RESEARCH PAPER

Role of Clinical Criteria and Oxygen Saturation Monitoring in Diagnosis of Childhood Pneumonia in Children Aged 2 to 59 Months

RASHMI RANJAN DAS,[1] AMIT KUMAR SATAPATHY,[1] APARNA MUKHERJEE,[2] JAGDISH PRASAD GOYAL,[3] JAVEED IQBAL BHAT,[4] VINOD H RATAGERI,[5] BHADRESH VYAS,[6] RAKESH LODHA,[2] AND ATU (ACUTE RESPIRATORY INFECTION TREATMENT UNIT) GROUP*

*From Department of Pediatrics, [1]AIIMS Bhubaneswar, Odisha; [2]Department of Pediatrics, AIIMS New Delhi; [3]Department of Pediatrics, AIIMS Jodhpur, Rajasthan; [4] Department of Pediatrics, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, J&K; [5] Department of Pediatrics, Karnataka Institute of Medical Sciences, Hubli, Karnataka; [6]MP Shah Medical College, Jamnagar, Gujarat. *List of ATU Group members provided in annexure I.*

Correspondence to: Dr Rashmi Ranjan Das, Additional Professor, Department of Pediatrics, AIIMS, Bhubaneswar 751 019, Odisha. rrdas05@gmail.com

Received: April 02, 2020; Initial review: April 11, 2020; Accepted: December 26, 2020.

Background: Current WHO algorithm has retained the signs and symptoms used in the older version for classifying severity of childhood pneumonia.

Objective: To study the role of clinical features (including that of current WHO criteria), and oxygen saturation (SpO2) in the diagnosis of childhood pneumonia.

Study design: Multicenter prospective cohort study.

Participants: Children, 2 to 59 months of age, suffering from acute respiratory infection (ARI).

Outcome measures: Sensitivity, specificity, and likelihood ratios were calculated for clinical features, and SpO2.

Results: Of a total 7026 children with ARI enrolled, 13.4% had pneumonia (37% of them had severe pneumonia), according to WHO criteria. Based on any abnormality on chest x ray (CXR), 46% had pneumonia. The sensitivity and specificity of the existing WHO criteria for diagnosis of pneumonia was 56.5% and 66.2%, respectively, when compared against abnormalities in CXR. Cough and fever, each had sensitivity of >80%. Audible wheeze and breathing difficulty, each had a specificity of >80%. Sensitivity and specificity of tachypnoea were 58.7% and 63.3%, respectively. None of the clinical features alone had a sensitivity and specificity of >80%. Addition of SpO2 of <92% to chest indrawing alone or WHO criteria increased the likelihood of diagnosis of pneumonia.

Conclusions: Current WHO criteria based on rapid respiratory rate and/or chest indrawing has modest sensitivity and specificity, considering CXR abnormalities as gold standard for diagnosis of pneumonia. Addition of SpO2 of <92% to chest indrawing alone or WHO criteria increases the probability of pneumonia diagnosis, and is important in the management of a child with pneumonia.

Keywords: *Acute respiratory infection, Sensitivity, Specificity.*

Pneumonia is a leading cause of death in under-five children [1,2]. Over 80% children with community acquired pneumonia (CAP) present with cough and fever, while other features like breathing difficulty, nausea, vomiting, and poor feeding are seen with variable frequencies [3]. One of the major issues of CAP in children is making a correct diagnosis.

For uniform management of childhood acute respiratory infection (ARI) including CAP, WHO (World Health Organization) developed an algorithm based on evidences generated in the early 1980s [4]. The clinical criteria adopted in this WHO algorithm used a combination of clinical manifestations including fast breathing in a child with cough and/or difficult breathing for diagnosing pneumonia [4]. The sensitivity of the WHO algorithm was found to range between 59-81% and there has been concern about its specificity, resulting in unnecessary use of antibiotics [3, 5-11].

