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Childhood Pneumonia in India: The Public Health Significance

Guest Editors

JOSEPH L MATHEW, NARENDRA KUMAR ARORA

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Special Issue

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Childhood Pneumonia Research in India: Current and Future Perspectives

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Childhood community acquired pneumonia (CAP) continues to remain a problem of great clinical and public health significance. Its impact on individual children, the community, and the healthcare system, is probably unrivalled by any other childhood disease. For several decades, India has been faithfully following the formal and informal guidance provided by international agencies including the World Health Organization (WHO), reputed global funding agencies, and prestigious universities/institutions/organizations promoting research. Local data has generally been limited in terms of quality as well as quantity. In that context, it is laudable that Indian Pediatrics has focused this issue on research and topics related to childhood pneumonia. This has been possible largely through the support of the International Clinical Epidemiology Network (INCLIN) based in New Delhi, which initiated and executed a national-level research program on childhood pneumonia.

This issue of the Journal carries seven publications flowing from this initiative [1-7], besides two other independent research studies [8,9]. An external evaluation of the entire initiative, by a team of globally renowned researchers, is also presented in this issue [10]. Some of these studies have provided confirmation of known results, but in the Indian context. Most have used standard methods and/or tools to re-explore issues that are generally accepted or expected.

This begets the question of what has been achieved through the excellent effort initiated by INCLIN. First, almost all the studies [1-7] highlight considerable attention to methodological rigor, including clearly articulated research questions, appropriate study designs, *a priori* sample size calculations, multi-centric nature of some studies, fairly large sample sizes, and efforts to limit some sources of bias. This clearly reflects the role of INCLIN, in terms of design, execution, mentorship, and oversight of the research studies. The second, and perhaps greater, gain is the establishment of a network of institutions and researchers across the length and breadth of the country (except Eastern region), with an interest in childhood pneumonia. This bodes well for the

reasons highlighted subsequently. Third, previous experience with INCLIN supported research studies, shows that this prestigious agency continues working beyond the completion of the research studies, towards widespread dissemination of the data, advocacy with policy-makers and other key decision-makers, and translating the evidence into actionable plans. Thus, INCLIN has acted much more, and much better than a traditional “funding agency”. Its efforts will provide great thrust not only to research on childhood CAP, but its practical translation to policy and practice.

Although the external evaluation [10] identified that the program met its objectives, some areas of concern remain. The program itself was funded by the Bill and Melinda Gates Foundation, hence the selection of research project proposals was based on alignment to the priorities of the Foundation, not necessarily our country. This raises the issue of what our country’s priorities should be, in the area of childhood CAP research. To my mind, the following questions provide a broad outline:

- What is the microbial etiology of pneumonia in individual children in the community (and not hospitalized children alone)?
- How to distinguish bacterial from non-bacterial etiology in individual children with CAP, at presentation, and at the point-of-care?
- Which features in individual children, at presentation, and at the point-of-care, are associated with clinical deterioration and/or adverse outcome?
- What tools and support can be provided to (community) healthcare workers for appropriate (i.e., not merely empiric) management of children at the point-of-care?
- What is the impact of environmental (external and internal) factors in the initiation, progression, and final outcome of children with pneumonia?
- Which internal host factors influence the onset, course, and outcome, of pneumonia (beyond the well-recognized macro-level factors such as nutritional

status, breastfeeding, vaccination, exposure to smoke, etc.)?)

- What is the prevalence, pattern and outcome of CAP in infants younger than 2 month and older than 5 year?
- Given that measles pathophysiology starts with lower respiratory tract infection, what strategies could/should be used to rapidly eliminate measles in the country?
- What is the burden of RSV infection in childhood pneumonia (distinct from bronchiolitis), and can we rapidly generate evidence to manage it appropriately?

These questions reflect three important facts. First, hospital-based studies may be inappropriate to address the questions related to disease affecting children in the community. Second, the focus of research should shift from cohorts to individual children. Third, research needs to focus on host and environmental issues rather than microbes alone. Additionally, the first two questions are critical to evolve appropriate treatment and prophylaxis decisions, rather than indiscriminately following the approach handed-down by external agencies.

Current global research has already shifted focus from Pneumococcus to RSV [11-15], setting the ground for the anticipated roll-out of vaccines and/or other prophylaxis strategies. Therefore, the last question highlighted above needs urgent answers, lest India be caught in the unenviable position of lacking local data, but facing pressure to initiate expensive prophylaxis programs. Previous experience of our country with several other vaccines suggests that this scenario is very likely to recur.

Although the program did not address any of these crucial issues, it still carries great potential, provided (i) the network of institutions and individual researchers can be preserved despite the completion of the studies; (ii) the sites in the tertiary-care institutions can begin engaging with the local community for future community-based research; (iii) funding can be attracted from local and international agencies; (iv) additional institutions along with their satellites can be added; and (v) the same level of mentorship, oversight, and monitoring can be maintained. I believe that this will not only make our country self-reliant in evidence-based policy and practice decision-making for childhood pneumonia, but pave the path for similar self-reliance in other areas of child health also.

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INCLLEN - BMGF Research Program to Emphasize Context Sensitive Approaches for Addressing the Challenges of Childhood Pneumonia in India

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Acute respiratory infection (ARI) and pneumonia scenario in children have changed enormously in the last 20 years; there is global reductions in its morbidity and mortality, and changes in aetiology due to introduction of effective vaccines and improvements in case detection and management. Notwithstanding these gains, huge variation in pneumonia morbidity and mortality emerge between, and within, different countries. In 2015, India was the top contributor to pneumonia disease burden globally (32%) [1]. During the Millennium Development Goal era (2000-2015), India contributed to the highest to the clinical pneumonia burden globally (32%) and observed only 3% decline in the number of pneumonia episodes [1,2]. Noticeable socio-cultural and economic changes have occurred in India since the 90s: lifestyle changes, urbanisation, migration, and, aspiration for better living conditions. Vaccines for *H. influenza* and *Pneumococcus* have been introduced in addition to expanding coverage for measles as part of the Measles Rubella Elimination campaign. These contrasting observations emphasize importance of context-sensitive control strategies and focus for equity if the country desires to witness decline in the pneumonia burden and related deaths.

To support and accelerate India's efforts towards reducing pneumonia deaths and emphasize its public health significance, a research program was supported by Bill and Melinda Gates Foundation (BMGF) through the INCLLEN Trust International. This research program aimed to provide catalytic support to the Indian investigators and institutions for generation of context specific evidence and knowledge on childhood pneumonia that has policy and program relevance. This childhood pneumonia research program in India was coordinated and managed by INCLLEN under guidance of a Joint Working Group (JWG) with membership (14 members) from Ministry of Health and Family Welfare, Department of Biotechnology, Indian Council of Medical Research, and Government of India, World Health Organisation (WHO), Unicef and technical experts of national and international repute. Seven focus areas for

funding were finalized: (i) determinants of pneumonia burden and deaths; (ii) improving case management with better access that mitigates barriers to care seeking; (iii) aetiology, determinants and outcome of neonatal pneumonia; (iv) diagnostic tools and point of care diagnosis; (v) respiratory syncytial virus pneumonia, particularly in neonatal and early infancy; (vi) pneumococcal conjugate vaccine scheduling and immunogenicity; and (vii) epidemiological tools for monitoring and surveillance of pneumonia and ARI program and impact assessment of different interventions. Overarching expectation from these studies has been of understanding subnational variation and contextual factors.

A multidisciplinary Technical Advisory Group (TAG) (n=32) including national and international experts from child health, pneumonia, microbiology, public health, social science, biostatistics, health economics, and health program reviewed 94 concept notes, down selected 29 applicants for full proposal submission and finally, approved ten proposals for funding. The selected proposals were not only from established researchers from leading institutions, but also included innovative ideas from four young and less-experienced investigators. Hand-holding and mentoring framework was embedded in to program governance particularly for young and new investigators. The TAG members designated for specific projects provided technical mentoring through progress review and site visits. The investigators were provided opportunity to attend Research LAMP (Leadership and Management Program) conducted regularly by INCLLEN; one research methodology workshop was also organised for the young investigators and research team members. The young investigators were also supported for data management, analysis and manuscript writing.

The ten supported studies focused on care-seeking behavior and determinants, case diagnosis and management, impact of alternate vaccine schedule, and cost effectiveness and etiology of neonatal pneumonia. It is interesting that the research projects supported under this program overlapped with seven priority research domains

identified in a recent ARI and pneumonia review commissioned by maternal, neonatal, child and adolescent health (MNCAH) division of WHO for exploring contextual challenges to decrease ARI related morbidities and mortality [3].

From these ten supported projects under this pneumonia research program, 29 manuscripts were submitted. While 14 articles have been already published in other international and national peer reviewed indexed journals [4-17], six research articles and one systematic review are included in this issue. Eight additional articles are under review. Two investigators have strengthened the research infrastructure at their institutions, and seven investigators have generated new research proposals catalysed by this program.

An external evaluation of the program was conducted by a three-member team to assess the public health appropriateness, program implementation and contribution to the research pool in Indian context [18].

The BMGF-INCLIN program was conceived in alignment with the mission and vision of The INCLIN Trust International. We expect this model of targeted research investment attempting to answer local challenges along with proactive efforts to expand the pool of young researchers will stimulate similar programs in future as well.

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Risk of Hospitalization in Under-five Children With Community-Acquired Pneumonia: A Multicentric Prospective Cohort Study

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Objective: To evaluate factors associated with risk of hospitalization in children with community-acquired pneumonia (CAP).

Design: Prospective cohort study.

Setting: Multi-site hospital based study.

Intervention: A separate acute respiratory tract infection (ARI) treatment unit (ATU) was established. The revised WHO case definition for ARI was used across all the study sites to ensure uniformity in management of ARI patients (2-59 months). Clinical history, examination findings and investigations of enrolled patients were recorded on a predesigned case record form. Children were followed up at 1 week (\pm 1 day).

Main outcome measure: Risk factors for hospitalization among pneumonia patients.

Results: A total of 7026 children with the diagnosis of ARI were enrolled. Pneumonia was diagnosed in 938 (13.4%) patients (median (IQR) age: 15 (8, 25) months; 63.5% boys). Hospitalization was needed in 56.8% of pneumonia patients. On multivariate analysis, factors associated with risk of hospitalization were: Oxygen saturation on pulse oximetry (SpO_2) $<$ 92% in room air (OR 7.04; 95% CI 1.6, 30.8, $P=0.01$), procalcitonin level $>$ 0.5 ng/mL (OR: 7.5, 95% CI: 1.0, 57.7, $P=0.05$), and lower weight for height z-score (OR 0.8; 95% CI: 0.6, 0.9, $P=0.02$).

Conclusion: Present study found SpO_2 $<$ 92% at room air, serum procalcitonin level $>$ 0.5 ng/mL and lower weight for height z-score to be predictors for risk of hospitalization in under-five children presenting with community acquired pneumonia. These factors can be utilized to assess a child with CAP regarding the need of hospitalization.

Keywords: Hypoxia, Outcome, Procalcitonin, Underweight.

Community-acquired pneumonia (CAP) is one of the leading causes of morbidity and mortality in under-five children [1]. CAP is more common in the developing world, accounting for 95% of all cases [2]. In India, an estimated 4 lakh pneumonia deaths occur annually [3]. Efficient case management is a cornerstone of pneumonia control strategies. Simple clinical signs like rapid breathing, chest in drawing and general danger signs have been used by WHO to classify the severity of pneumonia in under-five children [1].

WHO revised case definition for CAP in under-five children has two categories – ‘pneumonia’, which is treated at home with oral amoxicillin and ‘severe pneumonia, which requires hospitalization and parental antibiotics. Despite the improvement in case management of childhood pneumonia, mortality and morbidity still remains high, especially in resource-constrained settings. The early identification of important risk factors for hospitalization among these

patients could help to prioritize the management and potentially increase their likelihood of surviving. This prospective study was conducted to evaluate the factors associated with risk of hospitalization in children with CAP.

METHODS

This was a multisite prospective cohort study conducted from June, 2016 to May, 2018 in following tertiary care hospitals of India: *i*) Sher-e-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, *ii*) All India Institute of Medical Sciences (AIIMS), Jodhpur, *iii*) AIIMS, Bhubaneswar, *iv*) Karnataka Institute of Medical Sciences, Hubballi, and *v*) MP Saha Medical College, Jamnagar. AIIMS, New Delhi was a coordinating center for the study. Prior ethical approval was obtained from institutional Ethics Committee of AIIMS, Delhi and all other five study sites.

Previously healthy children, 2 to 59 months of age, with acute respiratory infection (ARI) of less than 2 weeks duration were assessed for inclusion in the study. Children

suffering from chronic respiratory diseases (asthma, cystic fibrosis, bronchopulmonary dysplasia (BPD), airway anomalies), congenital heart disease, gastroesophageal reflux disease (GERD)/recurrent aspirations, suspected/known immunodeficiency, patient living outside the city where the study site was based, history of radiologically confirmed pneumonia in last 2 months, and very sick child requiring immediate ICU care, were excluded.

A separate acute respiratory tract infection treatment unit (ATU) was established to manage all ARI patients. The ATU team comprised of a pediatrician and a trained nurse. All children between 2 months to 59 months of age with history of ARI were directed to attend ATU during working hours of the hospital. The revised WHO case definition for ARI was used across all the study sites to ensure uniformity in management of ARI patients. The revised classification includes two categories of pneumonia; 'pneumonia' with fast breathing and/or chest in drawing, and 'severe pneumonia,' pneumonia with any general danger sign [1]. Children were enrolled in the study after obtaining written, informed consent from parents or legal guardians. A detailed history was taken, and physical examination, including respiratory rate, presence of chest in drawing, pulse, temperature, oxygen saturation by pulse oximetry and anthropometry was done by the research nurse under the supervision of research officer. Each child's respiratory rate was counted for a full minute when the child was calm and quiet. If the child presented with fever and fast breathing, appropriate paracetamol dose was given and respiratory rate was reassessed after 30 minutes. Children presenting with wheeze and fast breathing were administered salbutamol nebulization (0.15 mg/kg single dose) and respiratory rate was reassessed after 10-15 minutes. Weight was measured to the nearest 0.1 kg using calibrated electronic scales, and height was measured to the nearest 0.1 cm using a standardized stadiometer. If a child was less than 2 years of age, recumbent length was measured by using an infantometer. Clinical history and examination findings of enrolled children were recorded on a predesigned case record form.

Every fifth child with ARI underwent a chest X-ray. The chest radiographs were interpreted by site investigator at the time of enrolment, thereafter, either original films or digital copies were sent to the coordinating centre at AIIMS, New Delhi. All chest X-rays were read by two independent pediatricians, who were blinded for the clinical diagnosis of the patient. In case of disagreement about the presence or absence of pathology, chest X-rays were read by a third pediatrician without knowledge of the previous evaluations and final findings matching for two of them were considered for purpose of analysis. Patients with suspected pneumonia underwent serum quantitative procalcitonin (PCT)

estimation. All children were followed till 7 days (± 1 day) after enrolment. Parents were given reminder telephone call one day prior to the anticipated follow-up. All admitted patients were examined daily until discharge.

Management of children with pneumonia was done according to the WHO recommendations [1]. Any child with severe pneumonia was hospitalized; the treating physicians' assessment was the deciding factor in other cases.

The aim was to enrol about 4000 children per site giving a total data of about 20000 children across all the sites. Of these 30-40% may be because of respiratory problems. Approximately 6000-8000 children with ARI, i.e. approximately 1200-1500/site were expected to be enrolled. About 10% children with acute respiratory infection may develop pneumonia. As the primary aim of the ATU project was to improvise clinical case definition (combine clinical features) of CAP with a sensitivity and specificity of 80% (sensitivity of tachypnea with/without chest indrawing is about 69%) and precision of 5%, we needed a total of 256 children with pneumonia. We expected that this sample size could be easily achieved.

Statistical analysis: A data entry program in Microsoft Access was developed at AIIMS, New Delhi. The data from all the study sites were sent to AIIMS for analysis. Children with CAP (as per WHO criteria) needing hospitalization were compared to those who did not, by univariate analysis, followed by multivariate analysis using a logistic regression model; the dependent criteria was whether hospitalization occurred or not, independent covariates were the ones which emerged statistically significant in univariate analysis. The z-scores for weight for age, height for age and weight for height were calculated using the WHO Anthro software.

RESULTS

A total of 18159 under-five children were screened; 7026 (39% of screened) children assessed to have ARI were enrolled in the study. Using the WHO criteria, pneumonia was diagnosed in 938 (13.4%) patients; remaining 6088 patients were labelled as having upper respiratory tract infection. Hospitalization was needed in 533 (56.8%) children with pneumonia including 7 patients who were initially given ambulatory treatment and were later admitted in view of deteriorating respiratory distress. Four hundred and five (43.2%) children with pneumonia received ambulatory treatment. The baseline demo-graphic and clinical characteristics of the study population are shown in **Table I**. Amongst children with pneumonia, reportable chest X-rays were available in 563 cases (total X-rays 571).

Factors associated with hospitalization in children with pneumonia were younger age, lower weight- and height-for-age z-scores, higher PCT levels, lower SpO₂, and higher

percentage of significant pathology in chest-X-rays as compared to those receiving ambulatory treatment (**Table II**).

On multivariate analysis, factors associated with hospitalization were SpO₂ <92% in room air [OR (95%CI) 7.04 (1.6-30.8); *P*=0.01], PCT level >0.5 ng/mL [OR (95%CI) 7.5 (1.0-57.7); *P*=0.05] and low weight for height z-score [OR (95%CI) 0.8 (0.6-0.9); *P*=0.02].

DISCUSSION

In this multi-site prospective observational study, hospitalization was needed in 56.8% of patients diagnosed with pneumonia as per current the WHO criteria. Risk factors associated with hospitalization were SpO₂ < 92% on room air, serum PCT levels >0.5 ng/mL, and lower weight for height z-score.

Majority of the patients of ARI can be managed safely in the community [5,6]. Hospital admission in revised WHO case definition for CAP management in under-5 children is recommended when the child is brought with general danger signs like not able to drink, persistent vomiting, convulsions, lethargy or unconsciousness, stridor in a calm child or severe malnutrition [1]. The WHO recommendations; however, do not include several parameters which have been proven to predict severity of pneumonia in under-five children more accurately [7,8]. Studies from different parts of the world have observed that hypoxic children are more likely to die than adequately oxygenated children [9,10]. In a systematic review, the median prevalence of hypoxemia in WHO-defined severe and very-severe pneumonia was 13% [11]. The British Thoracic Society guideline recommends that SpO₂ below 92% in childhood CAP warrants hospital admission and optimal management [5]. We have utilized pulse oximetry for measurement of SpO₂ in our study, which has been recommended as a standard point of care for SpO₂ monitoring in children with pneumonia [12,13]. A recent meta-analysis also concluded that the pulse oximetry is a useful tool for hypoxemia screening and optimal oxygen

Table I Demographic and Clinical Details of Children with Community-acquired Pneumonia (N=938)

Characteristics	Values
Age, mo ^a	15 (8,25)
Boys	596 (63.5)
Weight for age z-score ^a	-1.34 (-2.5, -0.18)
Height for age z-score ^a	-1.2 (-2.6, 0.12)
Weight for height z-score ^a	-0.77 (-1.96, 0.3)
Respiratory rate /min, mean (SD)	54 (11)
Chest indrawing present	455 (48.5)
SpO ₂ %, mean (SD)	94.3 (5.1)
Procalcitonin level, ng/mL (<i>n</i> = 12) ^a	0.1 (0.05, 0.44)
Significant pathology in CXR (<i>n</i> =563)	331 (58.8)

Values in no. (%) or ^amedian (IQR). CXR: chest X-ray.

supplementation to prevent pneumonia deaths in children [14]. Our study findings corroborates with these observations. Detection of hypoxemia by pulse oximetry should be an important component for assessment of a child with CAP so that a decision regarding the severity of pneumonia and need for hospitalization can be taken.

Serum PCT level > 0.5 ng/mL had a higher odds of hospitalization in our cohort of children with CAP. Multiple studies in both adults and children have shown that serum PCT is a surrogate tool to differentiate between viral and bacterial pneumonia, and the latter has higher probability of hospitalization [15,16]. Serum PCT levels can be used as a point of care diagnostic tool to assess severity of pneumonia in children with CAP as this investigation is becoming increasingly available even in smaller hospitals in our country.

Malnourished children have a higher incidence and severity of CAP. Mortality increases proportionately with severity of malnutrition [18]. We also found significantly increased risk of hospitalization among children with

Table II Factors Associated With Hospitalization in Community-acquired Pneumonia (N=938)

Characteristics	Hospitalized children (<i>n</i> =533)	Ambulatory treatment (<i>n</i> =405)
Age, mo ^a	12 (7,20)	18 (9,35)
Boys, <i>n</i> (%) ^b	342 (64.2)	254 (62.7)
Weight for age z-score ^a	-1.67 (-2.75, -0.53)	-0.84 (-2.02, 0.22)
Height for age z-score ^a	-1.37 (-2.72, -0.12)	-0.9 (-2.46, 0.6)
Weight for height z-score ^a	-1.11 (-2.36, 0.03)	-0.27 (-1.43, 0.54)
Significant pathology in CXR, <i>n</i> (%) ^c	268 (63.9)	63 (43.7)
Procalcitonin level, ng/mL ^d	0.14 (0.05, 0.54)	0.05 (0.05, 0.07)
SpO ₂ %, mean (SD)	93 (5.9)	95.9 (3.1)

Values are expressed as median (IQR) unless specified. All *P*<0.001 except ^a*P*=0.008 and ^b*P*=0.65. ^cChest X-ray available in 563 (419 inpatients and 144 out patients); ^dprocalcitonin levels available in 312 (284 inpatients and 28 outpatients).

WHAT IS ALREADY KNOWN?

- Delayed hospitalization in children with severe community-acquired pneumonia is associated with increased mortality.

WHAT THIS STUDY ADD?

