

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid





Under treatment of pneumonia among children under 5 years of age in a malaria-endemic area: population-based surveillance study conducted in Manhica district- rural, Mozambique



Sozinho Acácio ^{a,b}, Jennifer R. Verani ^c, Miguel Lanaspa ^{a,d}, Tarayn A. Fairlie ^c, Tacilta Nhampossa ^{a,b}, Maria Ruperez ^{a,d}, Pedro Aide ^{a,b}, Brian D. Plikaytis ^c, Charfudin Sacoor ^a, Eusebio Macete ^a, Pedro Alonso ^{a,d}, Betuel Sigaúque ^{a,b,*}

ARTICLE INFO

Article history: Received 13 January 2015 Received in revised form 27 April 2015 Accepted 4 May 2015

Corresponding Editor: Dr. Eskild Petersen, Aarhus, Denmark

Keywords: Pneumonia Mozambique Guideline Adherence

SUMMARY

Background: Integrated Management of Childhood Illness (IMCI) guidelines were developed to decrease morbidity and mortality, yet implementation varies across settings. Factors associated with poor adherence are not well understood.

Methods: We used data from Manhiça District Hospital outpatient department and five peripheral health centers to examine pneumonia management for children <5 years old from January 2008 to June 2011. Episodes of IMCI-defined pneumonia (cough or difficult breathing plus tachypnea), severe pneumonia (pneumonia plus chest wall in-drawing), and/or clinician-diagnosed pneumonia (based on discharge diagnosis) were included.

Results: Among severe pneumonia episodes, 96.2% (2,918/3,032) attended in the outpatient department and 70.0% (291/416) attended in health centers were appropriately referred to the emergency department. Age<1 year, malnutrition and various physical exam findings were associated with referral. For non-severe pneumonia episodes, antibiotics were prescribed in 45.7% (16,094/35,224). Factors associated with antibiotic prescription included age <1 year, abnormal auscultatory findings, and clinical diagnosis of pneumonia; diagnosis of malaria or gastroenteritis and pallor were negatively associated with antibiotic prescription.

Conclusion: Adherence to recommended management of severe pneumonia was high in a hospital outpatient department, but suboptimal in health centers. Antibiotics were prescribed in fewer than half of non-severe pneumonia episodes, and diagnosis of malaria was the strongest risk factor for incorrect management.

© 2015 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Background

Pneumonia causes nearly one million deaths per year in children less than 5 years of age and is the most common infectious cause of death in that age group, causing more deaths per year than malaria, HIV, and measles combined; most deaths occur in low to middle income countries. Learly diagnosis and treatment of pneumonia can prevent substantial morbidity and mortality, but are often challenging in resource-poor settings. The Integrated Management of Childhood Illness (IMCI) is a strategy developed by

^a Centro de Investigação em Saúde de Manhica - Road 12. Manhica, Mozambique

^b Instituto Nacional de Saúde, Ministério de Saúde – Av. Eduardo Mondlane 1008, Maputo, Mozambique

^c Centers for Disease Control and Prevention - 1600 Clifton Road, Atlanta, GA 30329 USA

d Centre de Recerca en Salut Internacional de Barcelona, Hospital Clínic, Universitat de Barcelona – Rosselló 132, 08036, Barcelona, Spain

^{*} Corresponding author. Centro de Investigação em Saúde da Manhiça, Road 12. P.O. Box 1929; Tel.:/Fax: +25821810002 Manhiça Maputo, Mozambique. E-mail addresses: sozinho.acacio@manhica.net (S. Acácio), jverani@cdc.gov (J.R. Verani), miguel.lanaspa@cresib.cat (M. Lanaspa), t.fairlie@gmail.com (T.A. Fairlie), taciltanha@yahoo.com (T. Nhampossa), maria.ruperez@cresib.cat (M. Ruperez), Pedro.Aide@manhica.net (P. Aide), bdplikaytis@gmail.com (B.D. Plikaytis), Charfudin.Sacoor@manhica.net (C. Sacoor), Eusebio.Macete@manhica.net (E. Macete), pedro.alonso@isglobal.org (P. Alonso),

the World Health Organization (WHO) and United Nations Children's Fund to reduce child morbidity and mortality.⁴ IMCI provides standardized, integrated, evidence-based guidelines for the management of the most common causes of child death, including pneumonia. These guidelines were developed for the use of health workers at first-level health facilities in high-infant mortality settings, and rely on detection of simple clinical signs.⁴ The IMCI guidelines have undergone several revisions, most recently in 2012.⁵

Implementation of IMCI has been shown to reduce pediatric morbidity and improve the quality of health services provided to ill children.³ However, studies have described sub-optimal adherence to the guidelines in a variety of settings.^{6–10} Within the context of on-going pneumonia surveillance we assessed the management of pneumonia in children less than 5 years of age in Manhiça, Mozambique, a low-income country with high mortality rate for children less than 5 years and a high burden of illness and death due to pneumonia and malaria.^{11,12} Our objectives were to assess adherence to locally-adapted IMCI guidelines for management of severe and non severe pneumonia in children less than 5 years of age at outpatient facilities and to describe factors associated with correct pneumonia case management.