The WHO algorithm for pneumonia was revised in 2014, combining severe and very severe pneumonia as one category, with pneumonia being defined as fast breathing and/or lower chest indrawing (LCI) [12]. However, this revised algorithm retained the signs and symptoms used in the older version for classifying severity of pneumonia in children. As per a recent systematic review, absence of cough was a significant negative predictor, while SpO2 of ≤95% or increased work of breathing (nasal flaring, grunting or lower chest indrawing) were significant diagnostic predictors of pneumonia [3]. There is as yet no study from the Indian setting, assessing the diagnostic accuracy of clinical signs and symptoms (including WHO criteria) of pneumonia, with or without SpO2 measurement.

METHODS

This prospective, multicentric cohort study was conducted in tertiary care teaching hospitals in five sites in India over a 2 year period (June 2016 to May 2018). Children aged 2-59

months with ARI (any cough and/or breathing difficulty for <2 weeks) were enrolled. Those with chronic respiratory diseases (asthma, cystic fibrosis, broncho-pulmonary dysplasia, airway anomalies), congenital heart disease, gastro-oesophageal reflux/ recurrent aspirations, immunosuppression, radiologically confirmed pneumonia in last 2 months, residing outside the study city, and who were critically ill (impending respiratory failure, cyanosis at room air, shock), were excluded. The study was initiated after clearance by the respective Ethics Committees of all five study sites. Children were enrolled after obtaining written, informed consent from parents or legal guardian.

Details regarding clinical features, nutritional and immunization status, treatment history, demographic information, and examination findings were recorded. A staff nurse was trained to assess breathing difficulty by counting respiratory rate, and identifying chest indrawing under supervision of a trained research officer. Ausculta-tory findings were also recorded. Fever was defined as an axillary temperature of ≥37.5 ºC. Tachypnea was defined and clinical diagnosis of pneumonia was made as per the WHO criteria [12]. SpO2 was recorded using Nellcor portable pulse oximeter (measurement range 60% to 100%). As previous studies had reported an SpO2 of <92% to indicate pneumonia with good sensitivity and specificity, we used the same cut-off in the present study [3,13]. Antipyretic was given for fever and respiratory rate was reassessed after 30 minutes. In case of wheezing, salbutamol nebulization (0.15 mg/kg/dose) was adminis-tered and respiratory rate reassessed after 10-15 minutes.

A chest *X*-ray (CXR) was obtained in all children clinically assessed to have acute lower respiratory tract infection (ALRI/pneumonia) as per the WHO criteria. CXR was also obtained in every fifth child assessed as no pneumonia (URI) [14]. Radiographic findings were recorded in a standardized form based on previously published WHO standards and definition for epidemiological studies [15]. The digital CXR films or hard copies of CXRs were sent to the co-ordinating center. All CXRs were read by two independent pediatricians, who were blinded for the clinical diagnosis of patients. In case of disagreement, CXRs were read by a third pediatrician without knowledge of the previous evaluations, and findings matching with previous two were considered final. Radiographic pneumonia was diagnosed if there was agreement on presence of any abnormality (pulmonary infiltrate or pleural effusion) in two independent assessments. The site investigator managed the patient as per his interpretation based on WHO guidelines [16].

To improvise clinical case definition CAP with a sensitivity and specificity of 80% (sensitivity of tachypnea with/without chest indrawing is about 69%) and precision of 5%, a total of 256 children with pneumonia were needed. Considering that 10% children with ARI have a probability of pneumonia [17], 2560 children with ARI were needed to be screened.

Statistical analysis: For analysis, the data were entered into Microsoft excel sheet and analyzed using Stata v.14 (Stata Corp LLC) statistical software. Categorical data were analyzed by Chi-square test. For studying the association between WHO pneumonia classification and CXR findings, risk ratio (RR) with 95% confidence interval (95% CI) was calculated. Sensitivity, specificity, likelihood ratio (LR), and post-test probability were calculated. A P value <0.05 was taken as significant.