- Hypoxia (SpO₂ <92% in room air), higher serum procalcitonin levels (>0.5 ng/mL) and lower weight for height z-score can predict hospitalization in under-five children with community-acquired pneumonia.

undernutrition. The variable used was weight for height z-score. With one unit increase in weight for height z-score, the odds for hospitalization was 0.8. Our study has some limitations. Since the readmission rate was very low in our study, no meaningful analysis of factors determining hospitalization after starting ambulatory treatment could be done.

To conclude, our study found SpO₂ < 92% by pulse oximetry, serum procalcitonin level >0.5 ng/mL, and low weight for height z-score as important predictors for risk of hospitalization in under five children presenting with CAP. Routine monitoring of SpO₂ by pulse oximetry and serum PCT levels can be used to identify high risk patients who would require inpatient care.

Contributors: JIB, BAC, RA: involved in data collection and manuscript writing; AM, RL: involved in development of protocol, supervision of the study, data analysis; JPG, RRD, VHR, BV: data collection, manuscript review. All authors approved the final version submitted.

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ANNEXURE I


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

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CLIPPINGS


 **Antimicrobial therapy for pediatric community-acquired pneumonia – The SAFER randomized clinical trial** (JAMA Pediatr. 2021;175:475-482)

Optimum antibiotics duration for community-acquired pneumonia (CAP) is not established, with lot of variation in management practices. Short-Course Antimicrobial Therapy for Paediatric Respiratory Infections (SAFER) Trial, a non-inferiority randomized clinical trial, was conducted in 281 children (6 months to 10 years) at the emergency departments of two pediatric emergency departments in Canada to determine non-inferiority of 5 days high-dose amoxicillin compared to 10 days regimen in uncomplicated CAP being managed on outpatient basis. Primary outcome was clinical cure at 14 to 21 days (defervescence within the first 4 days, no more than 1 additional fever spike after day 4, improvement in work of breathing, resolution of tachypnea and no need for additional antibiotics/hospital admission). Secondary outcomes included duration of absence from school/daycare, caregiver work disruption, mild/serious adverse drug reactions, adherence and recurrence. Per-protocol (PP) analysis revealed clinical cure in 88.6% children in the 5-day arm vs 90.8% in the 10-day arm (risk difference -0.016, 97.5% CI -0.087). In intention-to-treat (ITT) analysis, clinical cure was seen in 85.7% in the 5-day arm vs 84.1% in the 10-day arm (risk difference 0.023; 97.5% confidence limit -0.061). Median caregiver absenteeism was shorter in intervention group than control group (2 days vs 3 days). Though noninferiority could not be concluded in PP analysis, ITT analysis found short-course treatment to be statistically noninferior, concluding that 5-day course may be non-inferior to 10-day course. An ongoing multicenter, randomized superiority trial Short Course vs Standard Course Outpatient Therapy of CAP in children (SCOUT-CAP) will provide further evidence for the same.

 **The influence of chest X-ray results on antibiotic prescription for childhood pneumonia in the emergency department** (Eur J Pediatr. 2021;180:2765-772)

This study was done to evaluate influence of chest X-ray (CXR) results on antibiotic prescription in children suspected of lower respiratory tract infections (LRTI) in the emergency department (ED) and included 597 children (1 month to 5 years) with uncomplicated LRTI. Fifty five percent were hospitalized and 30% were prescribed antibiotics. CXR was done in 18% children and showed focal infiltrates in 48%, diffuse or perihilar findings in

28% and no abnormality in 24%. Of the 48% showing focal infiltrate on the CXR, all but nine received antibiotics. More than half (56%) of the children with diffuse/perihilar or no abnormalities on CXR received antibiotic treatment. Overall 69% children prescribed CXR received antibiotics compared to 21% who were not. CXR as part of the diagnostic work-up was associated with more frequent antibiotic prescription and this association remained after correcting for hospital variation, clinical signs and symptoms and result of the CXR. The study showed that antibiotic prescription decisions depend on the physician's overall clinical assessment rather than CXR result. Routine use of CXR in non-complicated LRTI in ED should be discouraged.

 **Antibiotic therapy versus no antibiotic therapy for children aged 2 to 59 months with WHO-defined non-severe pneumonia and wheeze** (Cochrane Database Syst Rev. 2021;1:CD009576)

Current WHO guidelines recommend treating non-severe pneumonia, defined as acute episode of cough or difficulty in breathing with fast breathing and/or chest indrawing, with oral antibiotics. However, pneumonia is more commonly caused by viruses that do not warrant antibiotic therapy. This systematic review was done to evaluate efficacy of antibiotic therapy versus no antibiotic therapy for children aged 2-59 months with WHO-defined non-severe pneumonia and wheeze. Three multi-centre, double-blind, randomised, placebo-controlled trials carried out in Malawi, Pakistan, and India, involving 3256 children with non-severe pneumonia with wheeze were included for analysis. Children were treated with a three-day course of amoxicillin or placebo. Primary outcomes were clinical cure and treatment failure while secondary outcomes were relapse, mortality and treatment harms. Antibiotic therapy resulted in no difference to clinical cure (RR 1.02, 95% CI 0.96 to 1.08; 1 trial; 456 participants; moderate-certainty evidence), relapse (RR 1.00, 95% CI 0.74 to 1.34; 3 trials; 2795 participants; low-certainty evidence) and treatment harms (RR 0.81, 95% CI 0.60 to 1.09; 3 trials, 3253 participants; low-certainty evidence). Though the results showed reduction of treatment failure by 20% (RR 0.80, 95% CI 0.68 to 0.94; 3 trials; 3222 participants) in intervention group, certainty of evidence was found to be low. So authors concluded that we do not have enough evidence to support or challenge continued use of antibiotics for treatment of non-severe pneumonia with wheeze.

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

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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. Auscultatory findings were also recorded. Fever was defined as an axillary temperature of ≥ 37.5 °C. 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 administered 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 re-recorded 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 ^ano. (%). 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 pneumonia. 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 pneumonia [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)

<i>Chest X-ray findings</i>	<i>Pneumonia</i>	<i>No pneumonia</i>	<i>Relative risk (95% CI)</i>
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.

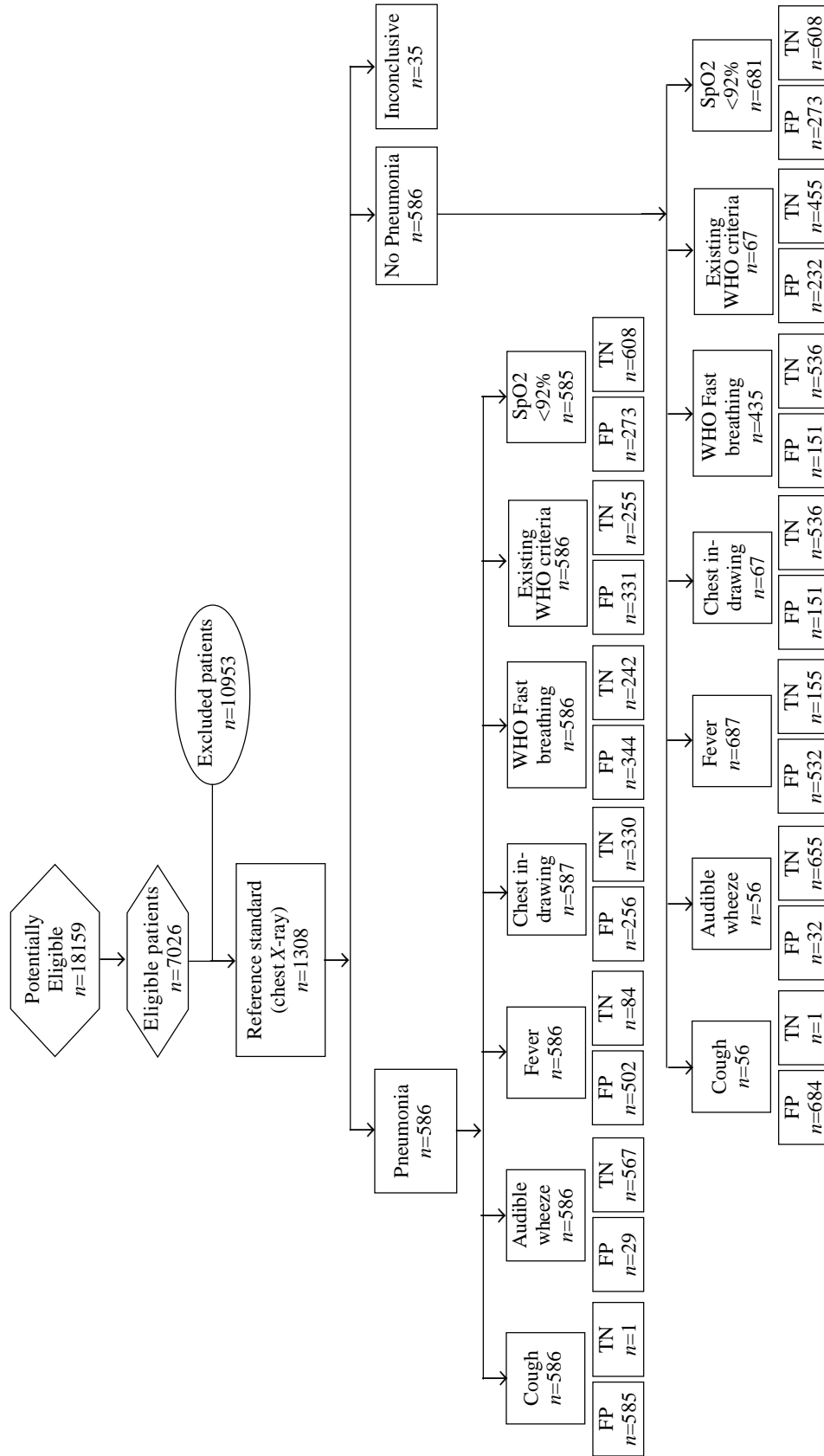


Fig. 1 Study flow chart.

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 $\leq 95\%$ 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 SpO₂ 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.

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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.

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ANNEXURE I

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

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Web Table I Diagnostic Accuracy of Different Parameters for the Diagnosis of Pneumonia Against Any Abnormality on Chest X-Ray as Gold Standard (N=1273)

Parameters	Number (n)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Post-test probability (% change) ^d
Cough	1271	99.8 (99.04 – 99.97)	0.15 (0.03 – 0.82)	1.0 (0.99 – 1.0)	1.2 (0.07 – 18.7)	-
Audible wheeze	61	4.9 (3.5 – 7.0)	95.3 (93.5 – 96.7)	1.1 (0.65 – 1.7)	0.99 (0.97 – 1.0)	-
Difficulty in breathing	254	24.1 (20.8 – 27.7)	83.5 (80.6 – 86.1)	1.5 (1.2 – 1.8)	0.91 (0.86 – 0.96)	-
Fever	1034	85.7 (82.6 – 88.3)	22.6 (19.6 – 25.8)	1.1 (1.0 – 1.2)	0.64 (0.5 – 0.81)	-
Fast breathing ^a	596	58.7 (54.7 – 62.6)	63.3 (59.7 – 66.8)	1.6 (1.4 – 1.8)	0.65 (0.58 – 0.73)	-
Chest in-drawing	407	43.7 (39.7 – 47.7)	78.0 (74.8 – 80.9)	1.9 (1.7 – 2.4)	0.72 (0.67 – 0.78)	-
Pneumonia ^b	563	56.5 (52.4 – 60.4)	66.2 (62.6 – 69.7)	1.7 (1.5 – 1.9)	0.66 (0.59-0.73)	-
SpO ₂ <92% (n=1266)	213	23.9 (20.6 – 27.5)	89.3 (86.7 – 91.4)	2.2 (1.72 – 3.0)	0.85 (0.81 – 0.9)	66% (+20%)
Existing WHO criteria + SpO ₂ <92% (n=1266)	196	22.2 (19.0 – 25.8)	90.3 (87.9 – 92.3)	2.3 (1.7 – 3.0)	0.86 (0.82 – 0.9)	66% (+20%)
Existing WHO criteria and/or SpO ₂ <92%	580	58.2 (54.2 – 62.1)	65.2 (61.6 – 68.7)	1.7 (1.5 – 1.9)	0.64 (0.57 – 0.71)	-
Chest in-drawing + SpO ₂ <92%	184	21.9 (18.7 – 25.4)	91.8 (89.5 – 93.6)	2.7 (1.9 – 3.6)	0.85 (0.81 – 0.89)	69% (+23%)
Existing WHO criteria +ve and SpO ₂ <92% ^c (n=561)	196	39.3 (34.2 – 44.6)	71.3 (65.2 – 76.7)	1.4 (1.1 – 1.7)	0.85 (0.76 – 0.96)	-

^aFast breathing as per who criteria. ^bWHO criteria for pneumonia are presence of fast breathing for age and/or chest in-drawing. ^cfirst the children were classified into pneumonia or no pneumonia according to WHO criteria as explained above; in the children who had pneumonia, SpO₂ was used to determine presence or absence of pneumonia (SpO₂<92%: pneumonia, SpO₂ ≥92%: no pneumonia). ^dPost-test probability was calculated for parameters having a LR+ of ≥ 2.0 and/or a LR- of ≤ 0.5 considering the prevalence (pre-test probability) of pneumonia to be 46% (586/1273). LR + : Likelihood ratio for positive test; LR - : Likelihood ratio for negative test

Optimizing Care-Seeking for Childhood Pneumonia: A Public Health Perspective

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Objective: This study examined the pattern of care-seeking behavior for childhood pneumonia and factors influencing it, in Madhya Pradesh (MP), Uttar Pradesh (UP) and Tamil Nadu (TN).

Methods: Using a mixed-methods design, consenting mothers of children less than 5 years with probable pneumonia participated in a household survey to assess their care-seeking behavior. A purposively selected sub-sample participated in semi-structured interviews (SSIs) to understand their perceptions on care sought, decision making abilities and cultural influences that governed these behaviors. Health care providers (HCPs) participated in SSIs and focus group discussions.

Results: A total of 2194 children were identified with probable pneumonia during the survey. 40 mothers and 41 HCPs participated in semi-structured interviews and focus group discussions. In MP, utilization of private allopathic care was high

at 74%, about 8% went to unqualified care providers. In UP, 71% went to unqualified care providers and 5% did not seek care at all. In TN, 75% went to private allopathic doctors, and utilization of government care was higher (19%) compared to MP and UP. Qualitative findings revealed that cultural beliefs coupled with poor decision making abilities, poor understanding of illness and inappropriate care-seeking practices resulted in delays in care seeking, particularly in MP and UP. Inadequacies in government health infrastructure also contributed to their poor utilization.

Conclusion: Promoting health literacy in communities and strengthening the reach of government health facilities will help in optimizing appropriate health care utilization for childhood pneumonia.

Keywords: Health literacy, Health service utilization, Respiratory tract infection.

Pneumonia contributes to about 15% of all deaths among children below 5 years of age in India and thus is a major public health problem for the country. Apart from enhancing health care infrastructure and personnel, research is also emerging regarding the care seeking behavior of families, which is a key towards formulating strategies for reducing pneumonia-related childhood morbidity and mortality [1,2]. Faith in supernatural causes, poor understanding of the disease and use of home remedies have led to delays in care seeking by families in India. In addition, poor recognition of danger signs/symptoms of pneumonia and seeking care from unqualified rural medical practitioners, have been shown to cause undue delay in care seeking by families in India [3-5]. Considering the recommendations by WHO and UNICEF [6] about the need to enhance capacities of families to seek prompt care in order to reduce mortality and morbidity from pneumonia, a deeper understanding of the socio-cultural influences that govern these behaviors and issues related to availability, accessibility and affordability of health systems are needed.

Using the Andersen and Newman framework [7] for health service utilization we examined factors influencing care-seeking behavior for childhood pneumonia in the community towards gaining insights into optimizing healthcare utilization. The framework is based on three characteristics, namely predisposing factors, enabling factors and need factors. Predisposing factors refers to culture, decision making abilities and knowledge and attitudes of individuals towards the health system. Enabling factors refers to the logistics of obtaining care. Need factors include perceived need by families- how people understand their illness -and evaluated need by health care providers - judgment about people's health status and need for medical care.

METHODS

This paper is part of a larger study [8] carried out in three districts in the states of Tamil Nadu (TN), Madhya Pradesh (MP) and Uttar Pradesh (UP) from 2016-2017. While UP and MP were chosen because of high infant mortality rate (IMR), TN served as a comparator on account of its lower IMR. The selection of districts was made following consultations with

the state health authorities and after reviewing the prevailing IMR in these districts. Probable pneumonia was defined as the presence of fast breathing with or without chest indrawing, stridor/grunt in a child <5 years of age occurring over the preceding three months [9], with the mother serving as the respondent. Considering 'not sought care' in about 30% of population [4], taking a 5% absolute margin of error and a design effect of 2, a sample size of 740 children <5 years, per state (250 per district), with probable pneumonia was obtained. From the list of health sub-centers (HSCs) in a district, 30 per district were selected using population proportionate to size method. The list of eligible children in each HSC was obtained from the field health worker and a household survey was undertaken until the desired sample size of 8 children with probable pneumonia per HSC was achieved.

Mothers consenting for participations were administered a structured questionnaire to assess their care-seeking behavior. A sub-sample of these mothers was purposively selected to participate in semi-structured interviews to understand the cultural and familial influences that governed their care-seeking behaviors. We also conducted semi-structured interviews (SSIs) and focus group discussions (FGDs) with healthcare providers (HCPs), such as doctors from the private and public sector, community health workers (CHWs) and wherever possible with untrained care providers (UCPs). State and district level governmental permissions and ethics approval were obtained by each of the respective site investigators.

Statistical analysis: Statistical analyses of the quantitative data was done using SPSS software version 16.0 (SPSS Inc). Data on type and time of seeking care was recorded as frequencies and percentages. All qualitative data were audio recorded, transcribed verbatim into (Hindi for MP and UP, and Tamil for TN), translated into English and entered into NVIVO, a qualitative analysis software. A framework analytical approach [10] was applied which began with gaining familiarity with the data through repeated readings of the transcripts. Following a careful review of the data, themes were identified, quotes were sorted and placed under

appropriate thematic categories and final interpretations were made.

RESULTS

Out of a total of 13,544 households, we identified 729, 752 and 713 children with symptoms of probable pneumonia from the states of MP, UP and TN, respectively. Forty mothers across the three states participated in the SSIs (12 from MP; 11 from UP and 17 from TN). Mothers, aged 20 to 35 years, included 10 non-literate women (4 from MP and 6 from UP). While majority were housewives, 7 were engaged in farming or casual labor (4-MP, 2-UP, 1-TN). Forty one HCPs from the three states participated, including 25 doctors from the government and 10 from the private sector. Six UCPs participated, none of whom were from TN. Thirteen FGDs were conducted with CHWs across the three states (MP-3; UP-5; TN-5).

Health service utilization: In MP, utilization of private allopathic care was highest at 74% with 12% seeking care from government health facilities (**Table I**). In UP, majority (71%) went to UCPs' with only 5% not seeking care for their child. Mothers in TN predominantly sought care from private allopathic doctors (75%). Utilization of government care was higher compared to the other two states at 19.6, but no mother reported going to a UCP. Data by district is presented in **Web Table I**. More than half the sample of mothers from each state (59%-MP, 70%-UP, 80%-TN) sought care for their child within 24 hours of symptom presentation (**Table II**). As compared to UP where 70% went to UCPs, in MP and TN, private allopathic care was the preferred choice (75% and 74%, respectively). Going to government health facilities was highest in TN at 18.9%. Data by districts is presented in **Web Table II**.

Factors influencing health service utilization: Cultural practices, either personal, or due to familial pressure, in TN, included exposing the child to incense fumes (*Sambrani*), feeding a concoction made from *Tulsi* (Basil), application of *Karpuravalli Thaillam* (oil extracted from a medicinal herb), seeking the blessings of priests and tying a sacred thread around the babies wrist or waist. However, these mothers

Table I Care-Seeking for Childhood Pneumonia in Three States in India, 2016-2017

State (no. with probable pneumonia)	Type of healthcare sought			No care sought
	Allopathic care Care from			
	Government, n=282	Private, n=1203	UCP, n=590	
Madhya Pradesh (729) ^a	89 (12.2)	541 (74.2)	57 (7.8)	42 (5.8)
Uttar Pradesh (752) ^b	53 (7)	127 (6.9)	533 (70.9)	39 (5.2)
Tamil Nadu (713) ^c	140 (9.6)	535 (75.0)	0	38 (5.3)

Data provided as no. (%). Numbers in each district: ^aBhopal-247, Panna-237, Satna-245; ^bKanpur Nagar-254, -Shravasti-267, Faizabad-231; ^cErode-149, Tirunelveli-314, Krishnagiri-250. UCP-Unqualified care provider.

Table II Health Service Utilization: Sought Care Within 24 hours in Three States in India, 2016-2017

State (no. with probable pneumonia)	Taken to health facility within 24h, n=1551	Allopathic care UCP, n=495		
		Government, n=199	Private, n=915	
Madhya Pradesh, (n=729)	428 (58.7)	57 (13.3)	357 (83.4)	10 (2.3)
Uttar Pradesh, (n=752)	530 (70.5)	30 (5.7)	99 (18.7)	395 (74.5)
Tamil Nadu, (n=713)	593 (83.2)	112 (18.9)	459 (77.4)	-

Data provided as no. (%). Row totals do not match as data was missing for 4, 6 and 22 children in MP, UP and TN, respectively. UCP - Unqualified care provider.

simultaneously sought care from qualified allopathic doctors. Beliefs in cultural and traditional practices were more prevalent in MP and UP, with mothers resorting to home remedies like use of mustard oil, *Ajwain* (carom seeds), *hing* (*Asfoetida*), *haldi* (Turmeric), for treating cough or cold. Oil massages using mustard oil and *barasingha* (a piece of deer horn that is finely ground) were believed to be effective in treatment of chest in-drawing *Jhaad phoonk* (a type of exorcism) was seen to protect the baby against the evil eye. These were usually the first steps taken by mothers when their child fell ill. If this failed, care was sought from a care provider.