2. Methods

2.1. Study setting

The study was carried out in Manhica District, a rural area in southern Mozambique. A Demographic Surveillance System (DSS) has been operating in the district since 1996, covering an area of approximately 500 km², with 84,000 persons under surveillance. Demographic surveillance is conducted via household interview; each household is interviewed every 6 months. Persons residing in the DSS area are assigned a unique identifier number. Of those residing in the DSS area, 17.3% are less than five years of age. 13 In 2010, the prevalence of HIV among pregnant women attending the antenatal centers in the health system was high (29.4%) and the vertical transmission rate in the first month of life of children born from mothers infected by HIV is 9%;14 the prevalence of HIV in Manhiça among adults over 18 years is among the highest in the world with prevalence rates reaching 39.9% [95% confidence interval (CI) 35.9 to 43.8] peaking to 44% in individual age 38 to 47 years (95% CI 38.4 to 51.2). 15

Pediatric morbidity surveillance is carried out in health facilities within the DSS area. Data are routinely gathered using standardized forms for all pediatric admissions to Manhiça District Hospital (MDH), as well as all outpatient pediatric visits to five peripheral health centers and the MDH outpatient department. MDH is the referral hospital for the district and has physician staffing as well as radiology and laboratory facilities. The peripheral health centers and the MDH outpatient department are staffed by health agents (health workers with 2 years of formal training) and offer basic laboratory services, including assessment o2\f hematocrit and microscopy to diagnose malaria. For all clinical encounters, discharge diagnoses are assigned by the treating clinician based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD). Transportation is available to carry severely ill patients from the peripheral health centers to MDH free of charge; the travel time ranges from approximately 30 minutes to over one hour. Patients transferred from peripheral health centers to MDH are evaluated in the MDH outpatient department on arrival. Severely ill children attended initially at the MDH outpatient department are transferred to the hospital emergency room, which is located in a building adjacent to the outpatient department.

2.2. Data sources and definitions

We used data from outpatient visits for pneumonia among children <5 years from January 2008 to June 2011, restricted to children residing in the DSS area so that a unique identifier could be used to detect multiple visits or episodes of pneumonia.

Local IMCI guidelines in Manhica district classify children with cough or difficult breathing plus tachypnea (respiratory rate >60 if age <2 months, >50 if age 2 months to <1 year, and >40 if >1year) as having pneumonia, and those with pneumonia plus chest wall in-drawing (intercostal retractions) as having severe pneumonia. The recommended management of non-severe pneumonia is oral penicillin or amoxicillin; if neither is available clinicians may treat non-severe pneumonia with chloramphenicol, erythromycin, or cotrimoxazole. Antibiotics are prescribed by clinicians and can be purchased at pharmacies located in the health centers for approximately USD \$0.03 or at the MDH pharmacy for USD \$0.16 per course of antibiotics. The recommended management for children with severe pneumonia is referral to MDH, where they can be evaluated and if needed admitted to receive intravenous antibiotic therapy (Ampicillin and Gentamicin <2 months of age Penicillin G for children >= 2 months as first choice and Ceftriaxone as second choice in cases of failure of Ampicillin and Penicillin G and Gentamicina). According to the local guidelines, no antibiotics are administered to patients with severe pneumonia prior to transfer from the peripheral health centers to MDH, where blood culture and chest X-ray are performed. Hospital care is free of charge. The recommended management for children <2 months of age with pneumonia is the same as that for all children <5 years with pneumonia.

Visits with a primary or secondary discharge diagnosis of pneumonia (ICD-10 codes J13-18, J22), and/or in which the child had criteria for pneumonia (e.g. cough, difficulty breathing, tachypnea) were included in the analysis. Episodes in which the patient had criteria for pneumonia but no diagnostic code for pneumonia were excluded if there was a diagnostic code for asthma, since we presumed the respiratory signs were due to asthma. Visits for pneumonia occurring within 2 weeks of a prior visit for pneumonia were considered part of a single pneumonia episode; we examined management during the first outpatient visit for each pneumonia episode.

Pneumonia episodes were classified as non-severe or severe based on information documented in the medical record at the initial visit for each episode. Clinician-diagnosed pneumonia (based on discharge diagnosis only, without meeting criteria for pneumonia) could not be classified with regards to severity. For episodes classified as severe pneumonia, we examined whether the patient was referred from either the peripheral health centers to the MDH outpatient department or from the MDH outpatient department to the emergency room at MDH. For episodes classified as non-severe pneumonia, we assessed whether the patient was prescribed antibiotics based on documentation of one or more of the following oral antibiotics in the medical records: penicillin, amoxicillin, erythromycin, chloramphenicol, or cotrimoxazole. Referral is not recommended for non-severe pneumonia; we excluded episodes of non-severe pneumonia in which the initial visit resulted in referral, since those children were presumed to have some other type of severe disease necessitating transfer (i.e., anemia, suspected bacterial meningitis, severe malaria, dehydration, etc.).

