	487	488	Off
	Follow up	477 479	480	481	-	482	483	Off
4 th week (18/09-24/09)	New cases	490	492	494	495	497	498	Off
	Follow up	484 485	487	488	-	490	492	Off
5 th week (25/09-01/10)	New cases	499	500	-	-	-	-	Off
	Follow up	494 495	497	498	-	499	500	Off

 New cases
  Follow up
  Amoxicillin
  Co-trimoxazole

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