Decision making: Mothers in TN reported having higher autonomy and decision-making capacity. They had the support of their in-laws and elders in the family who encouraged them to seek appropriate care for their child and would even accompany them to the hospital if required. Instances of joint decision making with the husband were also reported. On the other hand, decisions regarding care seeking in MP and UP were mostly made by family elders or husbands, with mothers usually acquiescing to such decisions. In nuclear families decisions were either made jointly by husband and wife or else only by the husband.

Enabling factors: The health system infrastructure in TN, both government and private allopathic sector, is well developed and fairly equitably distributed across the districts (**Web Table III**). Added to this, the presence of private care facilities provides rural folk with an alternative choice. In contrast, the numbers of primary health centers (PHCs) and community health centers (CHCs) in MP and UP are distinctly inadequate for their large populations. Besides Bhopal in MP and Faizabad in UP, the number of government hospitals are exceedingly low in these states. Private allopathic healthcare facilities are also few. The presence of UCPs was ubiquitous in these districts, although we do not have any reliable data on their numbers.

Our qualitative interviews with mothers revealed that in TN, both government and private care facilities were equally accessible. Preferences for private care were clearly evident with families switching between doctors depending on how well the child responded to treatment. Doctors in the private

sector were believed to be more effective, easily accessible and available till late in the evenings. They also administered injections, believed to bring about rapid cures. Further, doctors and paramedical staff in government hospitals were perceived as unfriendly providing unsatisfactory answers to queries unlike in the private sector. Despite this preference for doctors in the private sector, several mothers gave positive feedback regarding care provided in government hospitals. They described it as being affordable, accessible, of good quality and comparable to that of private facilities. Others spoke of the CHWs who made home visits and provided advice regarding the health of their child. Use of government health facilities for seeking care for children was more evident in TN as compared to the states of MP and UP.

In MP and UP, need for travelling long distances to access care in government health services, coupled with unavailability of doctors in these facilities, acted as major deterrents to care seeking. Connectivity was particularly poor in Shravasti (UP). Seeking care from the *jhola chaap* (UCP) was common in UP as compared to MP, where they were easily accessible, were cheaper than private doctors, made home visits and usually dispensed allopathic medicines. In MP, preferences for seeking care from private care providers dominated as mothers considered the money well-spent. However, we were unable to ascertain if these private care providers were qualified or unqualified. The belief that government facilities were lacking in cleanliness and competent doctors, involved long waiting time and had inadequate supply of drugs, added to the general negative opinion. Mothers in UP said that even the 24-hour government facilities did not have doctors, thereby defeating the purpose for which they were set up.

Perceived need: Regarding the 'need factor', we found that in TN mothers were unfamiliar with the term pneumonia and unaware of its cause or presenting symptoms. Although symptoms of fever, cough and cold were well understood, mothers rarely reported seeing cases of pneumonia. Only those who had sought care for treatment of pneumonia for their child or whose child had died following pneumonia had better awareness about the condition. In MP and UP, some mothers were reasonably aware of pneumonia and described

a range of symptoms. Others spoke of the importance of vaccination and cleanliness as protection against pneumonia, indicating satisfactory awareness about the disease. If the child's cold and cough was perceived to be very heavy, it was referred to as 'double pneumonia'. Some, while unfamiliar with the term, were nevertheless aware of symptoms like chest indrawing and appreciated the need to seek care for its treatment. Others subscribed to the traditional belief that children were at risk for contracting pneumonia if they had "cold in their bodies" as compared to "heat". Difficulties in recognizing severity of illness were also expressed.

Evaluated need: In TN, the HCPs stated that though awareness about pneumonia was poor in the community, the ability to recognize symptoms of respiratory distress in the child was adequate, which influenced timely and appropriate care seeking. They believed that there was not much delay in care seeking among families and as a back-up, families kept paracetamol syrup and nasal drops at home for use in case of such symptoms occurring. Doctors in the government sector appreciated the sustained health literacy efforts provided by CHWs during antenatal visits. They also credited government run school health programs for increasing health literacy among mothers. Although there was a trend of preferring private over government facilities, especially during an emergency for reasons of faster accessibility, for regular care, families would go to government facilities. According to the CHWs, negative beliefs about the poor quality of health care and long waiting time in the government hospitals influenced many to seek care from the private sector, even at great financial cost. Seeking care for their child from UCPs however, was not reported. In MP, care providers in the government sector, felt that awareness about pneumonia in the community was good perhaps due to its high prevalence. They felt that it was rare for families not to seek care however, the type of care sought was not always appropriate and often delayed due to use of home remedies and magico-religious practices. The CHWs said that many poor families chose to seek care from UCPs who were easily accessible, dispensed allopathic medicines and gave injections. Physicians, both public and private, agreed that there was a preference for private over government care because of the distances involved in accessing these facilities and because doctors in government hospitals were not always available. They also said that decision making concerning care-seeking for children remained with the elders of the household or with the woman's husband. The HCPs in UP felt that, awareness about pneumonia was poor and care was sought only when symptoms became serious. Resorting to home remedies was usually the first step. The CHWs said that the easy availability of UCPs combined with the faith people had in them influenced people's preferences

for them. They also spoke of people's preferences for private care as against government care as it was believed to be better and more prompt. In addition, women's dependence on their husbands or elder members in their household to make decisions on care-seeking contributed to delays in care-seeking.

DISCUSSION

Three key findings emerge from our study. Firstly, cultural beliefs, color attitudes and practices, which coupled with poor understanding of illness and their appropriate treatment seem to delay care seeking. Secondly, women, particularly in MP and UP have poor decision making capabilities contributing to delays in appropriate care seeking. Thirdly, inadequacies in the number and infrastructure of primary health-care facilities have created a negative impression regarding their effectiveness and quality in MP and UP resulting in their poor utilization. Although government health infrastructure and its utilization are better in TN, the preferred choice of care was still the private care provider.

Cultural beliefs regarding use of home remedies for child care in India are deeply venerated, have been practiced for generations and play an important role in the lives of most Indian families. Earlier studies [2,3,11], too have described their use in the management of symptoms of pneumonia. In our study this was evident in the states of MP and UP where home remedies and magico-religious practices were often the first and only steps adopted by mothers towards management of symptoms of probable pneumonia. In TN, resorting to home remedies was much less and usually done alongside of allopathic care. Early care-seeking practices in TN can be explained by better awareness promoted by effective educational messages provided by the government health facilities specifically the CHWs. Other studies [12] too have demonstrated the role of the lady health worker in bringing about better health literacy among mothers regarding newborn care. Adedokun, et al. [13] reported that increased exposure to mass media resulted in greater utilization of health care services. In addition to highlighting the value of seeking care within 24 hrs of symptom presentation, health messages need to be simple, easy to remember and must be constantly reiterated to ensure their better retention.

The findings from our study that mothers from MP and UP had little to no role in decision-making concerning care-seeking for their child has been corroborated by other studies [14,15]. A study from Nigeria [16] described two scenarios leading to negative consequences: when fathers had no role in child rearing mothers did not have support for their decision making and when mothers were restricted in movements and social interactions they did not seek timely and appropriate care. In contrast, mothers from TN, in our

WHAT THIS STUDY ADDS?

- Strengthening government health infrastructure and its reach, improving health literacy targeting communities, families and mothers will optimize health care utilization.

study, had more autonomy in decision-making regarding child care and were better informed due to the information provided by the CHWs and other health personnel resulting in timely and appropriate allopathic care for their children. Health care from UCPs was not sought and home remedies if used, were always alongside allopathic care. These findings underscore the value of women's empowerment in the context of child care.

The presence of a good network of well equipped, functioning, and well-connected health care facilities in the government sector in TN has significantly contributed to their better utilization as well as towards a more positive attitude towards them unlike what was observed in MP and UP. Chandwani and Pandor [17] highlighted the lack of accountability among HCPs, and poor credibility of the public health facilities as reasons contributing to their poor utilization. Further, respondents from MP and UP had to contend with poor road connectivity to access government health facilities and frequently with non-availability of doctors and medicines which served as major deterrents to their use. The under-utilization of public sector health-services as observed in MP and UP, is well acknowledged in resource poor countries [18,19]. The private health sector on the other hand, has shown remarkable growth and utilization, attributable to its easy access, availability of adequate health personnel and medicines [20]. Given the high cost of care that the poor are forced to bear, a coordinated effort to strengthen government health systems in terms of both availability and accessibility of manpower and appropriate treatment will greatly improve health care utilization in this sector.

In terms of limitation, our study could perhaps have benefited from interviews with family members, who play a critical role in decision-making for seeking care

To conclude, government health facilities in UP and MP are under-utilized, a feature that could be addressed if infrastructure is strengthened and facilities made more accessible. With UCPs proliferating in these states, these would be critical steps to attract appropriate care seeking. Secondly, promoting health literacy using simple easy to follow messages among families including mothers will be another important strategy considering the key role family members play in decision making. These could help optimize care seeking for childhood pneumonia.

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Note: Additional material related to this study is available with the online version at www.indianpediatrics.net

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Web Table I Health Service Utilization- Type of Care Sought by Districts in Three States in India, 2016-17

District	Cases of probable pneumonia	Allopathy		Unqualified care providers	Not sought care
		Government	Private		
<i>Madhya Pradesh</i>					
Bhopal	247	26 (10.5)	172 (69.6)	39 (15.8)	10 (4.0)
Panna	237	28 (11.8)	181 (76.4)	16 (6.8)	12 (5.1)
Satna	245	35 (14.3)	188 (76.7)	2 (0.8)	20 (8.2)
<i>Uttar Pradesh</i>					
Kanpur Nagar	254	19 (7.5)	69 (27.2)	160 (63.0)	6 (2.4)
Shrawasti	267	23 (8.6)	13 (4.9)	212 (79.4)	19 (7.1)
Faizabad	231	11 (4.8)	45 (19.5)	161 (69.7)	14 (6.1)
<i>Tamil Nadu</i>					
Erode	149	28 (18.8)	111 (74.5)	0	10 (6.7)
Tirunelveli	314	64 (20.4)	244 (77.7)	0	6 (1.9)
Krishnagiri	250	48 (19.2)	180 (72.0)	0	22 (8.8)

Values in no. (%).

Web Table II Health Service Utilization- Sought Care Within 24 hours by Districts in Three States of India, 2016-17

District/ State	Cases of probable pneumonia	Taken to health facility within 24 h	Allopathy		Unqualified care providers	Not sought care
			Government	Private		
<i>Madhya Pradesh</i>						
Bhopal	247	172 (69.6)	21 (12.2)	142 (82.6)	7 (4.1)	0
Panna	237	116 (48.9)	14 (12.1)	101 (87.1)	1 (0.9)	0
Satna	245	140 (57.1)	22 (15.7)	114 (81.4)	2 (1.4)	2 (1.4)
<i>Uttar Pradesh</i>						
Faizabad	231	175 (75.8)	7 (4.0)	36 (20.6)	128 (73.1)	4 (2.3)
Shravasti	267	169 (63.3)	14 (8.3)	7 (4.1)	148 [87.6]	0
Kanpur Nagar	254	186 (73.2)	9 (4.8)	56 (30.1)	119 [64.0]	2 (1.1)
<i>Tamil Nadu</i>						
Tirunelveli	314	262 (83.4)	55 (21.0)	205 (78.2)	0	2 (0.8)
Krishnagiri	250	234 (93.6)	46 (19.7)	168 (71.8)	0	20 (8.5)
Erode	149	97 (65.1)	11 (11.3)	86 (88.7)	0	0

Values in no. (%).

Web Table III Health System Infrastructure in Study Districts in Three States of India, 2016-17

<i>Districts</i>	<i>Population^a</i>	<i>PHC</i>	<i>CHC</i>	<i>Govt. hospitals</i>	<i>Private hospitals</i>
<i>Madhya Pradesh</i>					
Panna	1016520	14	6	1	13
Satna	2228935	44	8	11	22
Bhopal	2368145	9	3	41	100
<i>Uttar Pradesh</i>					
Faizabad	2470996	33	6	46	6
Kanpur Nagar	1794184	31	6	2	40
Shravasti	1117361	12	6	1	3
<i>Tamil Nadu</i>					
Krishnagiri	1879809	46	10	11	36
Tiruneveli	3322644	70	19	14	110
Erode	2251744	68	14	8	139

^aas per Census of India, 2011. PHC: primary health center, CHC: community health center.

Web Box 1 Selected Quotes from Focused Group Discussions of Mothers of Children With Pneumonia and Healthcare Providers*Predisposing Factors*

Cultural beliefs We don't follow any of the Siddha or Ayurvedic medicines. We take only what is given in the hospital. I don't believe in all that because I am scared that it might produce side effects or harmful effects. All those primitive methods are not followed nowadays. Everyone goes to the hospital for treatment... though we are uneducated, we know this (Krishnagiri -TN).

I gave oil massage for 8 days. In the village everybody said to get 'jhad phookh' done, the child would be cured. We went to 'maulna hakim'.he did 'jhad phookh' but the 'pasli chalna' (chest in-drawing) did not get better. Then we saw 'ki pasli bohat tez chal rahi hai' (fast breathing) and was not getting better so we took him to another doctor. (Shravasti-UP)

We believe exorcism helps...it helps in improving the health of the baby. We give dhuni to the baby where he is exposed to smoke from this burning wood. Recently when he fell sick, we took him to a healer who did jhaad phoonk where holy ash is blown over the baby. (Bhopal- MP)

Decision-making

They don't expect me to get permission from them. My husband has never accompanied me to the hospital. If my children fall sick, I take them.... They will scold me only if I fail to take the children to hospital. (Krishnagiri- TN).

My husband only takes all the decisions. Usually he [husband] decides about going to the doctor and I do not go against him or suggest otherwise because if something happens to the baby or she does not get relief then everyone will say you told this that's why she was not relieved (Faizabad- UP)

Mother in law takes decision regarding yasodha (child). Father in law is not there. If husband is available then he also takes. I also say my opinion (Satna- MP).

Enabling factors

If the baby doesn't recover then we take him to a private hospital. If we go to government hospital (GH) for treatment, baby is not recovering.... If we go for treatment of phlegm GH is good. But for fever, it is not good. Though we give medicine... they don't put injection. They give only tonic. No result in giving tonic. So we go to a private hospital (Erode-TN)

They take money in private but they do proper check-up. In government there is only one doctor or none. Keep standing in the queue such that the child gets serious. There should be good doctors and good medicines should be available. And if patients go then they should be properly heard and checked. (Satna- MP)

Here at the crossroads of our village there is a jholachaap, who else would be found here! This is close for us and where we have been benefited we will go there only (Shravasti-UP).

Need factors

Perceived need (community perspective):

If he has phlegm and runny nose, he will start to develop fever. At that time itself I will keep in mind that this should not escalate, I will be careful. My child also tends to become weak after the fever. So looking at all this I will take him to the government hospital immediately. (Tirenelveli-TN)

Usually when my child has cold, hot fomentation will be done, if not cured then a village doctor comes then we consult him. When he had panjar (chest in-drawing), I applied oil and did hot fomentation for 1-2 days. When it didn't get relieved then we took him to the doctor. Firstly we consulted here in the village to the 'jhola chhap doctor' (quack), and then took child to private doctor. (Shravasti-UP)

Whenever we feel something, we apply balm and give syrup which is kept at home so she gets better. If she doesn't get better with home remedy then we take her to the doctor. I don't go outside the house so how do I ask the ASHA or the ANM. I take her to the doctor only when it is serious. (Panna-MP)

Evaluated need (health care provider perspective):

Even when the baby has cold, they bring the baby. And when the baby is making Karrrrr sound. Even when there are no symptoms or signs also.... when they feel like there is some sound.... They bring the patient. (PHC MO, Krishnagiri-TN)

They do Jhaad phoonk, in the name of God. They do oil massage and keep them under the sun. R: They give home remedies like asafoetida, turmeric mixed in warm milk etc so that the child gets relief. R: Sometimes the child's condition deteriorates as they take the child to untrained doctors. First they worsen the condition and then they tell us that we have given many medicines but there is no relief. (FGD CHWs, Satna- MP)

When the child is unable to breathe, they come to us mostly in that condition. Yes they keep them at home only, they give the child oil massage at home, they go to the quacks and to magico-religious healers.If the fever is not high enough they don't consider it as fever.. (Private Doctor, Faizabad- UP)

Risk Factors for the Development of Pneumonia and Severe Pneumonia in Children

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Objective: To identify the risk factors for pneumonia and severe pneumonia in children.

Design: Prospective cohort study.

Setting: Five tertiary-care teaching hospitals in India.

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

Main outcome measures: Risk factors for the development of WHO defined pneumonia and severe pneumonia.

Result: A total of 18159 children screened, and 7026 (39%) children with ARI were enrolled. According to the WHO criteria, 938 (13.4%) and 6088 (86.6%) of the enrolled children had

pneumonia and no pneumonia, respectively. Out of 938 children with pneumonia, 347 (36.9%) had severe pneumonia. On univariate analysis, younger age, male gender and low weight for height, were significant risk factors for pneumonia. On multivariate analysis, one-unit increase in age in months (OR = 0.97; 95% CI: 0.97-0.98) and weight for height z-score (OR = 0.76; 95% CI: 0.72-0.79) had a protective effect.

Conclusions: Young age and undernutrition (low weight for height/length) in children are significant independent risk factors for pneumonia.

Keywords: Acute respiratory infection treatment unit, Under nutrition.

Acute respiratory infections (ARI) are the most common cause of morbidity and mortality in children under five years of age. WHO estimate indicates 156 million new cases of pneumonia occurring annually worldwide in under-five children, with 95% of these occurring in developing countries [1,2]. Pneumonia accounts for 15% of all deaths in under-five children globally [3].

It is important to understand the risk factors of pneumonia at the global, regional, and national levels. Identification of risk factors is important for enhancing insight into the etiology of pneumonia, prevention, and adequate and timely diagnosis [4,5].

There is a wide variation in the risk factors for pneumonia in the published studies. Most of the studies for risk factors of pneumonia were hospital-based and represented only a small proportion of pneumonia cases. Few studies had focused on the risk factors that were associated with progression to severe or very severe pneumonia [6-8].

The identified risk factors for childhood pneumonia are undernutrition, incomplete immunization, use of solid fuels in

the household, over-crowding, lack of exclusive breastfeeding, low degree of maternal education, and limited access to secondary care. These risk factors are characteristics of low socioeconomic status and are inter-related. However, due to the linear relation of these risk factors, it is difficult to estimate their individual risk [9]. To study this problem, we conducted a large multi-center prospective study to determine the risk factors for the development of pneumonia and severe pneumonia in under-five children.

METHODS

This multi-centric study was part of a large prospective cohort study that was designed to develop acute respiratory infection treatment units (ATUs) and assess their utility in improving healthcare and research in pneumonia-related morbidity and mortality in India. The study was carried out at the following five different sites in India: *i*) Sher-e-Kashmir Institute of Medical Sciences (SKIMS), Srinagar; *ii*) All India Institute of Medical Sciences (AIIMS), Jodhpur; *iii*) All India Institute of Medical Sciences (AIIMS), Bhubaneswar; *iv*) Karnataka Institute of Medical Sciences (KIMS),

Hubbali; and v) MP Shah Medical College, Jamnagar. All India Institute of Medical Sciences, New Delhi, was the coordinating center for the study. Ethical clearance was taken from the institutional ethical committees from all the study sites.

Previously healthy children of either gender, 2 months to 59 months of age attending the Pediatrics outpatient department were recruited over 24 months (June, 2016 to May, 2018), with ARI – defined as any cough and/or breathing difficulty, for less than 2 weeks [10]. Children with any of the following were excluded from the study, a) Patients with chronic respiratory diseases (such as asthma, cystic fibrosis, bronchopulmonary dysplasia, airway anomalies), diagnosed in a health care facility; b) Patients with congenital heart disease (suspected based on the history of the suck-rest-suck cycle and cyanosis) – confirmed by echocardiography or presence of murmur; c) Patients with GER/ recurrent aspirations (based on the history of choking or coughing while feeding or barium swallow/GER scan); d) Known or suspected HIV positive/ immunocompromised patient – based on the history of recurrent, documented multisite infection or on immunosuppressive therapy; e) Place of residence outside the city where the study site is based; f) Unable to attend follow up; g) History of radiologically confirmed pneumonia in the last 2 months; h) Terminally sick children - impending respiratory failure, cyanosis at room air and shock.

The study was initiated after clearance by the respective Ethics Committees of all five study sites. All children who fulfilled the case definition of ARI [10], were enrolled in the study after written informed consent from parents or legally authorized representative. Children were assessed for a history of cough or breathing difficulty by counting respiratory rate and presence of chest indrawing by a trained study staff nurse under the supervision of the doctor. A detailed clinical history and examination findings of the enrolled patient were recorded on a pre-designed case record form before any radiological investigation. An X-ray film of the chest was obtained in every fifth child assessed to have ARI.

The outcome variable was the diagnosis of pneumonia defined by WHO criteria [11] as cough or difficulty breathing and age-specific tachypnea (>60 breaths per minute for children less than 2 months of age, >50 breaths per minute for children 2-11 months of age and >40 breaths per minute for children 1-5 years of age). Severe pneumonia was defined as oxygen saturation <90%, severe respiratory distress, inability to drink or breastfeed or vomiting everything, altered consciousness, and convulsions [11]. Variables examined as risk factors were age, gender, nutritional status, and immunization status.

Statistical analysis: Data were recorded on a pre-designed proforma and managed on an Excel spread-sheet. All the entries were double-checked for any possible typographical error. Data analysis was performed using STATA 11.0 (STATA Corp). Categorical variables were analyzed using both absolute and relative frequencies; continuous variables were analyzed based on the median. Pearson chi-square and Fisher exact tests were used to compare the categorical variables. Numerical variables were analyzed using the nonparametric Mann-Whitney U test. The odds ratio with 95% CI were calculated for risk factor for pneumonia which were identified as those with $P \leq 0.05$ in the univariate analysis. They were selected for inclusion in a stepwise forward logistic regression model to determine the significant independent risk factors for pneumonia. z-scores for weight and height for age were calculated using WHO Anthroplus software [12].