2.3. Data management and Statistical Analysis

Standardized visit forms are routinely double entered in FoxPro (v.2.6 Microsoft Corporation Redmond Washington) at CISM and discrepancies in data were resolved by referring to the original

form. Analyses were conducted using SAS, version 9.3. We described the frequency of adherence to recommended pneumonia management for severe and non-severe pneumonia at the initial visit for each episode of pneumonia, and used logistic regression to determine factors associated with correct management. Variables examined included demographics, symptoms, signs, physical exam findings, and diagnostic ICD-10 code. Weightfor-age z scores were calculated using WHO growth standards and a SAS macro available from WHO. 16 Variables with a p<0.2 on univariate analysis were considered for possible inclusion in multivariable models. We assessed for collinearity and two-way interaction for all variables in the final models. We constructed separate models for the management of severe pneumonia at the peripheral health centers and at the MDH outpatient department, since transfer from the peripheral health centers to MDH is more complicated than transfer from the MDH outpatient department to the emergency room in MDH.

3. Results

We identified 64,783 visits for pneumonia from January 2008 to June 2011, representing 60,919 episodes of pneumonia among 24,497 children < 5 years (Figure). The mean number of episodes per child was 2.5, with an interquartile range of 1 to 3 episodes. The median age at first visit for all episodes was 15.8 months, with an interquartile range of 8.3 to 26.2 months. Among the 60,919 episodes of pneumonia, 3,448 (5.7%) were classified as severe pneumonia, 42,331 (69.5%) as non-severe pneumonia, and for 15,140 (24.9%) it was not possible to classify based on available information in the medical record. Most episodes of severe pneumonia (89.0%) had both clinical criteria and a final diagnostic code for pneumonia. In contrast, for non-severe pneumonia, most

episodes (80.1%) had only clinical criteria and no diagnostic code for pneumonia.

Of 416 episodes of severe pneumonia attended initially in peripheral health centers, 291 (70.0%) were appropriately referred to the MDH outpatient department, 121 (29.1%) were not referred, and in 4 (1.0%) episodes the child was taken home from the clinic by a parent/guardian before a management decision was made. On multivariable analysis, factors significantly associated with referral included age <1 year (adjusted odds ratio [aOR] 1.69, 95% confidence interval [CI] 1.00 to 2.83), temperature >38 °C (aOR 2.39, 95%CI 1.25 to 4.60), weight-for-age z-score <-2 (aOR 2.17, 95%CI 1.18 to 4.02), vomiting (aOR 2.02, 95%CI 1.02 to 4.01), crepitations or rales (aOR 1.93, 95%CI 1.11 to 3.35), splenomegaly (aOR 22.69, 95%CI 2.87 to 179.35), and wheeze or rhonci (aOR 3.19, 95%CI 1.89 to 5.41) (Table 1). Among the 121 episodes of severe pneumonia not referred, 106 (87.6%) had a discharge diagnosis of pneumonia; of those, antibiotics were prescribed in 79 (74.5%). Among the 291 episodes of severe pneumonia referred from peripheral health centers to MDH, 157 (54.0%) resulted in the child receiving care at MDH that same day or the following day. The only factor significantly negatively associated with arrival to MDH among referred severe pneumonia cases was having been initially attended in the health center furthest from Manhica (Ilha Josina); 55.2% (74/134) of cases that did not arrive were seen at that clinic, compared with 8.92% (14/157) of cases that did arrive (OR 0.06, 95% CI 0.03 to 0.12, with the health center closest to the hospital being the reference).

Among 3,032 episodes of severe pneumonia attended initially at the MDH outpatient department, 2,918 (96.2%) were referred to the MDH emergency room, 107 (3.5%) were not referred, and in 7 (0.2%) episodes either the child was taken home from the clinic by a parent/guardian before a management decision was made or data on disposition were not available. For children with severe

Table 1
Factors associated with referral during initial visit for an episode of severe pneumonia among children <5 years from peripheral health centers (n=412), January 2008-June 2011