RESULTS

Out of a total 18 159 children screened across 5 sites, 7026 children with ARI were enrolled. According to WHO criteria, 938 (13.4%) and 6088 (86.6%) of the enrolled children had pneumonia and no pneumonia (URI), respectively. Severe pneumonia was diagnosed in 347/938 (36.9%) children. Baseline demographic and clinical characteristics of the enrolled children are given in **Table I**. The study flow chart as per the STARD (Standards for Reporting Diagnostic accuracy studies) guideline is provided in **Fig. 1**. A total of 6,341 (90%) children were managed on ambulatory basis while 685 (10%) required hospitalization, seven of whom died.

Using the rertcorded information, the enrolled patient were re-classified, based on the WHO criteria, and 938

Table I Baseline Demographic and Clinical Characteristics of Enrolled Children (*N*=7026)

Characteristics	*Value*
Age (mo)	23 (10,40)
Boys[a]	4251 (60.5)
Weight for age *z*-score	-0.69 (-1.83,0.35)
Height/Length for age *z*-score	-0.76 (-2.36,0.77)
Weight for height *z*-score	-0.29 (-1.14,0.53)
Mid upper arm circumference *z*-score	-1.47 (-2.13, -0.8)
Cough[a]	6995 (99.6)
Fever[a]	3998 (56.9)
Audible wheeze[a]	512 (7.3)
Fast breathing post-nebulization[a]	938 (13.4)
Chest indrawing[a]	478 (6.8)
Clinical URI[a]	6021 (85.7)
Clinical LRTI[a]	1005 (14.3)

Values in median (IQR) or [a]no. (%). URI/LRTI: upper/lower respiratory tract infection.

(13.4%) were found to have pneumonia. Of the 1308 CXRs available, abnormalities were reported in those films (n=1273), which were either adequate (features allowing confident interpretation of primary end-point as well as other infiltrates) or suboptimal (features allowing interpretation of primary end-point but not of other infiltrates or findings) for reading. Rest 35 CXRs were un-interpretable. The presence of any abnormality on CXR was considered as the gold standard for diagnosis of pneumonia. Abnormalities in CXR were identified based on points published by WHO: consolidation (alveolar shadows), infiltrates (small infiltrates involving multiple segments), interstitial shadows, and pleural effusion [15]. Around 46% (586/1273) children had pneumonia based on these criteria. The crude agreement between the two readers of CXR was 80.5% (kappa=0.6, P<0.001). As shown in **Table II**, a chest *X*-ray showing any abnormal finding, consolidation, and alveolar infiltrates was found to be significantly associated with a pneumonia diagnosis made as per WHO criteria.

The diagnostic accuracy of clinical parameters and SpO2 for pneumonia is detailed in **Web Table I**. Neither cough nor wheeze had a significant LR for ruling in or ruling out the diagnosis of pneumonia. The parameters like breathing difficulty, fast breathing, chest indrawing, existing WHO criteria for pneumonia, SpO2 <92%, existing WHO criteria + SpO2 <92%, existing WHO criteria and/or SpO2 <92%, chest indrawing + SpO2 <92%, existing WHO criteria present and SpO2 <92% applied serially had a significant positive LR as well as negative LR (except fever, which had a significant negative LR only). Positive LR among confirmed pneumonia cases ranged from 1.5 (for breathing difficulty) to 2.7 times (for chest indrawing + SpO2 <92%) in confirmed pneumonia cases compared to those without. Negative LR ranged from 0.85 (for chest indrawing + SpO2 <92%) to 0.64 (for fever, and existing WHO criteria and/or SpO2 <92%, both) in those with pneumonia compared to those without. The prevalence (pre-test probability) of pneumonia in the present study was 46%. We calculated the post-test probability for parameters having a LR+ of ≥2.0 and/or a LR– of ≤0.5. Addition of a SpO2 of <92% increased the post-test probability of diagnosing pneumonia to 66% in case of existing WHO criteria, and 69% in case of chest indrawing.