RESULTS

A total of 18159 children were screened, and 7026 (39%) children (4251 boys) with ARI were enrolled. Among them, 938 (13.4%) and 6088 (86.6%) had ‘pneumonia’ and ‘no pneumonia’, respectively, and 347 of the 938 (36.9%) children had severe pneumonia. The median (IQR) age of the enrolled children was 23 (10,40) months with baseline characteristics shown in (Table I).

The risk factors for pneumonia were evaluated as seen in (Table II). On multivariate analysis one-unit increase in age in months (OR = 0.97; 95% CI: 0.97-0.98) and weight for height (OR = 0.76; 95% CI: 0.72-0.79) led to a decreased odds of developing pneumonia. Therefore, younger age and low weight for height were considered as an independent risk factor for pneumonia. In the case of Hib vaccination, positive vaccination history increased the odds of developing community acquired pneumonia.

The risk factors for developing severe pneumonia were evaluated in univariate analysis (Table III).

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

Characteristics	Values
Weight for age, z-score ^a	-0.69 (-1.83, 0.35)
Height/length for age, z-score ^a	-0.76 (-2.36, 0.77)
Weight for-height, z-score ^a	-0.29 (-1.14, 0.53)
Mid-upper arm circumference, z-score ^a	-1.47 (-2.13, -0.8)
Cough	6995 (99.6)
Fever	3998 (56.9)
Audible wheeze	512 (7.3)
Fast breathing ^b	715 (10.2)
Chest indrawing	478 (6.8)

All values are n (%) or ^amedian (IQR). ^bas per WHO criteria.

DISCUSSION

In this multi-center prospective cohort study across five sites in India, younger age and low weight-for-height z-score were independent determinants of pneumonia.

Younger children were more prone for pneumonia possibly because of a relatively immature immune system in younger children [13,14]. Male gender was found to be significantly associated with pneumonia in univariate analysis, but not in multivariate analysis. Similar findings were reflected in the earlier study [15,16]. It may be because males are more vulnerable to pneumonia and are given more preference for hospitalization. Females may have a greater resistance due to their enhanced Th1 immune response [17]. Undernutrition is a significant risk factor for the development of pneumonia in children [18] as also seen by us. Undernutrition is associated with secondary immune deficiency and an increase in the risk of infections, including pneumonia [19,20].

Vaccination with Hib reduces the incidence of pneumonia in children [21], unlike the results of the present study. The possible reason may be the higher number of viral pneumonia than bacterial pneumonia in the present study as the etiology of pneumonia was not investigated. Pneumococcal and influenza vaccines are also associated with a decrease in the incidence of pneumonia [22,23]. In view of very few children immunized with these vaccines in this study, we were not able to find any significant association with these vaccines.

The major strength of this study was that it was a multi-centric study and conducted in the different geographic areas of the country with large sample size. This study has several limitations. First, children who did not have ARI were not compared. Second, some potential risk factors like exposure to smoking, indoor environment, use of cooking fuel were not studied. Moreover, X-ray chest was not done in all enrolled patients.

We conclude that younger and malnourished children are at increased risk of developing pneumonia. Further studies are required from developing countries considering host factors, etiology, including viral causes, and the effect of vaccination to understand the risk factors for pneumonia and severe pneumonia in children. At the same time, it is also important to address undernutrition in children, to reduce pneumonia-related mortality, and ensure their growth and development.

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Ethics clearance: Permission number AIIMS/IEC/2017/301; date 15/09/2017.

Contributors: JPG, PK: involved in data collection and manuscript writing; AM, RL: involved in development of protocol, supervision of study, data analysis; RRD, JIB, VR, BV: data collection, manuscript review and final approval of study.

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Table II Risk Factors Associated With Development of Community-Acquired Pneumonia

Characteristics	No pneumonia n=6088	Pneumonia n=938	P value ^a	OR (95%CI)	P value ^b
Age (mo) ^c	24 (11, 42)	15 (8, 25)	<0.001	0.97 (0.97, 0.98)	<0.001
Boys, n (%)	3655 (60.0)	596 (63.5)	0.04	1.12 (0.97, 1.29)	0.13
Weight for height/length z-score ^c	-0.24 (-0.99, 0.56)	-0.77 (-1.96, 0.3)	<0.001	0.76 (0.72, 0.79)	<0.001
<i>Vaccination, n=5687</i>					
Influenza, n (%)	15 (0.31)	4 (0.48)	0.51		
Pneumococcal, n (%)	15 (0.31)	6 (0.72)	0.07		
<i>H. influenzae</i> , n (%) ^b	3781 (77.9)	681 (81.7)	0.01	1.81 (1.53, 2.13)	<0.001

Community-acquired pneumonia defined as per World Health Organization guideline. ^aUnivariate analysis; ^bMultivariate analysis.

Table III Risk Factors Associated With Severe Community-Acquired Pneumonia

Characteristics	Pneumonia n=591	Severe pneumonia n=347	P value ^a	OR (95%CI)	P value ^b
Age, mo	16 (8, 28)	12 (7, 24)	0.001	0.99 (0.98, 0.99)	0.04
Male, n (%)	374 (63.8)	222 (63.9)	0.83	1.03 (0.78, 1.36)	0.82
Weight for height/length z-score	-0.98 (-2.2, 0.26)	-0.46 (-1.48, 0.33)	0.001	1.12 (1.04, 1.21)	0.002

Values are median (IQR) unless specified. ^aUnivariate analysis; ^bMultivariate analysis.

WHAT IS ALREADY KNOWN?

- Undernutrition, younger age, lack of immunization are well-known risk factors for community-acquired pneumonia

WHAT THIS STUDY ADDS?

- Risk factors for community-acquired pneumonia are reiterated through a large multi-centric study.

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ANNEXURE I**Acute Respiratory Infection Treatment Unit Study Group:**

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Predictors of Mortality in Neonatal Pneumonia: An INCLEN Childhood Pneumonia Study

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Background: Neonatal pneumonia contributes significantly to mortality due to pneumonia in the under-five age group, but the predictors of mortality are largely unknown.

Objective: To evaluate the clinical and microbiological characteristics and other risk factors that predict mortality in neonates admitted with pneumonia in tertiary care centres.

Study design: Prospective observational cohort study.

Participants: Term and preterm (32 weeks to 36^{6/7} weeks) neonates (<28 days of life) admitted with clinical and radiological features suggestive of pneumonia.

Intervention: Baseline sociodemographic data, clinical details, blood culture and nasopharyngeal swabs for virologic assay (RT

PCR for RSV, Influenza) were collected at admission and the neonates were observed throughout their hospital stay.

Outcome: The primary outcome was predictors of mortality in neonatal pneumonia.

Results: Five hundred neonates were enrolled in the study. Out of 476 neonates with known outcomes, 39 (8.2%) died. On multivariate analysis, blood culture positive sepsis was independently associated with mortality (adjusted OR 2.51, 95% CI 1.23 to 5.11; *P*-0.01).

Conclusion: Neonates with blood culture positive pneumonia positive are at a higher risk of death.

Key words: Burden, Early onset sepsis, Outcome, Risk Factors.

With a mortality rate of 37/1000 live births, India ranks among the top five nations with high under five mortality rates. Neonatal mortality, comprising 60% of under-five mortality, is markedly higher than that in any high-income group country [1]. Neonatal sepsis, the third most common cause of neonatal deaths, has a significant impact on long term neurodevelopment. Neonatal pneumonia alone accounts for 2% (0.136 million) of under-five mortality in children in the world [2].

Though the incidence of neonatal sepsis among NICU admissions in our country is reported to be 14.3%, the occurrence of neonatal pneumonia and the factors predicting mortality are not well studied [3-7]. Ventilator associated pneumonia is common among preterm, low birth weight or mechanically ventilated newborns [7]. In this study, we evaluate the clinical and microbiological characteristics and other risk factors that predict mortality in term and preterm (32 to 36^{6/7} weeks) neonates admitted with pneumonia, in tertiary care public sector pediatric hospitals, catering predominantly to outborn neonates.

METHODS

This multi-centre, prospective, cohort study, conducted in two tertiary level public sector hospitals, included neonates having tachypnea, respiratory distress (chest retractions/grunting) and evidence of pneumonia on chest X-ray [8]. Neonates having meconium aspiration syndrome, or respiratory distress developing within first 2 hours of life and improving within 12 hours of life or those with major congenital malformations or those admitted for >24 hours in another hospital or received antibiotics prior to admission, were excluded. Nodular or coarse, patchy non-homogenous infiltrates, air broncho-gram, lobar, multi lobar or segmental consolidation were considered as radiological evidence of pneumonia. Eligible infants were enrolled after obtaining consent from either parent. Blood culture and nasopharyngeal aspirates was taken at admission and case details, clinical course and the outcome data were recorded in a predesigned proforma. The clinical staff were trained to interpret X-rays and the diagnosis was made by the resident involved in study, was confirmed by a

consultant, and the neonates were managed as per standard treatment guidelines [9]. Echocardiography was done only when clinically indicated.

The primary outcome was predictors of mortality in neonatal pneumonia. Predictors evaluated included socio-demographic factors, maternal age, maternal fever, parity, mode of delivery, the clinical features at admission [10] and during the course of hospitalization as well as microbiological characteristics of the isolates. The secondary outcomes included overall blood culture positivity rate in neonatal pneumonia, the distribution of microbiological causes, the need for higher respiratory support and complications of pneumonia.

To ensure quality, the microbiological samples were processed at a NABL accredited laboratory with an active external quality assessment program. Apart from this, the unusual bacterial organisms and fungal isolates were confirmed using MALDI TOF assay at another NABL accredited laboratory. Further, interlab comparison of 10% of all positive and negative viral isolates were done. All data collected were cross-verified by the site investigators periodically.

Assuming a 10% prevalence of any of the predictors, an odds ratio of 2.5 for mortality and a mortality rate of 8% in neonatal pneumonia [11], the number of babies expected to die due to pneumonia was 121. To realize this target, 1500 neonates needed to be enrolled. In view of the slow recruitment and time constraints, an interim analysis was done on the data until June 2019 (353 neonates were enrolled till then) and using the proposed predictors, the sample size was revised to 606. Nasopharyngeal swabs were also collected from 100 healthy term neonates to look at the pattern of asymptomatic viral colonisation.

The study was approved by the individual ethics committees of the participating hospitals.

Statistical analysis: Comparison of categorical variables was done by Chi square test, while continuous variables were compared using Student *t*-test. Risk ratio along with 95% CI was presented. Univariate and multivariate binary logistic regression analysis was performed to test the association between possible risk factors and outcome variables. Variables with statistical significance (*P* value <0.1) in univariate analysis were used to compute multivariate regression analysis. Adjusted odds ratio with 95% CI was calculated, taking *P* value <0.05 as statistically significant. All statistical analysis was done on IBM SPSS version 22.

RESULTS

Out of a total of 915 eligible neonates, 500 were enrolled (Fig. 1). The mean (SD) birthweight of the neonates was

2635.16 (533) g with 8 (1.6%) being very low birthweight (VLBW). The mean (SD) gestational age was 37.29 (1.9) weeks, with 130 (25%) being preterm. Most of the families (52%) belonged to upper lower socioeconomic class followed by lower middle socioeconomic class (41.7%). Out of 476 neonates with known outcomes, 39 (8.2%) died. The comparison of parameters between surviving and non-surviving neonates is shown in Table I. There were significantly higher proportions of VLBW and preterm neonates in the non-surviving group, compared to survivors.

Onset of symptoms occurred at a mean of 5.6 days of life in the neonates who died, compared to 12.5 days in those who survived [mean difference 6.9 (95% CI 3.7, 10); *P*<0.001]. The most common presenting symptom was difficulty in feeding seen in 219 (46%) neonates, followed by fever, noted in 110 (23%) of the neonates. The most common sign was tachypnea, mean (SD) respiratory rate being 63.7 (6.8) breaths per minute and the median Silverman Anderson score at admission was 4 (IQR 3,6). At admission, 302 (60%) neonates required oxygen, with 143 (28%) being started on CPAP, and 55 (11%) requiring intubation. The comparison of clinical features and course between surviving and non-surviving neonates is shown in Table II

While blood culture positivity rate was significantly higher among neonates who died, viral isolates in the nasopharynx was significantly higher among survivors,

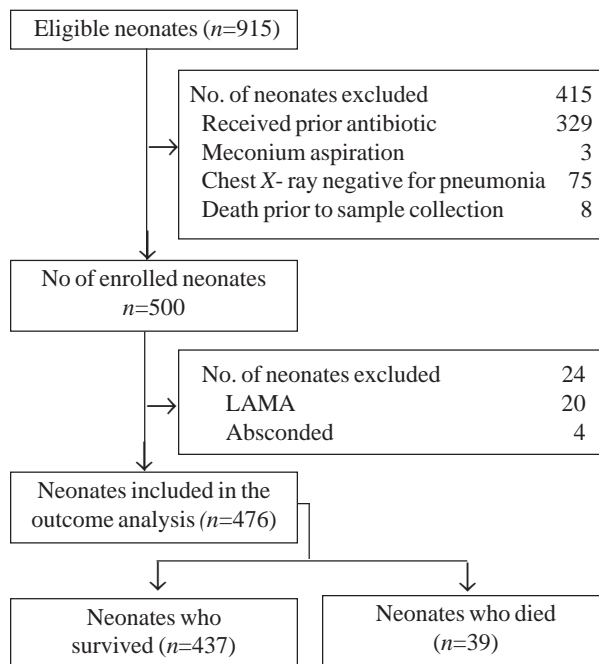


Fig. 1 Study flow chart.

Table I Comparison of Sociodemographic, Antenatal and Birth Parameters Between Surviving and Non-Surviving Neonates

Parameters	Non-survivors (n=39)	Survivors (n=437)	Relative risk (95%CI)
Birthweight (g) ^{a,e}	2403 (622)	2639 (515)	235.6 (63.4, 407.8) ^c
Birthweight ≥1500 g ^e	3 (7.7)	5 (1.1)	6.29 (1.88, 21.07)
Gestational age (wk) ^a	36.72 (2.69)	37.29 (1.93)	0.88 (0.77, 1.01)
Preterm birth	16 (41.0)	111 (25.4)	1.91 (1.04, 3.50)
Male gender	32 (82.0)	331 (75.7)	1.42 (0.65, 3.14)
Vaginal delivery	21 (53.8)	218 (49.9)	1.14 (0.61, 2.14)
Primigravida mother	38 (97.4)	382 (87.4)	4.99 (0.69, 36.32)
Antenatal visits ^b	4 (3,4)	3 (3,4)	0.95 (0.76, 1.19)
Maternal fever ^d	1 (2.6)	11 (2.5)	1.07 (0.15, 7.79)
Apgar score (1 min) ^b	5 (5,5)	5 (5,5)	0.81 (0.54, 1.19)
Apgar score (5 min) ^f	8 (8,8)	8 (8,8)	0.65 (0.47, 0.89)
Weight at admission (g) ^{a,e}	2382.44 (628.47)	2691.68 (569.66)	309.12 (120.6, 497.6) ^c
Age at admission (h) ^{a,e}	136.46 (173.07)	301.67 (232.74)	165.2 (90.03, 240.3) ^c
Hospital stay ^{a,g}	5.9 (6.8)	7.81 (5.6)	1.9 (-0.02, 3.84)

Values in n (%),^amean (SD) or ^bmedian (IQR). ^cmean difference (95% CI). ^dmaternal fever within 1 week prior to delivery. ^eP<0.001, ^fP=0.007, ^gP=0.05.

RSV B being the most common. (Table III). Overall blood culture positivity rate was 19.2%, Gram negative organisms were isolated in 45 (47%) and Gram-positive organisms in 23 (24%) neonates. *Klebsiella* was the commonest organism isolated and was seen in 22 neonates (23%). While 27 (28%) neonates showed fungal growth with *Candida species*, 190 (38%) neonates were positive for viral PCR. Among 100 healthy term neonates, 7 were found to have asymptomatic viral colonisation (Influenza B – 5, H1N1 – 1, both influenza A and B -1)

On multivariate analysis, positive blood culture (adjusted OR 2.51, 95% CI 1.23 to 5.11; P=0.01) emerged as the independent predictor of mortality in neonates with pneumonia.

DISCUSSION

In this study the mortality rate due to neonatal pneumonia was found to be 8.2%. The blood culture positivity was an independent predictor of mortality, though the type of organism did not affect mortality. The mortality rate is less than that reported (12%) in the multicenter national neonatal perinatal database report [11]. In the DeNIS cohort [3] though the overall blood culture positivity among neonates with pneumonia was almost similar to our study (15% vs 19%, respectively), the mortality rate was lower (45% vs 16%, respectively) and was probably due to differences in inclusion criteria and the higher prevalence of multidrug resistant organisms. In the present study, 50% of the bacterial isolates were Gram negative, *Klebsiella* being the commonest organism

reflecting community prevalence. On the other hand, two-third of the culture positive isolates were Gram negative in DeNIS study, *Acinetobacter* being the commonest isolate [3]. *Streptococcus pneumoniae*, increasingly found in possible serious bacterial infections (pSBI) among young infants, has been reported to contribute to mortality [12]. However, we did not isolate any *S. pneumoniae*, possibly due to inherent difficulty in isolating in blood cultures and the need for additional techniques. The overall microbiological yield was 53%, which is double than that reported in community-acquired serious bacterial infections [12].

The incidence of community-acquired fungal pneumonia in our cohort, confirmed by molecular diagnosis (MALDI TOF), was very high (25% of culture positive), compared to other studies [3,12], although this did not translate into higher mortality. This is intriguing as none of the neonates received any antibiotic nor were admitted in any hospital prior to enrolment.

The viral positivity rate in our study (38%) was similar to that of a community-based surveillance study (42%) involving infants with respiratory illness from Bangladesh, but neonatal pneumonia constituted only 11% in their cohort [13]. Several hospital based studies in neonates, from Asia, have reported 30% incidence of viral lower respiratory tract infections, especially due to RSV [14]. The in-hospital case fatality rate of viral pneumonia was 0.2% which is significantly lower than the reported incidence in LMIC countries [5-3% (95% CI 2-8 to 9-8)] possibly due to

Table II Comparison of Clinical Features and Course of Illness Between Surviving and Non-Surviving Neonates and Survivors

Parameters	Non-survivors (n=39)	Survivors (n=437)	Relative risk (95%CI)
Cough	2 (5.13)	65 (14.87)	0.34 (0.08, 1.40)
Running nose (cold)	1 (2.56)	38 (8.7)	0.29 (0.04, 2.15)
Fever	7 (17.95)	103 (23.57)	0.73 (0.32, 1.66)
Breathing difficulty	33 (84.62)	398 (91.08)	0.58 (0.25, 1.39)
Apnea ^b	5 (12.82)	14 (3.2)	3.35 (1.31, 8.57)
Cold to touch ^c	7 (17.95)	26 (5.95)	2.99 (1.32, 6.79)
Vomiting	4 (10.26)	32 (7.32)	1.43 (0.51, 4.02)
Diarrhea	0	6 (1.37)	-
Feeding difficulty	22 (56.41)	197 (45.08)	1.53 (0.81, 2.88)
Seizures ^b	8 (20.5)	33 (7.6)	2.74 (1.26, 5.97)
Movement only with stimulation ^b	10 (25.64)	46 (10.53)	2.58 (1.26, 5.29)
Heart rate >180/min	4 (10.26)	46 (10.53)	0.96 (0.34, 2.71)
SAS score ^{a,b}	5 (4, 6)	4 (3,5)	1.278 (1.054, 1.550)
Grunting	26 (66.67)	226 (51.72)	1.77 (0.91 to 3.45)
CFT>3 seconds	5 (12.82)	48 (10.98)	1.19 (0.47, 3.04)
Temp >37.5 °C	4 (10.2)	101 (23)	0.40 (0.16, 1.03)
Temp <36.5 °C	4 (10.26)	17 (3.89)	2.48 (0.88, 6.99)
Cyanosis ^c	8 (20.51)	16 (3.66)	4.71 (2.16, 10.24)
SpO ₂ < 90%	23 (59)	205 (46.9)	1.56 (0.84, 2.88)
Bulging anterior fontanelle	2 (5.13)	23 (5.26)	0.91 (0.22, 3.78)
Lethargy	18 (46.15)	150 (34.32)	1.56 (0.83, 2.94)
Abdominal distension ^b	6 (15.38)	22 (5.03)	2.95 (1.24, 7.05)
Hepatomegaly	4 (10.26)	51 (11.67)	1.19 (0.47, 3.04)
More than one skin pustule	1 (2.56)	1 (0.23)	6.55 (0.90, 47.73)
<i>Respiratory support at admission</i>			
Oxygen ^d	14 (35.9)	272 (62.24)	0.37 (0.19, 0.69)
Intubation ^c	16 (41.03)	38 (8.7)	6.28 (3.06, 12.86)
CPAP	9 (23.08)	127 (29.06)	1.36 (0.6, 3.14)

Values in (%) or ^amedian (IQR). ^bP<0.01; ^cP<0.001; ^dP=0.002. CPAP: continous positive airway pressure; SAS: Silverman Anderson score.

Table III Comparison of Microbiological Parameters Between Surviving and Non-Surviving Neonates

Parameters	Non-survivors (n=39)	Survivors (n=437)	Relative risk (95%CI)	P value
Blood culture positive	15 (38.4)	78 (17.8)	2.63 (1.38 - 5.01)	0.003
Gram positive	2 (5.1)	20 (4.5)	0.52 (0.12 - 2.25)	0.38
Gram negative	8 (20.5)	38 (8.7)	0.49 (0.06 - 3.71)	0.49
Fungal	5 (12.8)	20 (4.5)	1.46 (0.41 - 5.12)	0.56
Viral PCR positive	4 (10.3)	177 (40.5)	0.18 (0.06 - 0.525)	0.001
RSV B	3 (7.7)	118 (27)	0.24 (0.07 - 0.79)	0.01

Values in n (%). RS: respiratory syncytial virus.

better management in tertiary care centers [15]. Moreover, neonates with viral pneumonia had higher body weight and presented at a later age in the neonatal period, which could possibly explain better outcome., The most common viral

isolate in the present study was RSV, consistent with the global burden, but unlike the usual pattern, type B strain was dominant, which could be another reason for better survival [14-16].