Characteristic	Referred n=291	Not referred n=121	Univariate Odds Ratio (95% CI)	Multivariable Odds Ratio (95% CI)	
	n (%)	n (%)			
Demographics					
Age <1 year	165 (56.7)	58 (47.9)	1.42 (0.91, 2.23)	1.69 (1.00, 2.83)	
Male sex	170 (58.4)	76 (62.8)	0.83 (0.52, 1.31)	=	
Vital signs					
Temperature >38 °C	69 (23.7)	17 (14.3)	1.86 (1.02, 3.56)	2.39 (1.25, 4.60)	
Weight-for-age z score <-2	77 (27.4)	23 (19.0)	1.61 (0.93, 2.85)	2.17 (1.18, 4.02)	
Reported symptoms					
Fever	250 (86.2)	109 (90.1)	0.69 (0.32, 1.40)	=	
Cough	286 (98.3)	117 (96.7)	1.96 (0.38, 9.24)	=	
Difficult breathing	216 (74.2)	81 (66.9)	1.42 (0.90, 2.31)	1.69 (0.96, 2.99)	
Diarrhea	52 (17.9)	10 (8.3)	2.42 (1.16, 5.52)	=	
Vomiting	62 (21.3)	15 (12.4)	1.91 (1.02, 3.79)	2.02 (1.02, 4.01)	
Convulsions	5 (1.7)	1 (0.8)	2.11 (0.23, 100.39)	-	
Physical findings					
Crepitations or rales	220 (75.6)	75 (62.0)	1.90 (1.17, 3.06)	1.93 (1.11, 3.35)	
Splenomegaly	35 (12.0)	1 (0.8)	16.41(2.68, 671.74)	22.69 (2.87, 179.35)	
Pallor	39 (13.4)	6 (5.0)	2.97 (1.20, 8.80)	=	
Nasal flaring	177 (60.8)	68 (56.2)	1.21 (0.77, 1.90)	=	
Wheeze or rhonchi	171 (58.8)	43 (35.5)	2.58 (1.63, 4.12)	3.19 (1.89, 5.41)	
Ear discharge	17 (5.8)	12 (9.9)	0.56 (0.24,1.34)	=	
Hepatomegaly	2 (0.7)	0 (0)	=	-	
Skin tenting	9 (3.1)	0 (0)	-	-	
Lethargy	25 (8.6)	1 (0.8)	11.28 (1.80, 466.85)	=	
Laboratory findings					
Parasitemia	66 (26.6)	18 (16.7)	1.81 (0.99, 3.44)	=	
Discharge diagnoses					
Gastroenteritis	38 (13.1)	11 (9.1)	1.50 (0.72, 3.38)	=	
Malaria	63 (21.6)	19 (15.7)	1.48 (0.82, 2.77)	-	
Pneumonia	264 (90.7)	106 (87.6)	1.38 (0.66, 2.82)	=	

pneumonia initially seen in the MDH outpatient department, factors associated with referral included age <1 year (aOR 1.64, 95%CI 1.06 to 2.53), weight-for-age z-score <-2 (aOR 2.76, 95%CI 1.56 to 4.88), difficult breathing (aOR 8.01, 95%CI 5.14 to 12.47), diarrhea (aOR 2.23, 95%CI 1.00 to 4.95), crepitations or rales (aOR 2.44, 95%CI 1.60 to 3.71), and pallor (aOR 4.67, 95%CI 1.11 to 19.71)(Table 2). Among the 2,918 episodes that resulted in referral, only 24 (0.8%) failed to arrive at the MDH emergency room.

A total of 35.224 episodes of non-severe pneumonia were seen and managed at an outpatient facility (i.e. not referred on the initial visit) (Figure 1). Among those, 33 (0.09%) resulted in the child leaving before clinical management was determined. Among the remaining 35,191 episodes, 16,094 (45.7%) were correctly managed with an antibiotic prescription, and 19,097 (54.3%) were not (Table 3). For episodes in which an antibiotic was prescribed, amoxicillin was most common (n=11,308; 70.3%), followed by penicillin (n=2,488; 15.5%) and cotrimoxazole (n=1,788; 11.1%). Factors positively associated with antibiotic treatment included age <1 year (OR 1.60, 95%CI 1.52 to 1.69), crepitations or rales (OR 1.31, 95%CI 1.16 to 1.47), wheeze or rhonci (OR 2.86, 95%CI 2.69 to 3.05), ear discharge (OR 3.22, 95%CI 2.82 to 3.68), lethargy (OR 5.12, 95%CI 2.39 to 10.95), and clinical diagnosis of pneumonia (OR 2.72, 95%CI 2.44 to 3.04). A diagnosis of malaria (OR 0.20, 95%CI 0.19 to 0.22) or gastroenteritis (OR 0.38, 95%CI 0.35 to 0.42) and pallor noted on exam (OR 0.62, 95%CI 0.54 to 0.70) were significantly more common among episodes of non-severe pneumonia in which antibiotics were not prescribed.

4. Discussion

In rural Mozambique, a resource-limited area with a high burden of pneumonia and other infectious diseases, we found good adherence to recommended management for severe pneumonia in the outpatient department located next to the hospital, with >95% of episodes referred and nearly all of those resulting in a visit to the MDH emergency room. Management of severe pneumonia at peripheral health centers was suboptimal; only 70% were referred and nearly half of those referred failed to arrive at the hospital for care – a finding that highlights important challenges to appropriate pneumonia case management beyond the practices of health care workers. Implementation of the recommended management for non-severe pneumonia was also lacking, with fewer than half receiving antibiotics. Failure to recognize pneumonia criteria, particularly when signs or symptoms consistent with other childhood illnesses are present, appears to negatively impact adherence to the recommended management of non-severe pneumonia.