DISCUSSION

In this multi-center hospital-based observational study across five sites in India, none of the clinical parameters (either single or in combination) had a sensitivity and specificity of >80% for diagnosis of childhood pneu-monia. The overall analysis suggests that, the current WHO criteria for pneumonia have modest sensitivity (56.5%) and specificity (66.2%), which is in agreement with the findings of a previous meta-analysis [8].

The prevalence of radiological pneumonia in the present study was 46%, similar to previous studies [13]. Primary end point pneumonia is usually defined as presence of consolidation or pleural effusion with or without other infiltrates (e.g., interstitial infiltrates/thickening, atelectasis, peri-bronchial thickening, and alveolar infiltrates not sufficient to refer as a consolidation) [8]. Other infiltrates are commonly seen in viral or atypical pneumonia. In the present study, only consolidation and alveolar infiltrates were found to be significantly associated with WHO pneumonia, which probably means that majority had bacterial pneumonia [13], which is consistent with the finding of a relatively high proportion of severe pneumonia cases, in the present study (37%) [18].

As per the WHO algorithm, fast breathing/tachypnea is an important indicator of childhood pneumonia, and studies from developed countries also support this [19,20]. In the present study; however, the WHO defined fast breathing had a sensitivity of 58.7% and specificity of 63.3%. In a study from Mexico, WHO defined tachypnea as a sole clinical sign had 74% sensitivity and 67% specificity for the diagnosis of radiological pneu-monia [19]. The sensitivity was reduced, and specificity was increased (84%) when other clinical signs were combined. An additional observation in this study was that, in children with pneumonia of <3 days' duration, tachypnea had a sensitivity and specificity of 55% and 64%,

Table II Association Between WHO Pneumonia Classification and Chest *X*-Ray Findings (N=1273)

Chest X-ray findings	*Pneumonia*	*No pneumonia*	*Relative risk (95% CI)*
Any abnormal finding (n=586)[a]	331 (56.5)	255 (43.5)	1.64 (1.45-1.85)
Consolidation (n=112)[a]	75 (67)	37 (33)	2.56 (1.75-3.73)
Alveolar infiltrates (n=396)[a]	243 (61.4)	153 (38.6)	2.0 (1.69-2.37)
Peribronchial thickening (n=104)	52 (50)	52 (50)	1.26 (0.87-1.82)
Interstitial thickening (n=41)	19 (46.3)	22 (53.7)	1.09 (0.6-1.99)
Atelectasis (n=5)	3 (60)	2 (40)	1.89 (0.32-11.28)

All values expressed as n (%). [a]P<0.001. WHO: World Health Organization.