WHAT IS ALREADY KNOWN?

- Predictors of mortality in neonatal pneumonia are largely unknown.

WHAT THIS STUDY ADDS?

- Blood culture positivity independently predicts mortality in neonatal pneumonia.
- High prevalence of RSV B and *Candida* was seen in neonatal pneumonia.

The symptoms and signs used in our study were similar to those in integrated management of neonatal and childhood illness (IMNCI) and young infant study [17,18]. Though they have been shown to predict the occurrence of pBSI, our data failed to show their association with mortality.

The strength of our study was the use of a very strict case definition, which, to the best of our knowledge, is the first and largest of its kind. The limitation of the study was the inability to enroll the originally planned 1500 neo-nates, due to logistic constraints. Other etiological agents like *Mycoplasma*, *Chlamydia*, and *Pneumococcus* requiring special techniques for isolation, were not evaluated. The investigators involved in the interpretation of X-rays were not blinded to clinical features.

In conclusion we found blood culture positivity in neonatal pneumonia as an independent predictor of mortality. The role of fungus in community acquired neonatal pneumonia needs further exploration and there is need to be vigilant and consider early antifungal therapy especially in those who do not seem to respond. The high incidence of viral pneumonias in our study emphasizes the need to consider nasopharyngeal swab in the neonatal pneumonia work up. Vaccination against RSV immediately after birth may be a potential strategy to lower the burden of neonatal pneumonia. [19]

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Ethics clearance: (i) Ethics committee of Osmania medical college, Hyderabad; Reg No ECR/300/Inst/AP/2013 Date of approval June 23, 2015; (ii) Ethics committee of Gandhi Medical college, Hyderabad, ECR/180/Inst/AP/2013- October 13, 2015; and (iii) Ethics committee of Fernandez hospital, Hyderabad; ECR/933/Inst/TG/2017 – December 09, 2015.

Contributors: SK, SS, SM, JVR, MB: involved in the conception, design of the project; SK,SS,SM were also involved in data analysis, drafting of manuscript; MB, SP, NPB: designed and

conducted the microbiological aspects of the study; HS, AM, SL, SB, BN: involved in case enrolment and supervision. All the authors were involved in critical appraisal and have reviewed and approved the manuscript.

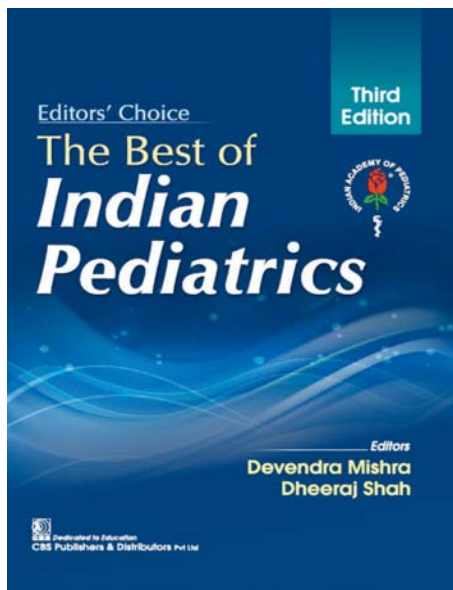
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Effect of Behavior Change Communication on the Incidence of Pneumonia in Under Five Children: A Cluster Randomized Controlled Trial

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Background: Improving health education of the mother by providing community-based interventions is known to help control pneumonia.

Objective: To determine the effect of behavior change communication (BCC) activities for mothers in reducing the incidence of childhood pneumonia.

Design: Open-label cluster randomized controlled trial.

Setting: Urban slums and villages in two districts of Maharashtra.

Participants/Cluster: Under-five children and their mothers from households in the randomly selected 16 clusters out of total 45 clusters, stratified into Pune and Sangli districts and further into rural and urban areas before randomization.

Intervention: Three forms of BCC activities were imparted, viz., interactive sessions of education using pictorial mothers' booklet,

screening of a audio-visual film, and virtual hand wash demonstration and use of flashcard. Routine care under the National health program was provided by the Accredited Social Health Activists (ASHA) workers in both the arms.

Outcome: The primary outcome was pneumonia as per the IMNCI criteria assessed during fortnightly visits of the ASHA/anganwadi workers to the houses of under-five children, who received at least one follow-up visit in a period of one year.

Results: The incidence of pneumonia in 1993 and 1987 under-five children in the intervention and control arm was 0.80 and 0.48 episodes per child per year, respectively ($P=0.03$).

Conclusion: BCC for mothers is not sufficient to reduce the incidence of childhood pneumonia.

Keywords: Community intervention, Health education, Mothers, Surveillance.

Trial Registration: CTRI/2017/12/010881

Pneumonia is one of the commonest cause of under-five mortality [1] with estimates showing that 23% of global pneumonia cases (around 43 million cases) occur in India annually [2,3]. Lack of exclusive breastfeeding, under-nutrition, low birth-weight, overcrowding, lack of immunization and poor healthcare-seeking behavior are a few of the leading risk factors for pneumonia in India and other low and middle-income countries (LMICs) [4,5]. Only one in five caregivers in the developing world know the two key symptoms of pneumonia -fast and difficult breathing [6,7]. One of the recommended critical activities in WHO's and UNICEF's Global Action Plan for the Control of Pneumonia and Diarrhea is improving health education of the mother by providing community-based interventions (CBI) [8,9]. Our study was conducted to determine the effect of behavior change communication (BCC) activities directed at mothers in reducing the incidence of childhood pneumonia.

METHODS

An open-label cluster randomized control trial was conducted between December, 2015 and March, 2018 in Pune and Sangli districts of Maharashtra in the urban and rural field practice area of two medical colleges. Approval was obtained from institutional ethics committee, and written consent from the mothers was obtained prior to the enrolment.

Based on the reported incidence of childhood pneumonia of 0.2-0.5 per child per year in under-five children [10], and assuming the coefficient of variation (k) to be 0.4, the sample size was calculated as 15 clusters. The study enrolled sixteen clusters to cover for unforeseen eventualities precluding the BCC activities in any cluster.

A cluster was defined as one of the 45 notified slums or revenue villages in the field practice area of the two medical colleges. The 45 eligible clusters were first stratified into two

districts, further into urban and rural clusters, urban clusters were stratified based on the East or West. The rural clusters were stratified based on the primary health center (PHC). These clusters were then randomized into intervention and control arms, based on a computer-generated randomization schedule and two clusters per site were randomly selected, thus 16 clusters were included. Participants were under-five children and their mothers from the households in the selected clusters (Web Fig.1).

Families residing for more than six months with under-five children were included in the study. All the under-five children and their mothers (including expectant mothers) were enrolled as study participants. Fig. 1 shows the participant flow diagram. The new births were enrolled throughout the trial period ensuring that they receive at least nine months of surveillance. We excluded those children who completed five years of age during the surveillance period from further visits. All the children who had received at least one follow-up visit were analyzed. The literacy status of the mother was reported as per the census definition [11]. Ventilation status of the house was assessed using the availability of per capita floor space [12]. Due to the nature of the intervention provided, allocation concealment and masking were not possible after randomization.

The total study period included the following phases: preparatory (2 months), baseline survey and enrollment (3 months), intervention (4 months), and surveillance (12 months).

The components of the BCC activities for the mothers in the intervention arm consisted of imparting knowledge about

child feeding, including the importance of feeding of colostrum, exclusive breastfeeding till six months of age, gradual introduction of food from the age of six months, causes of malnutrition among children, the importance of taking weight and plotting of growth charts in anganwadi; imparting knowledge about steps to prevent pneumonia in their children, such as complete immunization, prevention of indoor air pollution, the practice of cough etiquettes; hand hygiene including occasions and steps of hand wash; and, providing information about the signs and symptoms of pneumonia.

The BCC intervention was administered by trained field supervisors to an invited group of 8-10 mothers at a time, in an interactive manner using a validated mothers' booklet, and a hand wash demonstration. The second BCC activity was imparted by screening an audio-visual film for a larger group of 15-20 mothers and virtual hand wash demonstration. These two BCC activities were separated by a gap of two months. ASHAs and anganwadi workers were involved in planning and coordinating the BCC activities, thereby ensuring maximum cooperation of the mothers. The third BCC or continued intervention, through the house-to-house visit, was done three months after the second BCC activity by using flashcards. A total of eight trained field supervisors were involved in imparting the BCC activities, under supervision of the site investigators. Routine care under the national health program was continued in both the arms of the study.

The primary outcome was the incidence of pneumonia. Trained doctors confirmed the episode of pneumonia using

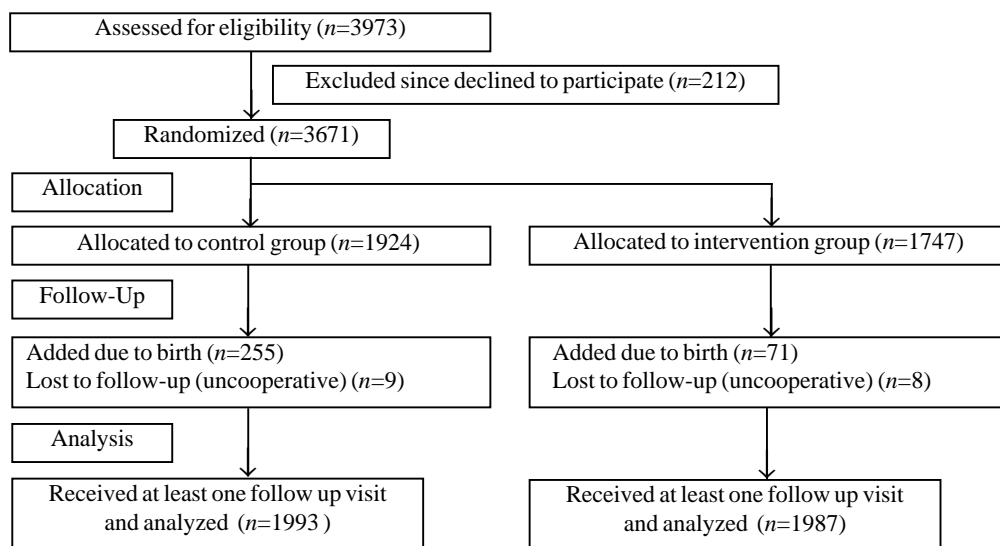


Fig. 1 Study flow chart.

WHO Integrated management of neonatal and childhood illnesses (IMNCI) guidelines [13]. The outcome was assessed by fortnightly visits conducted for one year by the respective ASHAs of each cluster, except in Pune (urban), where anganwadi workers enquired about the current status of the child's health from the mother during the house-to-house surveillance visits. For labeling a new episode of pneumonia in the same child, a symptom-free period of a minimum of 14 days was considered essential, otherwise, it was presumed to be continuation of the preceding episode [14]. Besides, information about other illnesses and death among under-five children was collected by the field supervisors.

Quality checks were done randomly by site investigators and field supervisors. Site investigators conducted once-a-week field visits or as and when a case of pneumonia was suspected. For data entry, the critical fields in the tools were identified as a proxy to completeness and accuracy – discrepancy up to 0.1% and 1%, respectively were considered acceptable. Additionally, alternate forms were physically cross-checked for discrepancies related to data entry.

Statistical analysis: Intention to treat analysis was done to analyze the incidence of pneumonia (as episodes per child per year follow-up) in the intervention and control arm. The relative risk was calculated to compare the incidence between two arms. *P* value <0.05 was considered statistically significant.

RESULTS

Sixteen clusters were randomly selected out of the 45 clusters, eight were in the intervention arm, and eight were in the control arm i.e., four in each urban and rural area of the two districts. The under-five children enrolled in the intervention arm were 1747 (20.1% aged <1 year) and in the control arm 1924 (20.8% aged <1 year) (**Fig. 1**). A total of 39 391 fortnightly follow-up visits were conducted in intervention and 40 288 in the control arm during one year. Baseline household and other demographic characteristics were similar between the arms except for higher unclean fuel use in control arm (20.1% vs 10.3%; *P*<0.05). Information related to the child was obtained from the mothers i.e., exclusive breast feeding for children between 6-12 months, primary immunization for children between 12-24 months, birthweight for children up to 6 months of age etc., hence the denominators varied as per the number of mother-child in that group (**Table I**).

There were a total of 5505 episodes of illnesses in the intervention arm and 6436 episodes in the control arm. Of these, there were 44 and 31 episodes of pneumonia in the intervention and control arm, respectively, constituting an

Table I Baseline Characteristics of Households and Under-Five Children Enroled in the Study

Characteristics	Intervention arm <i>n</i> =1448	Control arm <i>n</i> =1374
<i>Household characteristics</i>		
Joint family	871/1448 (60.2)	812/1373 (59.1)
Hindu religion	1278/1448 (88.3)	1166/1374 (84.9)
SC/ST caste	387/1448 (26.7)	333/1374 (24.2)
Literate mother	1295/1367(95.7)	1334/1413(94.4)
Overcrowding ^a	906/1444(62.7)	839/1371 (61.2)
Inadequate ventilation ^b	1349/1408 (95.8)	1289/1315 (98.0)
Smoking indoor	33/1442 (2.3)	52/1368 (3.8)
Unclean fuel ^c	149/1448(10.3)	277/1374(20.2)
<i>Child characteristics</i>		
	<i>n</i> =1747	<i>n</i> = 1924
Male sex	925/1747(52.9)	1014/1924(52.7)
Age (y) ^d	2.38 (1.36)	2.39 (1.37)
Birthweight (kg)	2.51 (0.61)	2.72 (0.60)
	(<i>n</i> =293)	(<i>n</i> =371)
Received colostrum ^e	313/330 (94.8)	333/370 (90.0)
Exclusive breast-feeding till 6 mo	86/172 (46.0)	111/249 (44.4)
Fully immunized ^f	309/335 (92.2)	296/304 (97.4)
<i>Nutritional status of the child^g</i>		
Wasting	295/1678 (17.5)	309/1852 (16.7)
Stunting	720/1685 (42.7)	916/1878 (48.8)
Undernutrition	565/1693 (33.3)	694/1864 (37.2)

Date presented as number/total number (%). ^aNumber of family members per room criteria was used; ^bInadequate ventilation was defined as households with less than 100 sq. ft. of floor area per person with, or without a fan; ^cUnclean fuel included biomass, coal stove, stove with kerosene for cooking purposes for most of the days of the week by the household; ^dThis information was collected from mothers of infants upto one year of age only to remove the possibility of recall bias, and the intention was to assess the most essential i.e., primary immunization; ^eInformation was analyzed for infants between >6 mo to one year of age only; ^fImmunization information was analyzed for children with cards and aged between 12-23 months. ^gWHO classification was used; results presented for <-2SD. Child characteristics are based on children enrolled during baseline phase only.

incidence of 0.80 and 0.48 episodes of pneumonia per child per year, respectively in the two arms [RR (95% CI) 1.66 (1.05-2.62); *P*=0.03]. Three children in the intervention and two in the control arm had two episodes each. There was no case of severe pneumonia and very severe disease. Twenty-six (59.1%) episodes in inter-vention arm and 21 (67.7%) episodes in control arm were reported in boys [RR (95% CI) 0.87(0.62-1.23); *P*=0.77]. For 93.2% of pneumonia episodes in the intervention arm, children were taken to the health care provider as the first action, in contrast to 54.9% from the control arm [(RR (95% CI) 5.06 (2.58 to 9.92); *P*<0.001)] (**Table II**). None of the children required hospitalization for pneumonia in both the arms. There were two deaths reported in each study arm, unrelated to pneumonia. The number of pneumonia episodes was highest in the winter season (51%).

Table II Episodes of Common Illnesses in the Intervention and Control Groups

Illnesses/action taken	Intervention arm, n=1747		Control arm, n=1924		RR(95% CI)	P value
	Number of episodes	Incidence (per child per y)	Number of episodes	Incidence (per child per y)		
Total illness episodes documented/total visits	5505/39391	13.98	6436/40288	15.97	—	—
Pneumonia	44	0.80	31	0.48	1.66 (1.05 to 2.62)	0.030
Cold/cough	2738	49.74	2770	43.0	1.15 (1.11 to 1.20)	<0.001
Diarrhea	128	2.32	242	3.76	0.62 (0.50 to 0.76)	<0.001
Vomiting	52	0.94	88	1.37	0.69 (0.49 to 0.97)	0.03
Contacting a HCP ^a	41/44	-	7/31	-	5.06 (2.57 to 9.92)	<0.001

Symptoms were assessed from mothers of the children, only pneumonia was diagnosed using IMNCI criteria. ^aContacting a health care provider as a first action taken in case of pneumonia episodes.

Out of all the episodes of illness, diarrhea contributed to 2.32 and 3.76 episodes per child per year in the intervention and control arm, respectively ($P < 0.001$).

DISCUSSION

Our study shows that the incidence of all illnesses taken together, was significantly less with BCC intervention. The low incidence of pneumonia in both the arms of the study was comparable to that reported in South East Asian countries [10,13]. This low incidence may reflect the fact that Maharashtra has better health indicators, compared to other states of India [14]. A three-year follow-up study completed in 2008 in a Southern state of India reported an incidence rate of 0.4 (95% CI=0.3-0.7) in its first year [15]. However, the incidence of pneumonia in the current study was higher in children less than one year of age compared to those in 1-5 year age group, similar to the findings reported by other studies [16,17].

Like other studies, the fortnightly follow-up visits in the current study, for one calendar year, took into account the seasonal variation in the incidence of pneumonia [18,15]. Possibly, a more extended follow-up period or revisiting the clusters after a gap of two years might be required to observe benefits from these activities on health outcomes [19]. Though the WHO IMNCI tool for confirming pneumonia lacks specificity, it is the best measure of reporting pneumonia in children under five years of age [20]. The possibility of overdiagnosis of pneumonia by non-physician healthworkers was addressed by confirmation of these episodes by an expert. The seasonal trend of pneumonia in the current study was similar to those reported by other studies [15,21,22].

The care-seeking pattern for illness was similar in both groups with the commonest healthcare provider contacted being private practitioners. These findings are similar to other studies in India [23-26]. The current study reported

fewer hospital admissions for pneumonia compared to other studies in India [15]. It may be due to early case detection and ambulatory management of pneumonia. Another study from India had concluded that trust in the public health system is essential for making the community-based pneumonia management program successful [27].

The overall morbidity and diarrheal episodes during follow-up were less than other studies in India [20]. The incidence of pneumonia was slightly higher in the intervention than the control arm, probably reflecting higher reporting by mothers about illness episode in their children in the intervention arm than in the control arm. There were significantly fewer diarrhea episodes in the intervention arm than in the control arm.

The current study has the potential for generalizability as the community health workers i.e., ASHA and anganwadi workers, were involved in surveillance visits. Routinely, ASHA and Anganwadi workers deliver incentive-based maternal and child health - related work, but in this trial, they received surveillance-related training, enabling them to timely identify sickness in a child as recommended by WHO [28]. It also helped to gain cooperation from mothers and other family members. However, external validity is limited to states with similar health parameters. BCC may be valuable in states with high under-five mortality, but further studies need to be conducted in these states. The limitation of the present study was a relatively short follow-up duration, which may be inadequate to observe the impact of BCC activities.

BCC alone is unlikely to be effective for the reduction of the incidence of pneumonia. The reduction in the incidence of pneumonia is influenced by factors such as economic status, birthweight, overcrowding, joint family, type of fuel, etc. So, intervention in the form of BCC activity may need support of additional strategies to reduce the incidence of pneumonia.

WHAT IS ALREADY KNOWN?

- Behavior change communication (BCC) interventions, alongwith efforts towards improving the immunization status of children and breastfeeding promotion, are documented to be efficient, cost-effective, and sustainable interventions in reducing the burden of childhood pneumonia.

WHAT THIS STUDY ADDS?

- BCC intervention alone, aimed towards mothers, was not found to be sufficient to reduce the incidence of pneumonia in under-five children.