The referral rate we observed for children with severe pneumonia initially seen at peripheral health centers is consistent with findings of several other evaluations of IMCI implementation, in which only 36 to 70% of severely ill children seen in first-level health care facilities were referred to hospitals. 6,7,17 Low arrival rate at the referral facility for children with severe disease has been attributed to a combination of geographic and financial barriers.^{6,18} We identified distance from the hospital as the primary risk factor for children with severe pneumonia failing to arrive at the hospital following referral from a peripheral health center, despite the availability of free transportation for patients in need of hospital-level care - a service that is very rarely available in lowincome settings. The barriers to optimal care of children with severe pneumonia are multi-faceted, and removal of transportation barriers may not be sufficient to ensure adequate care for a child with severe pneumonia. Studies have found that severe pneumonia without danger signs can be safely and effectively managed at first-level health facilities 18,19 and by health workers at the community level, potentially offering a promising approach to reducing barriers to adequate case management of severe pneumonia. 20,21

Table 2Factors associated with referral during initial visit for an episode of severe pneumonia among children <5 years from MDH outpatient department (n=3,025), January 2008-June 2011

Characteristic	Referred n=2,918	Not referred n=107	Univariate Odds Ratio (95% CI)	Multivariable Odds Ratio (95% CI)	
	n (%)	n (%)			
Demographics					
Age <1 year	1409 (48.3)	34 (31.8)	2.00 (1.31, 3.13)	1.64 (1.06, 2.53)	
Male sex	1597 (54.7)	51 (47.7)	1.33 (0.89, 1.99)	=	
Vital signs					
Temperature >38 °C	965 (33.1)	34 (31.8)	1.06 (0.69, 1.66)	=	
Weight-for-age z score <-2	876 (31.6)	15 (14.2)	2.80 (1.60, 5.23)	2.76 (1.56, 4.88)	
Reported symptoms					
Fever	2586 (88.6)	99 (92.5)	0.63 (0.26, 1.31)	=	
Cough	2825 (96.8)	105 (98.1)	0.58 (0.07, 2.20)	-	
Difficult breathing	2202 (75.5)	29 (27.1)	8.28 (5.29, 13.26)	8.01 (5.14, 12.47)	
Diarrhea	462 (15.8)	7 (6.5)	2.69 (1.25, 6.90)	2.23 (1.00, 4.95)	
Vomiting	606 (20.8)	14 (13.1)	1.74 (0.98, 3.33)	-	
Convulsions	84 (2.9)	0 (0)	-		
Physical findings					
Crepitations or rales	2276 (78.0)	64 (59.8)	2.39 (1.57, 3.60)	2.44 (1.60, 3.71)	
Splenomegaly	275 (9.4)	1 (0.9)	11.03 (1.92, 441.26)	6.86 (0.93, 50.75)	
Pallor	347 (11.9)	3 (2.8)	4.68 (1.54, 23.18)	4.67 (1.11, 19.71)	
Nasal flaring	1647 (56.5)	35 (32.7)	2.67 (1.74, 4.14)	-	
Wheeze or rhonchi	1560 (53.5)	48 (44.9)	1.41 (0.94, 2.13)	=	
Ear discharge	122 (4.2)	2 (1.9)	2.29 (0.61, 19.39)	=	
Hepatomegaly	32 (1.1)	0 (0)	-	=	
Skin tenting	96 (3.3)	0 (0)	-	=	
Lethargy	195 (6.7)	1 (0.9)	7.59 (1.32, 304.15)	=	
Laboratory findings					
Parasitemia	534 (20.8)	25 (25.3)	0.78 (0.48, 1.29)	-	
Discharge diagnoses					
Gastroenteritis	279 (9.6)	5 (4.7)	2.16 (0.88, 6.84)	-	
Malaria	362 (12.4)	23 (21.5)	0.52 (0.32, 0.87)	-	
Pneumonia	2596 (89.0)	90 (84.1)	1.52 (0.84, 2.62)	-	

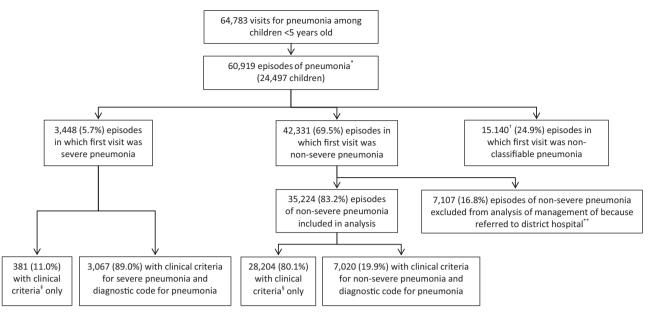


Figure 1. Pneumonia visits, episodes, and the classification of first visits as severe or non-severe pneumonia among children aged <5 years in Manhiça, Mozambique, January 2008 – June 2011