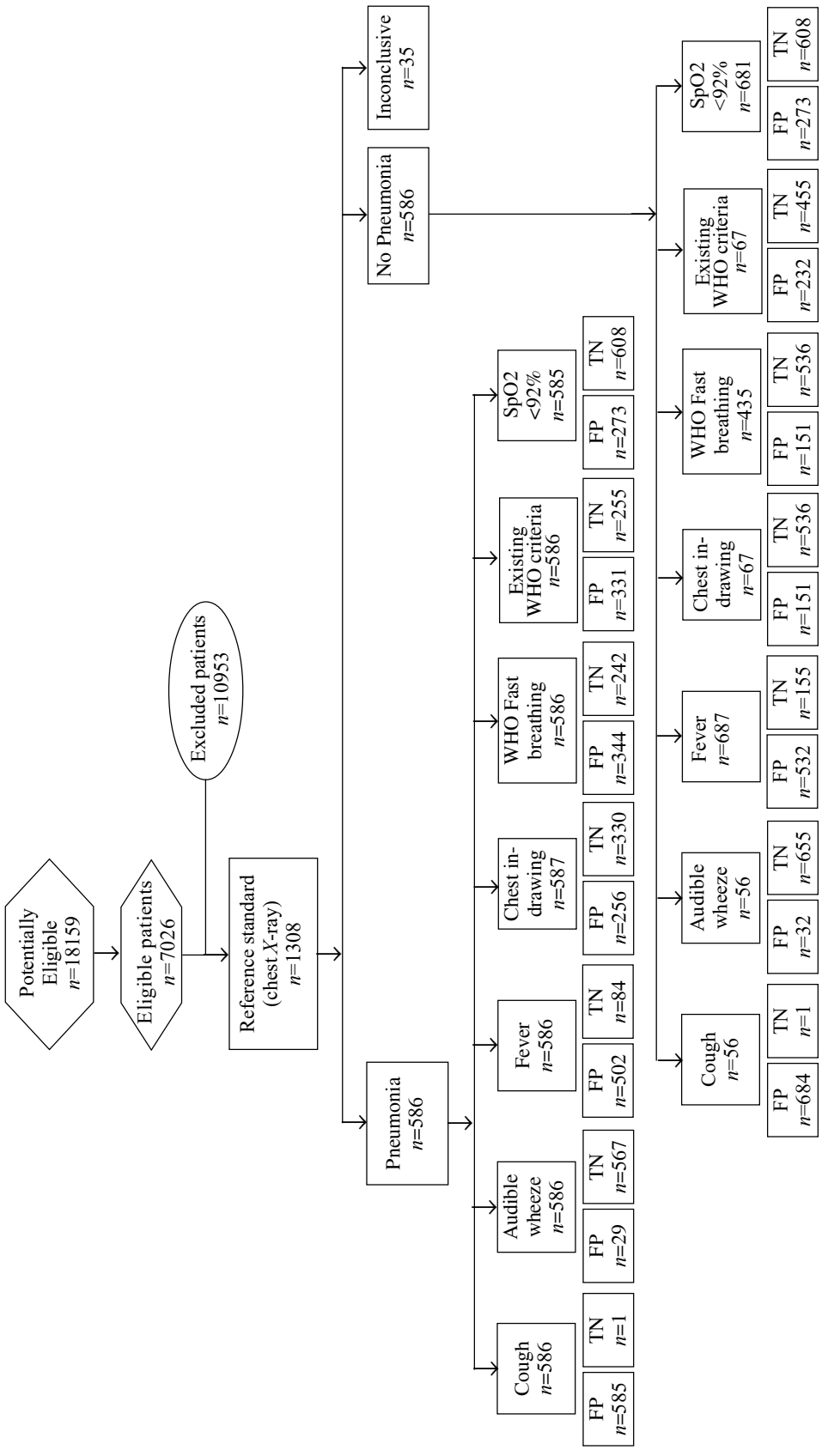

Fig. 1 Study flow chart.

WHAT IS ALREADY KNOWN?

- Current WHO case definition based on rapid respiratory rate and/or chest in-drawing has modest sensitivity and specificity considering CXR abnormalities as gold standard for diagnosis of childhood pneumonia.
- Addition of SpO2 <92% to chest indrawing alone or to WHO criteria increases probability of diagnosing pneumonia.

respectively. In a recent systematic review, presence of tachypnea (respiratory rate >40 breaths/min) in children beyond infancy, was not strongly associated with pneumonia diagnosis [3]. It is important to note that, absence of tachypnea does not rule out the diagnosis of pneumonia. in children under-five years of age [8,20].

Fever, which is commonly seen in pneumonia [21, 22], had a sensitivity of 85.7% and specificity of 26.6% for diagnosing pneumonia in the present study. The British Thoracic Society (BTS) Guideline mentions that, in children below 3 years, high fever along with chest indrawing and tachypnea (>50/min) is suggestive of pneumonia [22]. On the contrary, a systematic review showed that temperature >37.5°C was not strongly diagnostic of pneumonia [3]. Chest signs on auscultation (e.g., crackles, rales, or rhonchi) were neither sensitive nor specific for pneumonia [3].