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Contributors: JG, PD, PP, GD, SL: conceptualization; JG, PP, GD: data curation; JG, PP, GD, PD: formal analysis; JG, SK, PD: funding acquisition; JG, PD, PP, GD: methodology; JG, GD, PP, SP: project administration; SL, JG, PD: resources; PP, VW: software; SQ, SM, RP, VW, RD, KR, SP: supervision; JG, PD, SL: validation; JG, PP: writing – original draft preparation; JG, PD: Writing – review and editing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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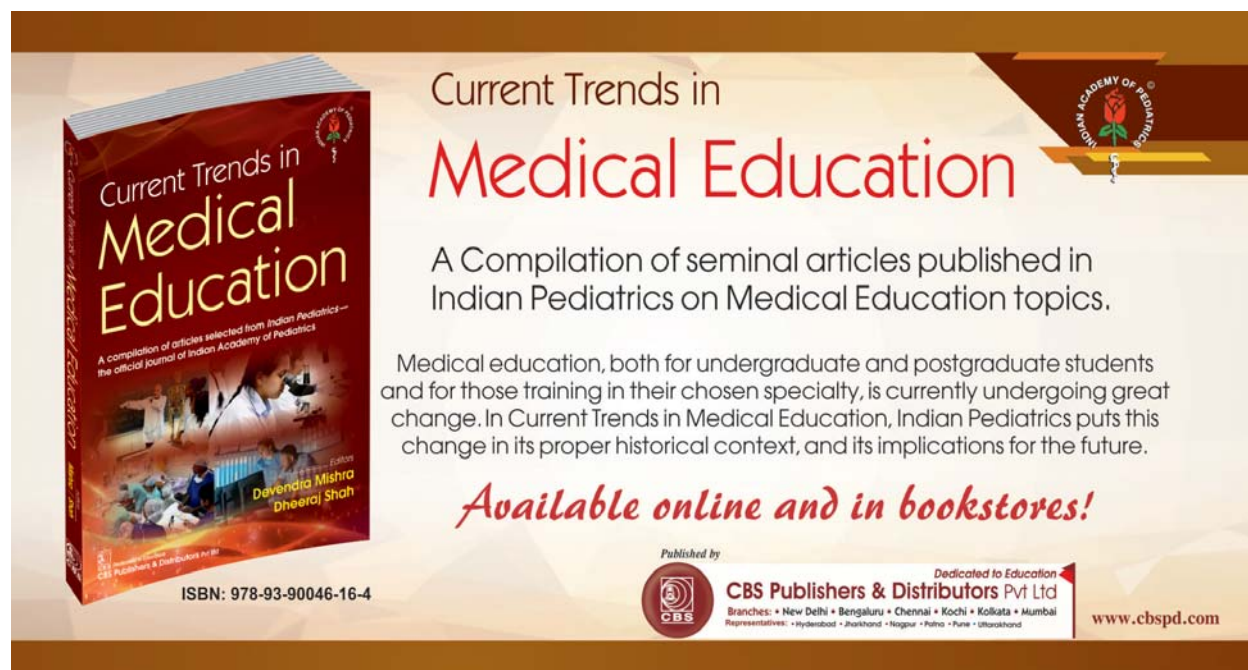
Note: Additional material related to this study is available with the online version at www.indianpediatrics.net

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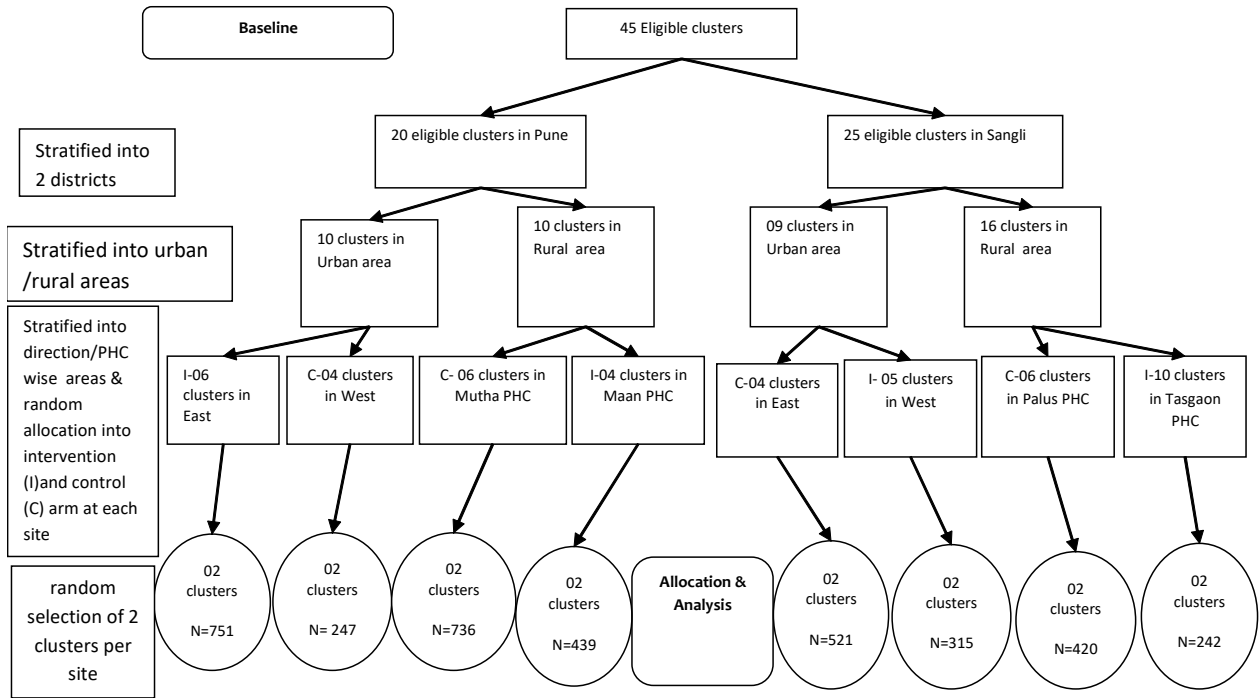
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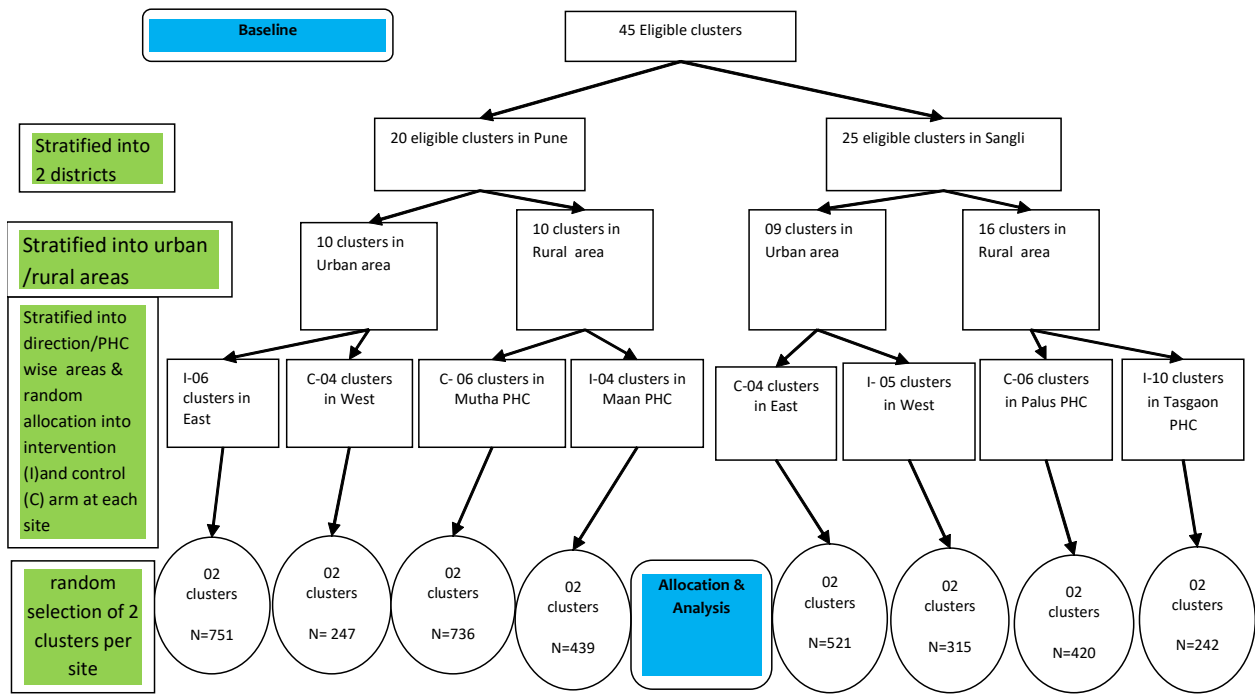
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Web Figure 1 Cluster flow diagram



Web Figure 1 Cluster flow diagram

Diagnosis and Assessment of Severity of Pediatric Pneumonia Using the Respiratory Index of Severity (RISC) Scoring System

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Objectives: To evaluate the correlation between the Respiratory Index of Severity (RISC) scoring system and the World Health Organization (WHO) interpretation of chest radiographs, and to evaluate the RISC scoring system in the diagnosis and assessment of severity of pneumonia in children against chest X-ray. **Methods:** 241 children presenting to a tertiary care center with a clinical diagnosis of pneumonia that necessitated a chest radiograph to be taken, were enrolled. The RISC scoring was done for all participants by a single pediatrician and chest X-ray graded by a single radiologist as per the WHO interpretation of chest radiographs. **Results:** There was a statistically significant positive correlation ($P=0.02$) between the two scores. RISC score of >1 had a sensitivity of 80.3%, and score ≥ 3 had a specificity of 88.3%, positive predictive value of 61.3% and negative predictive value of 76.8% for diagnosis and to predict severity of pneumonia. **Conclusion:** In a resource-limited setting, RISC scoring can be used to diagnose and predict the severity of childhood pneumonia.

Keywords: Community-acquired pneumonia, Severity, X-ray chest.

The Respiratory Index of Severity (RISC) scoring was formulated in South Africa to provide a standardized means of quantifying severity of respiratory illness among children during epidemiologic studies [1]. This score has a negative score for wheezing, which potentially excludes children with wheezing, a probable drawback of the Integrated Management of Childhood Illness (IMCI) developed by the World Health Organization (WHO).

The gold standard for diagnosis of pneumonia is the chest X-ray (CXR). In an attempt to improve the consistency of CXR interpretation between epidemiological studies, the WHO standardized the interpretation of CXRs for the diagnosis of pneumonia in children [2,3]. The CXR interpretation exercise was done and validated under WHO [4]. If the RISC scoring system correlates well with CXR, this scoring system could be of use in resource-poor settings where CXR is not routinely available. The aim of the study was to evaluate the correlation between the RISC scoring system and the WHO interpretation of chest radiographs. It also aims to evaluate the RISC scoring system in the diagnosis and assessment of severity of pneumonia in children by validating it against the CXR.

METHODS

This descriptive study was undertaken at a semi-urban tertiary care hospital in India from 1 February, 2018 to 31 July,

2018. The study was approved by the institutional ethics committee and informed consent from parents was taken prior to enrollment. Consecutive patients aged 1 month to 12 years, who visited the pediatric OPD and/or got admitted in the pediatric ward with a clinical diagnosis of pneumonia by the treating doctor, and which necessitated a chest radiograph to be taken, were enrolled for the study. Exclusion criteria were subjects with documented congenital heart disease, chronic respiratory illness, congenital lung problems, immunosuppressive conditions or known to have neuromuscular disorders with respiratory system involvement.

For calculation of sample size, prevalence of lower acute respiratory infection was taken as 28% [5]. At significance level of 5%, with 20% relative precision, and power of the study 80%, sample size was calculated as 240. To allow for potential recruitment failure rate, 285 children were assessed for eligibility for enrollment in the study.

A detailed history was taken and respiratory system examination done for all subjects, and RISC scoring for HIV non-infected children [1] was done by the principal investigator. Variables in the RISC score represent known risk factors for severe outcomes of pneumonia in children, with a maximum score of 8 points.

CXR scoring was done by a single radiologist, as per the WHO interpretation of chest radiographs [2,4].

Statistical analysis: Analysis was done using Spearman rho (\bar{r}) correlation to assess the correlation between RISC score and WHO CXR score. We divided the children into two groups by using the WHO CXR score of 3 (lobar pneumonia on X-ray) as a cut off. Group A with CXR score <3 were clinically suspected by physician but CXR was not suggestive of pneumonia, and group B with CXR score \geq 3, clinically suspected by physician and also CXR suggestive of pneumonia. By plotting the receiver operating characteristic (ROC) curve, we calculated specificity and sensitivity to determine the appropriate RISC score to diagnose and predict the severity of pneumonia. Analysis was done by Statistical Software Package for Social Sciences Version 23 (SPSS 23)

RESULTS

A total of 285 children with physician-diagnosed pneumonia were assessed for eligibility to be enrolled in the study (**Fig. 1**). Out of these, 20 were excluded based on exclusion criteria and 18 were excluded as a CXR was not taken/available. A total of 241 children were finally included in the study.

Baseline clinical characteristics are presented in **Table I**. Of the study subjects 34 (14.1%) had a RISC score \geq 3 and 61 (25.3%) had a CXR score \geq 3.

There was a statistically significant positive correlation between RISC score and WHO CXR score ($r=0.144$, $P=0.025$). The ROC curve was plotted (**Fig. 2**). Taking WHO CXR score of \geq 3 (lobar pneumonia score 3) as severe pneumonia, a RISC score of >1 had a sensitivity of 80.3% and specificity of 26.1%, suggesting it is a moderate screening test for pneumonia. A RISC score of \geq 3 had a sensitivity of 21.3% and specificity of 88.3% for diagnosis and to predict severity of pneumonia (**Table II**).

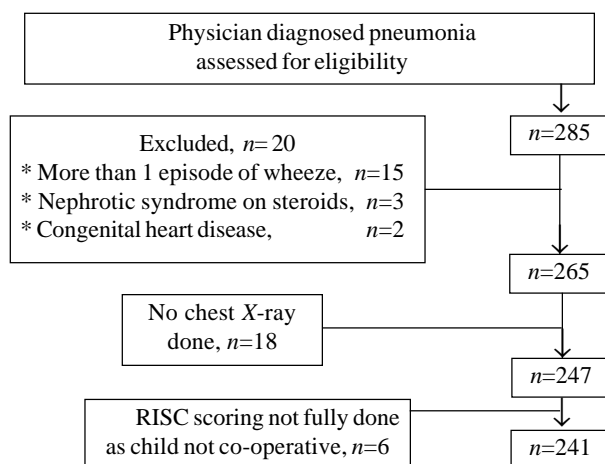


Fig. 1 Study flow chart.

Table I Clinical Profile, Respiratory Index of Severity (RISC) score, and Chest X-ray Score of Children With Physician-Diagnosed Pneumonia (N=241)

Characteristics	No (%)
Male	142 (58.9)
Age	
1mo-1 y	96 (39.8)
1y-5y	112 (46.5)
5-12 y	33 (13.7)
Symptoms	
Fever	205 (85)
URI symptoms	223 (92)
Breathlessness	40 (16.5)
Feed refusal	219 (90.8)
Immunization as per NIS	239 (99.2)
Disease severity based on treatment	
Outpatient treatment	90 (37.3)
Admission as inpatient	140 (58.1)
Pediatric intensive care unit admission	11 (4.6)
CXR score	
1	141 (58.5)
2	39 (16.1)
3	42 (17.1)
4	16 (6.5)
5	3 (1.2)
RISC score	
1	59 (24.6)
2	148 (61.2)
3	6 (2.5)
4	26 (10.9)
\geq 5	2 (0.8)

URI-Upper respiratory tract infection.

DISCUSSION

There are hardly any scoring systems which are validated for community-acquired pneumonia (CAP) in Indian children that would have high utility in resource-limited settings. We demonstrated a statistically significant correlation between RISC scoring system [1] and the WHO interpretation of chest radiographs [2].

Limitations of the study were that RISC score is not useful to differentiate between types of pneumonia based on etiology. RISC score is not useful to monitor resolution of symptoms. A negative score for wheeze (-2) may encourage false negatives. When developing detection tests, a balance must be chosen between risks of false negatives and false positives.

The major scoring systems designed to predict mortality risk and serve as guides for admission in community-acquired pneumonia (CAP) are for adults [6], and such scores

WHAT THIS STUDY ADDS?

- In a resource-limited setting, where chest X-ray is unavailable, RISC scoring can be used for diagnosing and predicting the severity of community-acquired pneumonia.

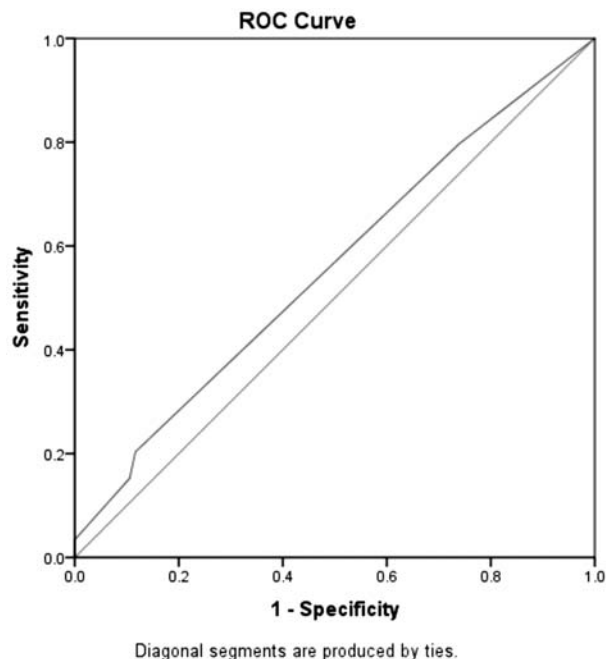


Fig. 2 ROC curve for Respiratory Index of Severity (RISC) scoring system in pediatric pneumonia.

for children are scarce [7,8]. Only the modified predisposition, insult, response and organ dysfunction (PIRO) score has so far been applied to children with CAP [6]. We used the RISC score for our study as it has six predictors for assessing the severity of pneumonia (hypoxia, chest indrawing, feed refusal, wheeze, malnutrition, age) and is easy to administer. Other risk models [9,10] are relatively cumbersome to administer.

The WHO introduced the Integrated Management of Childhood Illness (IMCI) to standardize and improve treatment and thus prevent major causes of death in children <5 years [10]. The first drawback of IMCI diagnostic criteria is of over-diagnosing pneumonia by including children with wheezing. In our study too, 36.5% of patients had a wheeze on presentation. However, the RISC scoring system overcomes this by giving a negative score for wheezing. The second drawback of IMCI is a missed diagnosis, as it has a low sensitivity [11,12].

Hooli, et al. [13] did an external validation of RISC by calculated classification performance measures at thresholds of 3 and 4. Using a RISC score of 3 had a

Table II Test Characteristics of the Respiratory Index of Severity (RISC) Score (N=241)

Characteristics ^a	RISC threshold score >1	RISC threshold score ≥3
Sensitivity (%)	80.3	21.3
Specificity (%)	26.11	88.3
PPV (%)	25.9	61.7
NPV (%)	79.6	76.8
Accuracy (%)	39.8	71.3

^aUsing CXR WHO score 3 as diagnosis of lobar pneumonia.

sensitivity of 59% and specificity of 78%. With a score threshold of 4, the sensitivity was 32.6% and specificity was 93.1%. A median RISC score of 1 corresponded with a risk of mortality of 0% (95% CI: 0%-0.6%) in the study by Reed, et al. [1]. In our study, using a RISC score of >1 had a higher sensitivity and was a moderate screening test to predict pneumonia.

Validation of Bacterial pneumonia score (BPS) score was done with multiplex PCR examinations of blood specimens by Imilda, et al. [14]. BPS had 69% sensitivity and 60% specificity, 42% positive predictive value, and 81% negative predictive value. In our study, which was validated with X-ray chest, a RISC score of ≥3 had a higher specificity and positive predictive value and almost similar negative predictive value for diagnosis and to predict severity of pneumonia.

To conclude, we propose that RISC score may be used for diagnosing pneumonia in resource-constrained areas to supplement IMCI protocols. Assessment of a combination of the two in community-based studies may provide additional information on this aspect.

Ethics clearance: Amala Institute of Medical Sciences; No. AIMSIEC/05/2018 dated January 22, 2018.

Contributors: KP: concept and design of the study; ERS: analyzed and collected data; drafted the manuscript; TPL: analyzing data; VKP: supervised cognitive and behavioral assessments. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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Clinical Patterns and Risk Factors for Pneumonia Caused by Atypical Bacteria in Vietnamese Children

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Objectives: To investigate clinical characteristics and risk factors for atypical community-acquired pneumonia (CAP) in children. **Methods:** Multiplex polymerase chain reaction and specific IgM determination were used to detect atypical bacteria in 661 hospitalized children aged 1-15 years with CAP. Clinical and epidemiological patterns were compared between typical and atypical CAP. **Results:** Children in atypical CAP group manifested significantly lower rates of wheezing, bronchial rales, and interstitial pneumonia and showed higher rates of asthma history, headache, chest pain, and lobar pneumonia. Age group, season of disease onset, asthma history, duration of symptom onset to hospital admission, and radiological findings were the significant risk factors for atypical CAP on multivariate logistic regression analysis. **Conclusions:** The clinical characteristics and risk factors can be used to identify a child at high risk of atypical CAP.

Keywords: Asthma, Evaluation, Identification, Lower respiratory tract infection.

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Childhood pneumonia is a considerable public health problem worldwide [1]. Atypical pathogens are increasingly being recognized as important causes of community acquired pneumonia (CAP) [2-4]. Since these atypical bacteria cannot be cultured using standard methods [5] and microbiological diagnosis of atypical CAP has been limited due to inadequate laboratory diagnostic facilities in developing countries, the clinical practice guidelines highlight the importance of signs suspicious for atypical CAP in children to help guide antibiotic selection [6,7]. However, such signs have not been well defined yet. The aforementioned problems prompted us to conduct the study to identify clinical characteristics of atypical CAP and the important risk factors which help pediatricians predict children with atypical CAP.

METHODS

The study was conducted at the National Hospital of Pediatrics from July, 2010 through March, 2012. The study proposal was approved by the Research Ethics Committee of the hospital. The detailed methodology has been previously reported [4]. In summary, the socio-demographic characteristics and potential risk factors were collected on standardized questionnaires by interviewing the patient's parents. After evaluating clinical manifestation and chest X-ray, bronchoalveolar lavage and two blood samples were

taken from all the recruited patients for laboratory diagnosis. Multiplex polymerase chain reaction [8-10] and IgM/IgG antibody-based enzyme-linked immunosorbent assay were used to detect *Mycoplasma pneumoniae*, *Chlamydomphila pneumoniae* and *Legionella pneumophila* [4]. Of the total 722 children aged 1-15 years with CAP, 661 children without mixed typical and atypical pneumonia were the study subjects.

Statistical analysis: Multivariate logistic regression analyses with backward stepwise method were performed to test several models for identifying risk factors of atypical CAP. The final model presented the most significant risk factors for atypical CAP. The area under a receiver operating characteristic curve (AUC) was calculated [11]. The selection of an optimal threshold was based on the Youden index [12], and the sensitivity and the specificity of the model were calculated. The nomogram for identifying an individual with high risk of atypical CAP was constructed based on the variable estimates from the final model. A *P* value of less than 0.05 was considered statistically significant. The statistical procedures were performed using SPSS version 16.0 (SPSS, Chicago, USA) and R statistics version 3.5.3 [13].

RESULTS

There was no statistical difference between atypical and typical CAP in socioeconomic status except for age group and season of disease onset (**Web Table I**).