*An episode of pneumonia is defined as a an initial visit for pneumonia plus any subsequent pneumonia visits occurring within a 2 week inter-visit interval † Included 15,135 episodes in which the first visit resulted in a diagnostic code for pneumonia but clinical criteria (cough and/or difficult breathing plus tachypnea) were not documented, and 5 episodes in which the first visit had diagnostic codes and/or clinical criteria for pneumonia however data on lower chest wall indrawing were missing ‡ Defined as having cough and/or difficult breathing and tachypnea, without chest in-drawing, and without a ICD-10 code for pneumonia, and excluding those with an ICD-9 code for asthma

§Defined as having cough and/or difficult breathing, tachypnea, and chest in-drawing, without a ICD-9 code for pneumonia, and excluding those with an ICD-9 code for asthma

**Episodes of non-severe pneumonia in which the initial visit resulted in a referral to Manhiça District Hospital were excluded from the analysis; referral is not recommended for non-severe pneumonia and therefore another severe illness (e.g. meningitis, complicated malaria) likely prompted the referral.

Table 3Factors associated with antibiotic prescription during initial visit for an episode of non-severe pneumonia among children <5 years (n=35,191°), Manhiça district, January 2008-June 2011

Characteristic	Antibiotic prescribed n=16,094	No antibiotic prescribed n=19,097	Univariate Odds Ratio (95% CI)	Multivariable Odds Ratio (95% CI)	
	n (%)	n (%)			
Demographics					
Age <1 year	6578(40.9)	4519(23.7)	2.23 (2.13, 2.34)	1.60 (1.52, 1.69)	
Male sex	8327(51.7)	9695(50.8)	1.04 (1.00, 1.08)	-	
Attended in health center †department	7935(49.3)	10075 (52.8)	0.87 (0.83, 0.91)	-	
Vital signs					
Temperature >38 °C	3428(21.3)	4584 (24.0)	0.86 (0.81, 0.90)	-	
Weight-for-age z score <-2	2189(13.7)	2916 (15.4)	0.87 (0.82, 0.93)	-	
Reported Symptoms					
Fever	12946(80.4)	17027 (89.2)	0.50 (0.47, 0.53)	-	
Cough	16083(99.9)	19078 (99.9)	1.46 (0.66, 3.39)	-	
Difficult breathing	404(2.5)	357 (1.9)	1.35 (1.17, 1.57)	-	
Diarrhea	1304(8.1)	3158 (16.5)	0.44 (0.42, 0.48)	-	
Vomiting	1259(7.8)	2008 (10.5)	0.72 (0.67, 0.78)	-	
Convulsions	11(0.1)	15 (0.1)	0.87 (0.36, 2.03)	-	
Physical findings					
Crepitations or rales	4454 (27.7)	1778 (9.3)	3.73 (3.51, 3.96)	1.31 (1.16, 1.47)	
Splenomegaly	302 (1.9)	812 (4.3)	0.43 (0.38, 0.49)	-	
Pallor	447 (2.8)	1213 (6.4)	0.42 (0.38, 0.47)	0.62 (0.54, 0.70)	
Nasal flaring	88 (0.5)	32 (0.2)	3.28 (2.16, 5.08)	-	
Wheeze or rhonchi	5391 (33.5)	1946 (10.2)	4.44 (4.19, 4.70)	2.86 (2.69, 3.05)	
Ear discharge	839 (5.2)	402 (2.1)	2.56 (2.26, 2.89)	3.22 (2.82, 3.68)	
Hepatomegaly	25 (0.2)	13 (0.1)	2.28 (1.12, 4.86)	-	
Skin tenting	12 (0.1)	29 (0.2)	0.49 (0.23, 0.99)	-	
Lethargy	20 (0.1)	13 (0.1)	1.83 (0.86, 4.00)	5.12 (2.39, 10.95)	
Laboratory findings					
Parasitemia	1447 (11.2)	6901 (40.6)	0.18 (0.17, 0.20)	-	
Discharge diagnoses					
Gastroenteritis	1130 (7.0)	2706 (14.2)	0.46 (0.42, 0.49)	0.38 (0.35, 0.42)	
Malaria	1429 (8.9)	6846 (35.8)	0.17 (0.16, 0.19)	0.20 (0.19, 0.22)	
Pneumonia	5189 (32.2)	1827 (9.6)	4.50 (4.24, 4.77)	2.72 (2.44, 3.04)	

^{*} Excludes episodes of non-severe pneumonia that were referred to the hospital or that resulted in the child leaving before clinical management was determined.