A LR+ of ≥2.0 and a LR ≤0.5 has been shown to change the post-test probability of disease appreciably. In the present study, neither cough nor audible wheeze (7.3% children) has a significant LR for ruling in or ruling out pneumonia diagnosis. This is an interesting observation, as cough has been the most sought symptom of pneumonia. A recent systematic review [3] found that none of the features including cough, audible wheeze, poor feeding, breathing difficulty, or duration of illness >3 days had a significant likelihood for diagnosing pneumonia, though absence of cough had a significant negative LR (LR 0.47; 95% CI 0.24 to 0.70) in ruling out the diagnosis of pneumonia. Also, SpO2 ≤95% and increased work of breathing (nasal flaring, grunting or lower chest indrawing) (LR+ 2.1) had a significant likelihood to diagnose pneumonia. Studies using other cutoff SpO_2 values (i.e., 96%, 92%, and 90%) had lower LR+, whereas, SpO2 >96% had a LR– of 0.47 [3,23]. The poor diagnostic performance of auscultatory findings (e.g., presence of wheeze or crackles) could be because these are subjective parameters. The present study shows that the probability of having pneumonia improved to 66% among those tested positive for WHO criteria with a SpO2 of <92%, and to 69% among those with chest in-drawing and a SpO2 of <92%. None of the parameters in the present study were found to have negative LR of ≤0.5, thus making them inappropriate for ruling out the pneumonia diagnosis. Our findings are different from previously published studies [3,8], probably because of variation in the age of included children (only few studies included children >5 years age), geographical location (e.g., high altitude, urban/rural), care-seeking behavior, duration of disease, and prevalence of malnutrition.

The limitation of the present study is that we could not carry out subgroup analysis of factors like age, duration of symptoms at presentation and severity, which are known to modify the diagnostic performances in a previously published study [19].

To conclude, current WHO criteria based on rapid respiratory rate and/or chest in-drawing has modest sensitivity and specificity, taking CXR abnormalities as gold standard for diagnosis of pneumonia. Addition of SpO2 of <92% to chest indrawing alone or to WHO criteria increases the probability of pneumonia diagnosis, and is important in the management of a child with pneumonia.

Acknowledgements: *AIIMS Bhubaneswar*: Ms Jyotshnarani Sahoo and Ms Manaswini Biswal; *AIIMS Jodhpur*: Mr Vikas Patwa; *KIMS Hubli*: Dr Prakash Wari (HOD Pediatrics), Vedasree and Gayatri; *SKIMS Srinagar*: Umaisa Zehra and Saba.
Ethical clearance: The study was approved by Institutional ethics committee of all the six study sites.
Contributors: RRD: involved in protocol development, supervision of study, data collection and analysis, and manuscript writing. AKS: involved in data collection, management of patients, and manuscript writing. AM, RL: involved in protocol development, data analysis, and manuscript writing. JPG, JIB, VHR, BV: involved in protocol development, and manuscript writing. All the authors have approved the manuscript version to be published.
Funding: This work was supported by Bill and Melinda Gates Foundation through The INCLEN Trust International (Grant number: OPP1084307). The funding source had no contribution in study design, implementation, collection and interpretation of data and report writing.
Competing interest: None stated.

REFERENCES

1. McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: A systematic analysis. Lancet Glob Health. 2019;7:e47-57.
2. Fadel SA, Boschi-Pinto C, Yu S, et al. Trends in cause-specific mortality among children aged 5-14 years from 2005 to 2016 in India, China, Brazil, and Mexico: An analysis of nationally representative mortality studies. Lancet.