Table I shows the clinical and laboratory characteristics among children with atypical and typical CAP. Fever (or high fever), cough, sore throat, and tachypnea were the most common signs and not different between atypical and typical CAP. Children showed significantly lower rates of wheezing, bronchial breathing, leukocyte counts, and interstitial pneumonia and higher rates of asthma history, headache, chest pain, and lobar pneumonia in atypical CAP compared to typical CAP.

The potential risk factors for atypical CAP were analyzed using multivariate logistic regression including factors found significant on univariate analysis. The final model involved the most significant risk factors for atypical CAP including age group, season of disease onset, asthma history, duration of symptom onset to hospital admission, and radiological findings (**Table II**). Based on parameter estimates of the final model, the prediction nomogram was constructed for individualizing the probability of atypical CAP (**Web Fig. 1**). The final model had AUC of 0.736 (95% CI

0.691-0.781), the optimal cut-off value of 17.8%, sensitivity of 79.9% and specificity of 57.0%.

DISCUSSION

The present study depicted the clinical patterns of atypical CAP compared with typical CAP. The risk factors and nomogram for identifying a child with high risk of atypical CAP were also reported.

To date, there have not been many reports on clinical signs suggestive of atypical CAP. In adults, the guidelines set up parameters and criteria for the differential diagnosis of atypical pneumonia and bacterial pneumonia based on clinical symptoms, physical signs and laboratory data [14]. In children, such parameters and criteria have not been well defined yet. We previously reported the clinical patterns of 52 children with atypical pneumonia caused by *M. pneumoniae* [15]. In agreement with our finding, a study in Thailand [16] reported that lobar pneumonia was associated with atypical CAP in children. Age has also been found as an important risk factor for atypical pneumonia in several studies [16,17].

The strength of the study was prospective recruitment of a large sample of children with CAP through four seasons of the year. Moreover, the investigations combining serologic and molecular tests were performed to maximize the diagnostic yield of atypical CAP. The study limitations were no urine test for detection of *L. pneumophila* antigen, and low sensitivity and specificity of the prediction model.

Table I Clinical Pattern and Laboratory Values in Vietnamese Children With Pneumonia (N=661)

Characteristics	Community-acquired pneumonia	
	Typical (n=507)	Atypical (n=154)
<i>Clinical</i>		
Fever	476 (93.9)	145 (94.2)
High fever (≥38.5°C)	345 (68.0)	113 (73.4)
Cough	498 (98.2)	151 (98.1)
Sore throat	404 (79.7)	123 (79.9)
Tachypnea	406 (80.1)	128 (83.1)
Wheezing ^c	392 (77.3)	97 (63.0)
Moist rales	364 (71.8)	98 (63.6)
Bronchial breathing ^d	334 (65.9)	86 (55.8)
Headache ^c	79 (15.6)	48 (31.2)
Chest pain ^d	69 (13.6)	32 (20.8)
Chest indrawing ^b	177 (38.7)	38 (35.5)
Diarrhea	178 (35.1)	49 (31.8)
Skin rash	51 (10.1)	24 (15.6)
<i>Radiological findings</i>		
Interstitial pneumonia ^{b,e}	95 (18.7)	14 (9.1)
Lobar pneumonia ^d	128 (25.2)	54 (35.1)
Asthma ^c	24 (4.7)	24 (15.6)
C-reactive protein (mg/L) ^a	18 (6-36)	24 (10-36)
Anemia	229 (45.2)	82 (53.2)
<i>Count</i>		
Leukocytes (X10 ⁹ /L) ^a	14 (10-19)	12 (8.5-18.5)
Neutrophils (%) ^a	58 (43-69)	56 (43-67)
Lymphocytes (%) ^a	30 (20-43)	31 (21-43)
Eosinophils (%) ^a	0 (0-1)	1 (0-2)
Platelets (X10 ⁹ /L) ^a	328 (259-399)	334 (259-422)

Data shown as no. (%) or ^amedian (IQR); ^bIn children aged <5 y; ^cP<0.001; ^dP<0.05; ^eP=0.005.

Table II Risk Factors on Multivariate Logistic Regression for Atypical Pneumonia in Vietnamese Children (N=661)

Independent risk factor	OR (95% CI)	P value
<i>Age group</i>		
1 - <2 y	1.0	-
2 - <5 y	1.50 (0.96-2.36)	0.07
5 - <10 y	5.63 (3.14-10.1)	<0.001
≥10 y	2.65 (0.94-7.48)	0.06
<i>Season</i>		
Spring	1.0	-
Summer	0.59 (0.34-1.03)	0.06
Fall	0.46 (0.27-0.77)	0.004
Winter	0.40 (0.22-0.72)	0.002
Asthma	4.63 (2.39-8.99)	<0.001
<i>Radiological findings</i>		
Interstitial pneumonia	1.0	-
Broncho-alveolitis	2.00 (1.03-3.87)	0.04
Lobar pneumonia	2.48 (1.23-5.01)	0.01
Pleuropneumonia and others	2.80 (0.86-9.15)	0.09
<i>Duration between symptom onset and hospital admission</i>		
<1 wk	1.0	-
1-2 wk	1.84 (1.21-2.78)	0.004
>2 wk	0.51 (0.25-1.03)	0.06

WHAT THIS STUDY ADDS?

- Age group, season of disease onset, asthma history, duration of symptom onset to hospital admission, and radiological findings identify a child at high risk of atypical community-acquired pneumonia.

Further independent studies should be conducted to validate and evaluate the performance of the prediction model.

In conclusion, the study indicated the clinical characteristics of atypical CAP in comparison with typical CAP. Age group, season of disease onset, asthma history, duration of symptom onset to hospital admission, and radiological findings were the independent risk factors for atypical CAP in children. The nomogram constructed from the risk factors may be used to identify a child at high risk of atypical CAP; although, confirmation of the findings from studies in various regions are required.

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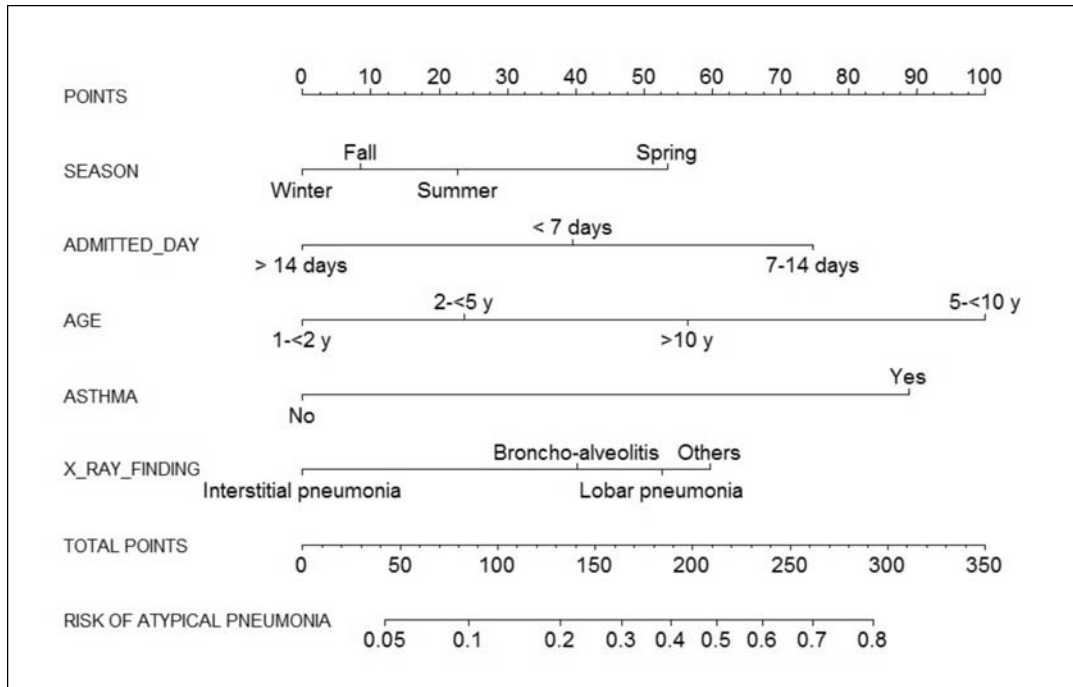
Ethics clearance: Research Ethics Committee Vietnam National Children’s Hospital; No. 1124/HDDD, dated 2 June, 2010.

Contributors: PLTH: conceptualized and designed the study, designed and performed laboratory analyses, drafted the initial manuscript, reviewed and revised the manuscript; PTH: recruited patients, collected and entered data, follow-up patients; NTPL: participated in laboratory analyses, reviewed the manuscript; DMT: designed the study, recruited patients, follow-up patients, participated in discussion and interpretation of the findings; DDA: had a substantial contribution in experimental design and interpretation of ELISA and multiplex PCR, critically reviewed the manuscript; TQB: cleaned data, supervised data collection, performed statistical analyses and interpretation of findings, critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Instructions for usage: Locate an individual value on each variable axis (season, admitted day, age, asthma, X-ray finding). Draw a vertical line from that value to the top “points” scale to determine the number of points assigned by variable value. Sum the points from each variable value. Mark the sum on the “total points” scale. Draw a vertical line down to meet the “risk of atypical pneumonia” axis to obtain a personalized risk of atypical pneumonia.

Web Fig. 1 Nomogram to identify an individual at high risk of atypical pneumonia.

Web Table 1 Socio-Demographic Characteristics of Study Groups

Characteristics	Community-acquired pneumonia	
	Typical (n=507)	Atypical (n=154)
<i>Age group</i>		
1- <2 y	276 (54.4)	53 (34.4)
2- <5 y ^a	181 (35.7)	54 (35.1)
5- <10 y	38 (7.5)	40 (26.0)
>10 y	12 (2.4)	7 (4.5)
<i>Season of disease onset^a</i>		
Spring	97 (19.1)	46 (29.9)
Summer ^b	119 (23.5)	37 (24.0)
Fall	180 (35.5)	43 (27.9)
Winter	111 (21.9)	28 (18.2)
Female gender	216 (42.6)	69 (44.8)
<i>Residence</i>		
Rural	235 (46.4)	60 (39.0)
Mountain	43 (8.5)	16 (10.4)
Urban	229 (45.2)	78 (50.6)
<i>Mother education</i>		
Elementary and intermediate	120 (23.7)	47 (30.5)
Secondary	240 (47.3)	62 (40.3)
Post-secondary	147 (29.0)	45 (29.2)
<i>Mother occupation</i>		
Unemployed	122 (24.1)	31 (20.1)
Farmer	116 (22.9)	45 (29.2)
Office staff	192 (37.9)	59 (38.3)
Other	77 (15.2)	19 (12.3)
<i>Income level^b</i>		
First quartile (lowest)	170 (33.5)	61 (39.6)
Second quartile	79 (15.6)	22 (14.3)
Third quartile	175 (34.6)	45 (29.2)
Fourth quartile (highest)	83 (16.4)	26 (16.9)
Having air-conditioning	231 (45.6)	71 (46.1)
Living condition polluted by dust	216 (42.6)	70 (45.5)
Contact with tobacco smoke	169 (33.3)	54 (35.1)

Data are shown as no. (%). ^aP<0.001; ^bP=0.03. ^aNorth Vietnam has 4 different seasons in a year: spring (February, March, and April); summer (May-July); fall (August-October) and winter (November-January). ^bAverage income per person/month in the previous year was calculated and classified into 4 categories based on IQR: first quartile (<1 mil VND), second quartile (1-1.8 mil VND), third quartile (1.8-3.0 mil VND), and fourth quartile (>3.0 mil VND).

Factors Associated With Neonatal Pneumonia and its Mortality in India: A Systematic Review and Meta-Analysis

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Background: Neonatal pneumonia remains a significant contributor to infant mortality in India and responsible for increased prevalence of infant deaths globally. **Objective:** To identify risk factors associated with neonatal pneumonia and its mortality in India. **Study design:** A systematic review was conducted including both analytic study designs and descriptive study designs, which reported a quantitative analysis of factors associated with all the three types of pneumonia among neonates. The search was conducted from August to December, 2016 on the following databases; CINAHL, EMBASE, Ovid MEDLINE, PubMed, ProQuest, SCOPUS, Web of Science, WHO IMSEAR and IndMED. The search was restricted to Indian setting. **Participants:** The population of interest was neonates. **Outcomes:** The outcome measures included risk factors for incidences and mortality predictors of neonatal pneumonia. These could be related to neonate, maternal and pregnancy, caregiver, family, environment, healthcare system, iatrogenic and others. **Results:** A total of three studies were included. For risk factors, two studies on ventilator-associated pneumonia were included with 194 neonates; whereas for mortality predictors, only one study with 150 neonates diagnosed with pneumonia was included. 11 risk factors were identified from two studies: duration of mechanical ventilation, postnatal age, birth weight, prematurity, sex of the neonate, length of stay in NICU, primary diagnosis, gestational age, number of re-intubation, birth asphyxia, and use of nasogastric tube. Meta-analysis with random-effects model was possible only for prematurity (<37 week) and very low birth weight (<1500 g) and very low birth weight was found to be significant (OR 5.61; 95% CI 1.76, 17.90). A single study was included on predictors of mortality. Mean alveolar arterial oxygen gradient (AaDO₂) >250 mm Hg was found to be the single most significant predictor of mortality due to pneumonia in neonates. **Conclusion:** The study found scant evidence from India on risk factors of neonatal pneumonia other than ventilator-associated pneumonia.

Keywords: *Alveolar-arterial oxygen gradient, Respiratory distress, Risk factors, Ventilator-associated pneumonia.*

Protocol registration: PROSPERO 2016 CRD42016044019 (risk factors); PROSPERO 2016 CRD42016045398 (mortality)

Neonatal pneumonia accounts for 6.1% of total global neonatal mortality whereas it contributes 5.1% to neonatal mortality in India and 5.6% in South Asia [1]. There is no international consensus regarding definition, diagnostic criteria and management of pneumonia among neonates [2, 3]. National nosocomial infections surveillance (NNIS) 1996 and original Centers for Disease Control (CDC) guidelines (pediatric modification) are commonly followed for diagnosis of neonatal pneumonia.

It has been observed that poverty, limited healthcare accessibility, and improper child-rearing practices are some of the risk factors for pneumonia in young children [4]. Other factors related to development of pneumonia, particularly in India, are financial status, malnutrition, poor immunization status, and household air pollution [5]. In South East Asia, poor prenatal care, home delivery, fever at birth, maternal urinary tract infections, prolonged rupture of membrane were found as notable risk factors of neonatal pneumonia [6,7].

There is scanty information available on neonatal pneumonia from India. Identification and elimination of risk factors associated with neonatal pneumonia is imperative to reduce its high prevalence and associated mortality, and implementing appropriate interventions to improve neonatal survival. With this review we intended to identify risk factors and mortality predictors associated with neonatal pneumonia in the Indian context.

METHODS

Protocol for these systematic reviews were registered with PROSPERO [8,9] and published as separate publications [10,11] where methodology is described in detail. Ethical clearance was obtained from institutional ethics committee of the host institution.

Studies reporting all types of neonatal pneumonia published in English language in journals, irrespective of peer reviewed or not were eligible for inclusion. Studies on neonatal sepsis were also searched to verify the presence or

absence of a ‘pneumonia’ subgroup as pneumonia is usually considered under the umbrella of neonatal sepsis. To be eligible for inclusion, these articles had to mention the outcomes specifically for neonatal pneumonia.

Both analytic study designs (case-control studies, cohort studies, cross-sectional studies) and descriptive study designs (case series, cross-sectional studies) which report a quantitative analysis of factors associated with all the three types of pneumonia among neonates were eligible for inclusion. Letters, editorials, commentaries, reviews, meta-analysis, qualitative research, conference papers and reports were excluded.

Neonates diagnosed with any form of pneumonia including community acquired pneumonia, congenital pneumonia and hospital acquired pneumonia (ventilator associated pneumonia) were included. The outcome measures included risk factors for neonatal pneumonia and its mortality. These could be related to neonate, maternal and pregnancy, caregiver, family, environment, healthcare system, iatrogenic and others.

Search methods: Articles were identified from nine databases (CINAHL, EMBASE, Ovid MEDLINE, ProQuest, PubMed, SCOPUS, WHO IMSEAR, Web of Science and IndMED) and government websites without time restriction. A separate search was undertaken to identify risk factors and mortality predictors associated with neonatal pneumonia. Detailed search terms and strategy for PubMed for both the outcomes has been provided in **Web Appendix 1**. The search on all the databases was conducted from August to December, 2016. Some of the search terms included were: “Risk factor” OR “determinant” OR “risk” OR “predictor” AND “Mortality” OR “fatal” OR “case fatality” OR “case fatality rate” AND “Neonate” OR “childhood” OR “neonatal” OR “newborn” AND “Pneumonia” OR “hospital acquired pneumonia”) OR “community-acquired pneumonia” OR “ventilator associated pneumonia” OR “early onset pneumonia” OR “late onset pneumonia.” Additionally grey literature search and snowballing were also conducted to find out potentially relevant studies. The authors were contacted in an attempt to retrieve missing information on important methodological aspects or outcomes measures.

Data extraction and quality assessment: Considering inclusion and exclusion criteria, three review authors (SM, MG, and TL) worked in two teams to screen, extract data and quality assessment of identified literature. The consensus for any discrepancies were sought through discussion with senior reviewers (NSN, LL, and BT). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart was generated to summarize the study selection process. Characteristics were summarized and

results were reported using tables and accompanied by a descriptive summary that compared and evaluated the methods and results of included studies. The results of the search were managed and screened using Endnote (v. x7). Microsoft Excel 2007 was utilized for data extraction.

Statistical analysis: Depending on methodological heterogeneity, a random-effects model was used. The summary measures were pooled based on study design. A Forest plot was generated and pooled estimates were reported with 95% CIs. Based on the availability of data, a subgroup analysis was also planned a priori with respect to study design, type of neonatal pneumonia, study setting, and onset of pneumonia. However, the subgroup analysis was not possible due to non-availability of relevant data. For meta-analysis, data were available only from two studies on VAP (ventilator-associated pneumonia) and meta-analysis was possible only for two factors i.e., very low birth weight and prematurity. Depending on data availability, a sensitivity analysis and meta-regression was planned but could not be performed due to limited data. Reporting bias could also not be assessed as included studies were less than 10.

The reporting has been done in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [12] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [13]. Quality assessment was done at the study level using the modified Quality Assessment Tool for Systematic Reviews of Observational Studies (QATSO) tool [14]. STATA (v.13) was used to perform statistical analyses.

RESULTS

A total of 8754 citations were subjected to title screening, and finally two articles were found to be eligible and were included for the meta-analysis (**Fig. 1**). For mortality predictors of neonatal pneumonia, a total of 6,955 citations were identified, of which, 303 articles were screened for full text and only one article was eligible for inclusion (**Fig. 2**). Meta-analysis was not possible as there was only one eligible study.

For risk factors, two studies [15,16] were included with data from a total of 194 neonates. For mortality predictors, only one study [17] with 150 neonates was included. **Table I** lists the characteristics of included studies [18].

Both studies used (NNIS) 1996 guidelines in conjunction with pediatric modification of the original center for disease control guidelines. [15,16]. Both studies (risk factors) found *Klebsiella* species as the most predominantly isolated organism from the endotracheal aspirate of neonates with ventilator associated pneumonia. None of the studies reported the socio-demographic characteristics of neonates with or without ventilator associated pneumonia. **Web Table**

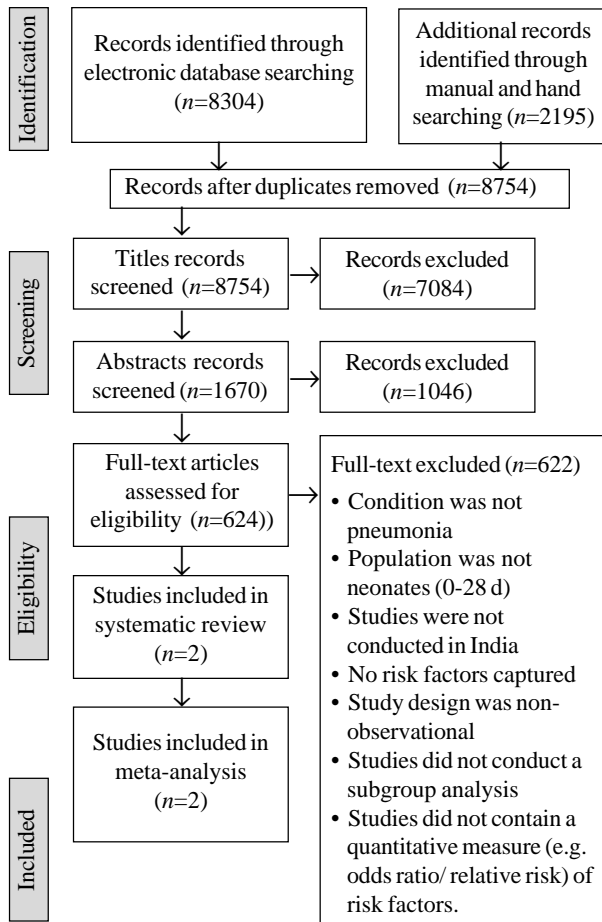


Fig. 1 PRISMA flow chart depicting the study selection process for risk factors of neonatal pneumonia.