[†] Compared with attended in hospital outpatient department

Adherence to recommended management for non-severe pneumonia in Manhica was worse than that of severe pneumonia. Health workers recoded a diagnosis of pneumonia in only 19.9% of all episodes in which children met criteria for non-severe pneumonia. A study of non-severe pneumonia case management in Benin reported that failure to diagnose pneumonia often preceded a failure to treat adequately.²² In this study, children with non-severe pneumonia were prescribed antibiotics in only 45.7% of episodes, and failure to treat was more common when another diagnosis or signs and symptoms consistent with other illnesses such as malaria or gastroenteritis were present. According to IMCI guidelines, children meeting criteria for multiple illnesses should be treated for the various diseases. 4 Yet a study of the management of severely ill children in Tanzania found that health workers consistently treated the specific diagnosis they assigned, while infrequently recognizing or treating concurrent illnesses.⁶

Distinguishing between pneumonia and malaria in young children is challenging, since many of the presenting clinical signs are the same and diagnostic tools for both diseases have important limitations.²³ A prior study in Manhiça found that among children admitted to MDH with severe pneumonia, 19% had clinical malaria, defined as fever and parasitemia. 11 Another study of children admitted to MDH that met clinical criteria for both severe pneumonia and IMCI-defined malaria (fever or a history of fever in the preceding 24 hours) reported that while true overlap of radiologically-confirmed pneumonia and laboratory-confirmed malaria was relatively uncommon, there were no clinical signs, symptoms, or other variables that reliably distinguished between the two.²⁴ It is possible that in a setting such as Manhica where microscopy is readily available at health facilities, health workers may be better able to distinguish between pneumonia and malaria. Therefore, the highly sensitive although nonspecific IMCI clinical pneumonia definition may not be the most appropriate way to determine which children should receive antibiotics in a setting were reliable malaria diagnosis is possible. However, it is also possible that cases of pneumonia are missed because of clinical overlap with malaria and appropriate treatment is delayed. Better diagnostic tools for pneumonia and malaria that are feasible and affordable in resource-poor settings could help improve case management.

We used pneumonia definitions that were consistent with locally-adapted IMCI guidelines during the study period. The most recent version of IMCI guidelines defines pneumonia as cough or difficulty breathing plus tachypnea or lower chest wall indrawing (with the recommendation that it be treated on an outpatient basis), and severe pneumonia as pneumonia with any general danger sign. Therefore, if Mozambique were to utilize the most recent guidelines, those cases we classified as severe pneumonia (because of chest wall indrawing) would be classified as pneumonia (non-severe) and eligible for outpatient treatment. Revised guidelines would not alter the classification or recommended management for children with cough/difficulty breathing and tachypnea (without indrawing); thus the deficiencies we observed in management of non-severe pneumonia would continue to be of concern even if revised guidelines were adopted.

This study was subject to several limitations. We only examined the management at the initial healthcare visit for each pneumonia episode; our findings do not reflect the care children received at subsequent visits for a single episode of pneumonia. Our analysis was focused on non-severe and severe pneumonia; our findings are not applicable to very severe pneumonia (cough and difficulty breathing plus danger signs). We did not evaluate the quality of the clinical encounters and do not have data on what factors guided health care workers' clinical decision making. Additional clinical information beyond what is noted in the surveillance data, such as HIV status, likely influenced management. We were unable to

determine the socio-economic status of the child or how far from the health post a child resided, both of which may have influenced the care received. We also do not have information on antibiotic dosage or whether the prescriptions were filled and taken completely; such factors can affect outcomes even if pneumonia cases are properly detected, prescribed antibiotics and/or referred. This observational study was also not designed to examine the impact of correct management, so it is unknown whether the observed lapses in recommended management resulted in worse outcomes.

Our evaluation revealed both strengths and weakness in the management of child pneumonia in a rural setting in Mozambique where locally adapted IMCI guidelines are the standard of care and the population benefits from free transportation for severely ill patients from peripheral health centers to the hospital. Our findings highlight the need for carefully follow of established and available guidelines from WHO for child pneumonia management both at health center level and community level as well. Further research is needed to understand the impact of multiple concurrent illnesses on the diagnosis and treatment of pneumonia in order to guide efforts to improve pneumonia case management and reduce pneumonia-related morbidity and mortality.

Source of funding: The study was supported by the GAVI Alliance Global Alliance through the Hib Initiative; Award No. 90022369 and also partially by the CISM core funding provided by the Spanish Agency for the International Cooperation and Development (AECID)

Conflict of interest: none

Acknowledgments

We would like to thank the participants and their parents in this study for allowing collecting data over the study period. The authors thank Sónia Machevo, Abel Nhama, Kizito Gondo and all medical officers and technicians for their special dedication in data collection and clinical management at health centers and referral hospital. The authors also thank other staff from CISM and Manhiça District Hospital for collecting and processing data, and Jorge Uqueio for the coordination of pediatric pneumonia surveillance at MDH.