2019;393:1119-27.
3. Shah SN, Bachur RG, Simel DL, Neuman MI. Does This child have pneumonia? The rational clinical examination systematic review. JAMA. 2017;318:462-71.
4. World Health Organization (WHO). The management of acute respiratory infections in children In: Practical guidelines for outpatient care. Geneva: WHO, 1995.
5. Sazawal S, Black RE, Pneumonia Case Management Trials Group. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. Lancet Infect Dis. 2003;3:547-56.
6. Hazir T, Qazi SA, Bin Nisar Y, et al. Comparison of standard versus double dose of amoxicillin in the treatment of non-severe pneumonia in children aged 2-59 months: a multi-centre, double blind, randomized controlled trial in Pakistan. Arch Dis Child. 2007;92:291-7.
7. Harari M, Shann F, Spooner V, Meisner S, Carney M, de Campo J. Clinical signs of pneumonia in children. Lancet. 1991;338:928-30.
8. Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V. Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. Lancet Infect Dis. 2015;15:439-50.
9. Mulholland EK, Simoes EA, Costales MO, McGrath EJ, Manalac EM, Gove S. Standardized diagnosis of pneu-monia in developing countries. Pediatr Infect Dis J. 1992; 11:77-81.
10. Singhi S, Dhawan A, Kataria S, Walia BN. Validity of clinical signs for the identification of pneumonia in children. Ann Trop Paediatr. 1994;14:53-8.
11. Redd SC, Vreuls R, Metsing M, Mohobane PH, Patrick E, Moteetee M. Clinical signs of pneumonia in children attending a hospital outpatient department in Lesotho. Bull World Health Organ. 1994;72:113-8.
12. Falade AG, Tschäppeler H, Greenwood BM, Mulholland EK. Use of simple clinical signs to predict pneumonia in young Gambian children: the influence of malnutrition. Bull World Health Organ. 1995;73:299-304.
13. Awasthi S, Rastogi T, Mishra N, et al. Chest radiograph findings in children aged 2-59 months hospitalised with community-acquired pneumonia, prior to the introduction of pneumococcal conjugate vaccine in India: a prospective multisite observational study. BMJ Open. 2020;10: e034066.
14. World Health Organization (WHO). Revised WHO classification and treatment of childhood pneumonia at health facilities, 2014. Accessed on 29 August, 2019. Available at: *https://www.who.int/maternal_child_adolescent/ documents/child-pneumonia-treatment/en*
15. Dowell SF, Schwartz B, Phillips WR. Appropriate use of antibiotics for URIs in children: Part I. Otitis media and acute sinusitis. The Pediatric URI Consensus Team. Am Fam Physician. 1998;58:1113-8,1123.
16. Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ. 2005;83:353-9.
17. Mathew JL, Patwari AK, Gupta P, et al. Acute respiratory infection and pneumonia in India: a systematic review of literature for advocacy and action: UNICEF-PHFI series on newborn and child health, India. Indian Pediatr. 2011;48:191-218.
18. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008;86:408-16.
19. Palafox M, Guiscafre H, Reyes H, Munoz O, Martinez H. Diagnostic value of tachypnoea in pneumonia defined radiologically. Arch Dis Child. 2000;82:41-5.
20. Leventhal J. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. Clin Pediatr. 1982;21: 730-4.
21. Campbell H, Byass P, Lamont AC, et al. Assessment of clinical criteria for identification of severe acute lower respiratory tract infections in children. Lancet. 1989;1:297-9.
22. British Thoracic Society. British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Childhood. Thorax. 2002;57:i1-24.
23. Mahabee-Gittens EM, Grupp-Phelan J, Brody AS, et al. Identifying children with pneumonia in the emergency department. Clin Pediatr (Phila). 2005;44:427-35.

ANNEXURE I

***Members of The ATU (Acute Respiratory Infection Treatment Unit) Group**

Partha Sarathi Ray, *AIIMS, Bhubaneswar, Odisha*; Kana Ram Jat, *AIIMS, New Delhi*; Bashir Ahmad Charoo, *SKIMS, Srinagar, J&K*; Daisy Khera, Prawin Kumar and Deepak Singhal, *AIIMS, Jodhpur, Rajasthan*; Samarendra Mahapatro, *AIIMS, Bhubaneswar, Odisha*; Kuldeep Singh, *AIIMS, Jodhpur, Rajasthan*; Sushil K Kabra, *AIIMS, New Delhi*.