References

- 1. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015 Jan 31;**385**(9966):430-40.
- Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012 Jun 9;379(9832):2151–61.
- Ahmed HM, Mitchell M, Hedt B. National implementation of Integrated Management of Childhood Illness (IMCI): policy constraints and strategies. Health policy 2010 Jul;96(2):128–33.
- Gove S. Integrated management of childhood illness by outpatient health workers: technical basis and overview. The WHO Working Group on Guidelines for Integrated Management of the Sick Child. *Bull World Health Organ* 1997; 75(Suppl 1):7-24
- WHO. Recommendations for Management of Common Childhood Conditions http://apps.who.int/iris/bitstream/10665/44774/1/9789241502825_eng. pdf?ua=1. Geneva 2012.
- 6. Walter ND, Lyimo T, Skarbinski J, et al. Why first-level health workers fail to follow guidelines for managing severe disease in children in the Coast Region, the United Republic of Tanzania. Bulletin of the World Health Organization 2009 Feb;87(2):99–107.
- Horwood C, Vermaak K, Rollins N, Haskins L, Nkosi P, Qazi S. An evaluation of the quality of IMCI assessments among IMCI trained health workers in South Africa. *PloS one* 2009;4(6):e5937.
- 8. Baiden F, Owusu-Agyei S, Bawah J, et al. An evaluation of the clinical assessments of under-five febrile children presenting to primary health facilities in rural Ghana. *PloS one* 2011;**6**(12):e28944.
- Irimu GW, Gathara D, Zurovac D, et al. Performance of health workers in the management of seriously sick children at a Kenyan tertiary hospital: before and after a training intervention. *PloS one* 2012;7(7):e39964.

- Rowe AK, Rowe SY, Holloway KA, Ivanovska V, Muhe L, Lambrechts T. Does shortening the training on Integrated Management of Childhood Illness guidelines reduce its effectiveness?. A systematic review. Health policy and planning 2012 May; 27(3):179–93.
- Sigauque B, Roca A, Bassat Q, et al. Severe pneumonia in Mozambican young children: clinical and radiological characteristics and risk factors. *Journal of tropical pediatrics* 2009 Dec;55(6):379–87.
- Sacarlal J, Nhacolo AQ, Sigauque B, et al. A 10 year study of the cause of death in children under 15 years in Manhica, Mozambique. BMC public health 2009;9:67.
- Nhacolo AQ, Nhalungo DA, Sacoor CN, Aponte JJ, Thompson R, Alonso P. Levels and trends of demographic indices in southern rural Mozambique: evidence from demographic surveillance in Manhica district. BMC public health 2006;6:291.
- 14. Moraleda C, de Deus N, Serna-Bolea C, et al. Impact of HIV exposure on health outcomes in HIV-negative infants born to HIV-positive mothers in Sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2014 Feb 1;65(2):182–9.
- 15. Gonzalez R, Munguambe K, Aponte J, et al. High HIV. prevalence in a southern semi-rural area of Mozambique: a community-based survey. *HIV Med* 2012 Nov;13(10):581–8.
- World Health Organization. Child growth standards, igrowup_sas macro.; 2011, http://www.who.int/childgrowth/software/en/Accessed July 1, 2013.
- Arifeen SE, Bryce J, Gouws E, et al. Quality of care for under-fives in first-level health facilities in one district of Bangladesh. Bulletin of the World Health Organization 2005 Apr;83(4):260–7.
- Chowdhury EK, El Arifeen S, Rahman M, et al. Care at first-level facilities for children with severe pneumonia in Bangladesh: a cohort study. *Lancet* 2008 Sep 6;372(9641):822–30.

- 19. El Arifeen S, Blum LS, Hoque DM, et al. Integrated Management of Childhood Illness (IMCI) in Bangladesh: early findings from a cluster-randomised study. *Lancet* 2004 Oct 30–Nov 5;**364**(9445):1595–602.
- Bari A, Sadruddin S, Khan A, et al. Community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Haripur district, Pakistan: a cluster randomised trial. *Lancet* 2011 Nov 19;378(9805): 1796–803
- Soofi S, Ahmed S, Fox MP, et al. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial. *Lancet* 2012 Feb 25:379(9817):729-37.
- 22. Osterholt DM, Onikpo F, Lama M, Deming MS, Rowe AK. Improving pneumonia case-management in Benin: a randomized trial of a multi-faceted intervention to support health worker adherence to Integrated Management of Childhood Illness guidelines. *Human resources for health* 2009;7:77.
- World Health Organization. The Overlap in the Clinical Presentation and Treatment of Malaria and Pneumonia in Children: Report of a Meeting; 1992.
- 24. Bassat Q, Machevo S, O'Callaghan-Gordo C, et al. Distinguishing malaria from severe pneumonia among hospitalized children who fulfilled integrated management of childhood illness criteria for both diseases: a hospital-based study in Mozambique. The American journal of tropical medicine and hygiene 2011 Oct; 85(4):626–34.
- WHO Revised WHO classification and treatment of childhood pneumonia at health facilities - EVIDENCE SUMMARIES - http://apps.who.int/iris/bitstream/ 10665/137319/1/9789241507813_eng.pdf?ua=1. 2014.