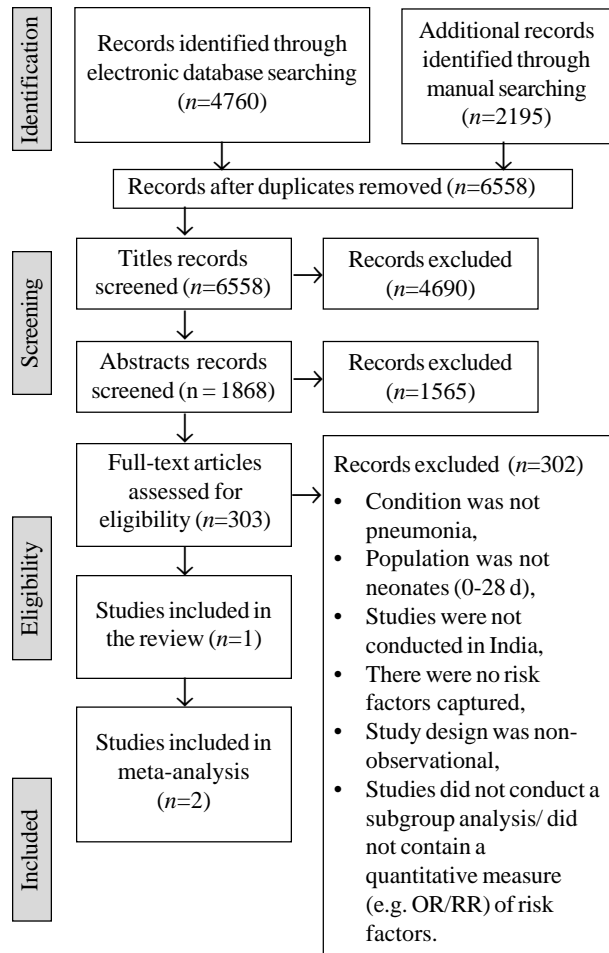


Fig. 2 PRISMA flowchart depicting the study selection process for factors associated with mortality.

I describes in detail diagnostic criteria used for ventilator associated pneumonia [15,16] and neonatal pneumonia [17]. The study on mortality predictors did not specify the guideline followed for diagnosis of neonatal pneumonia, the authors reported the use of the National Neonatology Forum (NNF) to diagnose ‘respiratory problems’. In both the studies [15,16] no primary criteria for mechanical ventilation was provided in the methodology; however, in one of the study results indicated four conditions for mechanical ventilation namely pneumonia, apnea, poor respiratory effort and Hyaline Membrane Disease [15].

In total, 11 risk factors were identified from two studies and six of them were common across both studies. **Table I** provides a risk factor profile of the included studies [15, 16]. A random effects model was used for the meta-analysis. Meta-analysis was carried out for only two factors from two studies namely very low birthweight (VLBW) and prematurity. In both the included studies, a significant association was found

between development of ventilator associated pneumonia and duration of mechanical ventilation and number of re-intubations; however, there was missing data and attempts at reaching the authors were unsuccessful, therefore a meta-analysis could not be performed for these factors.

Pooled OR for very low birth weight from random effects meta-analysis of two studies [15,16] is depicted in **Fig. 3**. The forest plot show that neonates with VLBW (<1500 g) were more likely to develop ventilator associated pneumonia compared to neonates who were normal to low birthweight (OR 5.61; 95% CI 1.76, 17.90). Very low birth weight was found to be significant risk factor for development of ventilator associated pneumonia. Pooled OR for prematurity is depicted in **Fig. 4** [15, 16]. The Forest plot shows that neonates with estimated gestational age <37 week or premature neonates were more likely to develop ventilator associated pneumonia compared to term neonates (OR 2.76; 95% CI 0.98, 7.73).

Table I Characteristics of Included Studies

<i>Study, year</i>	<i>Study design</i>	<i>Location & setting</i>	<i>Study duration</i>	<i>Outcome</i>	<i>Risk factors and mortality predictors</i>
Tripathi, 2010 [15]	Cross-sectional study	Lucknow, Uttar Pradesh NICU, tertiary care teaching hospital	1 y	VAP	<i>Risk factors</i> Duration of mechanical ventilation (h) Postnatal age (admission) Birth weight Prematurity Sex of the neonate Length of NICU stay Primary diagnosis Gestational age Number of re-intubation
Mir, 2015 [16]	Cross-sectional study	Srinagar, Kashmir NICU, teaching, referral hospital	10 mo	VAP	<i>Risk factors</i> Duration of mechanical ventilation (h) Postnatal age (initiation) Birth weight Prematurity Sex of the neonate Length of NICU stay Primary diagnosis Number of re-intubation Birth asphyxia Use of Nasogastric tube
Mathur, 2002 [17]	Cross-sectional study	New Delhi Referral neonatal unit of a teaching hospital	Not specified	NP	<i>Mortality predictors</i> AaDO ₂ gradient > 250 mm Hg Birth weight < 2000 g, Gestation < 34 weeks Age at presentation Lethargy Absent neonatal reflexes, Shock Silverman score (4 to 6), FiO ₂ > 40%, pH < 7.2, base excess > -10 Positive blood culture CRP positive mean arterial alveolar tension ratio (a/A ratio) < 0.25 positive ventilatory support

NICU-newborn intensive care unit, VAP-ventilator-associated pneumonia, NP-neonatal pneumonia.

Only one study [17] reported mortality predictors to neonatal pneumonia. The authors did not specify the list of independent and confounding variables considered as predictors for fatality due to pneumonia in neonates. However, they provided only *P* values for significant predictors which they considered for multiple logistic regression. These predictors included: <birthweight 2000 g, gestation <34 week, age at presentation, lethargy, absent neonatal reflexes, shock, Silverman score (4 to 6), FiO₂>40%, pH<7.2, base excess >-10, positive blood culture, C-reactive protein (CRP) positive, mean alveolar arterial oxygen gradient (AaDO₂)>250 mm Hg, mean arterial alveolar tension ratio (a/A ratio) <0.25 and positive ventilatory support. The authors found only AaDO₂ gradient >250 mmHg as a significant predictor of mortality due to pneumonia with respiratory

distress in neonates (OR 71.1; 95% CI 1.1, 4395).

Publication bias could not be assessed as there were fewer than 10 studies. **Web Table II** depicts quality assessment of studies using the QATSO Tool [14]. Four of the five items on the scale were used to assess (i) External validity, (ii) Reporting, (iii) Bias and (iv) Confounding. However, no scoring was done. For studies on risk factors, the measurement of pneumonia was only found to be objective in one study [15] i.e., clinical records or laboratory tests. Neither study reported any response rate. Regarding the control of confounding factors when analyzing associations, only one study partially accounted for this [15], while the other did not report adequately on the handling of variables during the analysis [16].

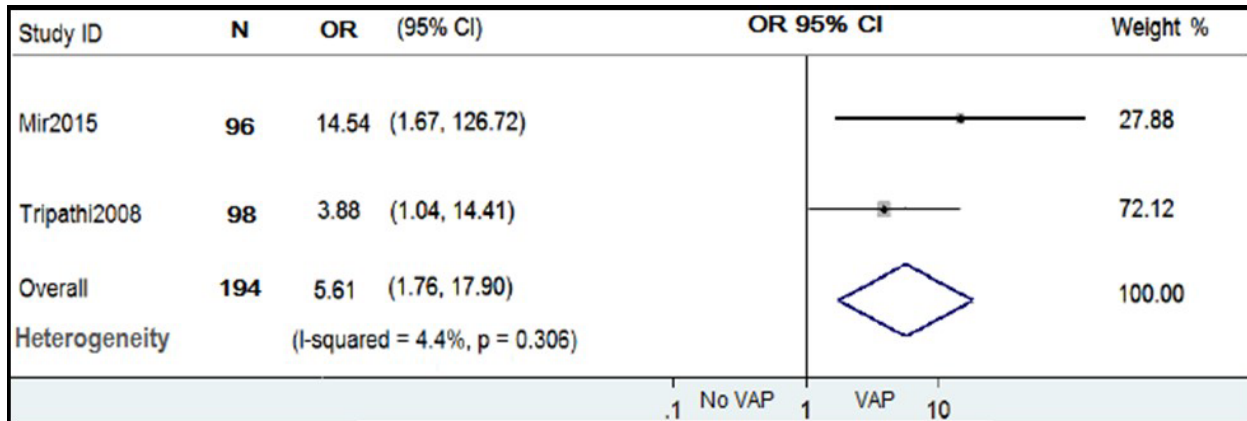


Fig. 3 Forest plot showing the effect of very low birthweight on ventilator-associated pneumonia.

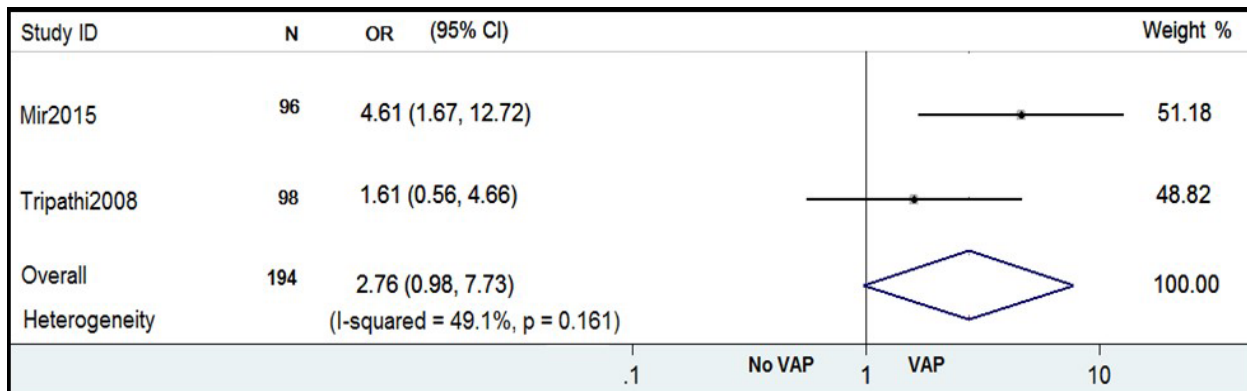


Fig. 4 Forest plot showing the effect of prematurity on ventilator-associated pneumonia.

For study on mortality predictors [17] dose response relationship could not be determined. The odds ratio in the study was very large with large confidence intervals (71.1; 95% CI 1.1, 4395). No event rates were reported for both the groups. Discrepancies exist in the numbers of participants included in the study. The authors mention the presence of two groups: respiratory distress with pneumonia and respiratory distress without pneumonia. However, information on socio-demographic characteristics, clinical and other important exposure and confounding information for the two groups was missing.

DISCUSSION

We conducted a series of systematic reviews to determine the risk factors associated with development of neonatal pneumonia and its mortality predictors in India. Literature is widely available on pneumonia in general and on neonatal sepsis. However there was near absence of data on neonatal pneumonia particularly with respect to its risk factors and mortality predictors in India. Only two studies were included

for risk factors and only one study on mortality predictors of neonatal pneumonia. Meta-analysis for prematurity and low birth weight was carried out and low birth weight was found to be significant for the occurrence of neonatal pneumonia. Only alveolar-arterial oxygen gradient (AaDO₂) >250 mm Hg was found as a significant predictor of mortality due to pneumonia with respiratory distress in neonates in present review.

To the best of our knowledge this systematic review is the first in India studying factors associated with pneumonia and its mortality in neonates. A rigorous effort was made to search the relevant studies without time restriction in Indian context by means of conducting search on nine electronic databases, hand searching, grey literature, by contacting authors and in consultation with clinical experts to include every possible study. Screening and data extraction was carried out independently by two authors and discrepancies were resolved by mutual discussion and by getting experts opinion.

Considering the limited evidence in this review, studies on neonatal sepsis were included up to full text screening to verify the presence or absence of a subgroup for pneumonia but no clear underlying etiology as risk factor for neonatal pneumonia was mentioned in these studies. Consequently we have excluded studies where pneumonia was part of the condition but further description for neonatal pneumonia was not given separately.

Another limitation of the review was the lack of response from authors of studies of neonatal sepsis that did not explicitly provide data on the pneumonia component of their sepsis cases. Due to lack of data in the papers, meta-analysis for all the identified risk factors was not possible. Results from our study on risk factors pertain only to cases of ventilator associated pneumonia, which is a subgroup of neonatal pneumonia, and therefore, the findings could not be extrapolated to all the cases of neonatal pneumonia.

The major limitation for mortality predictors of neonatal pneumonia was that we found limited evidence from a single study that was not sufficient to conclude despite the comprehensiveness of our search. One of the potential limitation could be the language as we have restricted the search only to articles published in English. Nonetheless, we might have not missed any relevant studies on neonatal pneumonia as scientific literature in India is mostly published in English.

Both the studies [15,16] in our review investigated ventilator-associated pneumonia in neonates that required mechanical ventilation for 48 hour or more as observed in other studies [19-23]. In our review the incidence of ventilator associated pneumonia ranged from 22 to 68 cases per 1000 MV days where as in another study from China it was 27.33 per 1,000 ventilator-days [21]. In contrast, in a study from USA, VAP rates were as low as 6.5 and 4 per 1000 ventilator days for patients with EGA <28 week and EGA >28 week, respectively [22]. Both the included studies [15,16] found *Klebsiella* species as the most predominantly isolated organism from the endotracheal aspirate of neonates with VAP. Similarly in studies from Egypt [23] and Western India [24], *K. pneumoniae* was also found to be the most common organism.

High AaDO₂ was found as a significant predictor of mortality due to pneumonia. Similarly, in a study from Bangladesh, high AaDO₂ was one of the factors significantly associated with change in antibiotics due to the worsening condition of the neonates diagnosed with pneumonia [25]. However, they did not specify the limit to describe AaDO₂ as high whereas AaDO₂ > 250 mm Hg was considered as high in the included study [17]. In a multivariate logistic regression, VAP was the single most important factor found to be significantly associated with

mortality, whereas marginally significant association was found with presence of an arterial catheter [22].

In contrast to our meta-analysis findings and few other studies [19,20,22,26-28], there is one study [29] where the occurrence of VAP was not associated with low birth-weight (<1500 g). Results from meta-analysis of two studies [15,16] found birth-weight of <1500 g as a significant risk factor to develop VAP (OR 5.61; 95% CI 1.76, 17.90). Our meta-analysis findings are comparable to a study from China where low birth weight and premature infants had more chances of developing VAP [28].

Differences in birth weight were observed amongst different studies when it comes to defining weight at birth as low. One study in our review [15] defined VLBW as less than 1500 g. The other study [16] defined it as in between 1000 to 1500 g and excluded extremely low birth weight babies less than 1000g weight. However, a study from Thailand reported a neonatal birth weight less than 750g as an independent risk factor for VAP [19] and another study established that VAP rates were high among extremely preterm neonates but birth weight was specified as ≤2000g [22]. A retrospective observational study conducted in Taiwan found that higher gestational age and weight at birth were significantly associated in bringing down the VAP occurrence [20].

Like other studies [27-29], duration of NICU stay and MV were found as the risk factors but due to lack of data, meta-analysis for these factors was not possible for our review. Some intervention studies focused on the association of the infection control program and VAP prevention [21, 23, 30] and NICU stay [23]. However, one possible explanation for this association could be the usage of humidifiers and closed-circuit ventilation in NICU which provide a major source for growth of microorganisms [28, 31]. Hence, NICU environment itself can be a determining risk factor for development of VAP.

Risk factors that other studies have attributed to neonatal pneumonia of early onset but were absent from our review were antacid therapy [29], abnormal gastric aspirate, and low APGAR score among high-risk infants [32]. However, it has also been reported that often risk factors are absent in pneumonia of early onset, and that sudden onset of preterm labor by its very nature; is considered as an important risk factor [33].

Pneumonia is one of the leading causes of death among neonates in India. Thus, factors that affect neonatal mortality due to pneumonia and its occurrence are of great importance for any effort to improve child survival. However our review concludes that data and primary studies itself is negligible to substantiate a holistic view on factors associated with incidences and mortality of neonatal pneumonia. There is no

conclusive evidence on risk factors of neonatal pneumonia other than ventilator associated pneumonia and hence it is recognized with this review that neonatal pneumonia, which comprises the majority of the burden of neonatal sepsis, continues to be an understudied issue in the Indian neonatal health scenario. To conclude, we can say that there is an emergent need to prioritize research toward generating evidence on neonatal pneumonia and determining factors for its development and mortality.

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Persistent Pneumonia in an Infant

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An eight month old boy presented with a subacute febrile illness and radiological evidence of multifocal cavitary consolidations in the lungs. He continued to worsen despite multiple oral and intravenous antibiotics. Preterminally, he developed respiratory distress, hepatosplenomegaly, bicytopenia, and hepatic dysfunction. Investigation for cause of persistent pneumonia resulted in a diagnosis of chronic granulomatous disease on the basis of Dihydrorhodamine assay and genetic analysis. Postmortem blood culture grew *Burkholderia cenocepacia*. Autopsy revealed necrotizing granulomatous inflammation with massive necrosis and abscesses in bilateral lungs. No organism could be identified by traditional stains on autopsy. Conventional PCR targeting 16S ribosomal DNA yielded *Nocardia pseudobrasiliensis*. In conclusion, an unusual course of pneumonia warrants invasive investigations for isolation of underlying organism, which not only provides guidance to choice of antimicrobials but also provides clue to an underlying disease.

Keywords: Autopsy, *Burkholderia cenocepacia*, Chronic granulomatous disease, *Nocardia pseudobrasiliensis*.

CLINICAL PROTOCOL

History and examination: An 8 month old boy presented with history of fever and insidious onset cough for 1 month. He was asymptomatic till the age of 7 months when he developed fever lasting for a week, for which he received oral antibiotics. After an afebrile period of 1 week, he started having intermittent episodes of fever upto 101°F. Child had loose stools transiently for 3 days. Subsequently, he developed cough which worsened gradually. He had received 1 week of oral amoxicillin-clavulanic acid and 2 weeks of intravenous ceftriaxone and amikacin without any response, before being referred to our centre.

He was second born to a nonconsanguineously married couple, immunized for age, as per National immunization schedule, with a normal development. During this admission, he weighed 7.5 kg with length and head circumference of 79 cm and 45 cm, respectively. Vitals were stable and systemic examination was unremarkable.

Course and management: Based on clinical and radiological investigations, the patient was treated along the lines of pneumonia, with presentral meropenem and vancomycin for 3 weeks, as the child had already received first and second-line antibiotics earlier. In spite of persisting fever, patient was discharged on parental request, only to be readmitted after 5 days with worsening respiratory distress. During the second admission, he was found to have hepatosplenomegaly and investigations showed severe anemia, thrombo-cytopenia, coagulopathy with very low fibrinogen and high d-Dimer, high serum ferritin and

transaminitis with conjugated hyperbilirubinemia (**Table I**). In view of persistent pneumonia, immuno-deficiency was considered and investigations were sent accordingly (**Table II**). His condition deteriorated fast and despite antibiotics, antifungals and supportive therapy, the child died. Preterminally he developed hypotension, hypo-glycemia and left pneumothorax. A family history of chronic granulomatous disease (CGD) in a paternal second-degree female cousin was elicited just prior to demise.

Unit's final diagnosis: *Burkholderia cenocepacia* sepsis with pneumonia (bacterial or fungal) with left hydronephrosis (infective or obstructive due to granulomatous inflammation) and secondary hemophagocytic lymphohistiocytosis (HLH), with underlying autosomal recessive (AR) CGD (p67 deficiency).

DISCUSSION

Important points of discussion in the index child are whether CGD could have been considered in the first admission, reason for a relatively early fatality and explanation for the other findings such as left hydronephrosis and preterminal events.

The index child presented with fever and insidious onset, progressive cough for 1 month. Investigations revealed leucocytosis, thrombocytosis, sterile blood and urine cultures, nonprogressive left hydronephrosis and radiological evidence of consolidation in both lungs. Consolidation is suggestive of an infectious pathology, and common bacteria responsible for community-acquired

Table I Hematological and Biochemical Laboratory Parameters

Day of hospitalization	Day 5	Day 27	Day 32	Day 42
Hemoglobin (g/dL)	6.3	6.6	7.1	4.7
Total leukocyte count (/ μ L)	21530	37,000	14,960	14,000
Platelets (/ μ L)	5,64,000	4,25,000	2,28,000	90,000
Differential count (%)	P ₄₆ L ₄₇ M ₅ E _{0.2}	P ₃₆ L ₆₀ M _{2.9} E _{0.2}	P ₅₇ L ₃₅ M _{6.1} E _{0.7}	P ₅₇ L ₃₅ M _{6.1} E _{0.7}
PT/APTT (s)	15/29.5			37/70.5
Fibrinogen (g/L)	–	–	–	0.48
d-Dimer (ng/ml)	–	–	–	1194
CRP (mg/dL)	125.4	231	–	107
Procalcitonin (ng/mL)	0.749	–		
Sodium/Potassium (mEq/L)	132/4.5	129/4.4	129/4.6	138/2.6
BU/Creatinine (mg/dL)	15/0.08	14/0.1	12/0.08	56/0.3
AST/ALT/SAP (U/L)	83/40	66/24/209	154/58	821/319/171
Bilirubin (mg/dL) ^a	0.33	0.66	0.68/0.20	3.3/2.4
Total protein/albumin (g/dL)	6.3/3.1	6.8/3.0	5.6/2.8	3.7/1.5
Triglycerides (mg/dL)	–	–	307	
Ferritin (ng/mL)	–	–	376	4000

PT-prothrombin time; APTT-activated partial thromboplastin time; BU-blood urea; AST-aspartate amino transferase; ALT-alanine aminotransferase; SAP-serum alkaline phosphatase. ^asecond value, when given, is conjugated bilirubin.

Table II Other Investigations in the Index child

Urine microscopy	No cells (30/9, 6/10, 31/10)
Blood culture	Sterile (30/9, 06/10, 26/10, 30/10); <i>Burkholderia cenocepacia</i> (06/11, postmortem culture)
Urine culture	Sterile (30/9, 6/10, 31/10)
Fluorodeoxyglucose positron emission tomography (FDG-PET)- CT scan (16.10.19)	FDG avid consolidations in the bilateral lungs FDG avid mediastinal lymph nodes Left hydronephrosis
USG abdomen (1.10.19, 5.10.19)	Left hydronephrosis with anteroposterior diameter 0.9-1.2 cm with few internal echoes and dilated left upper ureter
USG abdomen (02.11.19)	Liver 8 cm with no space occupying lesion; Gall bladder edematous wall; Spleen 7 cm with multiple tiny hypoechoic foci; Left kidney mild fullness of pelvis
Mantoux test	Not reactive
Gastric lavage for acid fast bacilli	Both smears and cultures: Negative (30/10, 01/11, 02/11)
Parents' chest X-ray	Normal
Echocardiography	No evidence of infective endocarditis
HIV serology	Not reactive
Serum IgG (04.11.2019)	841 mg/dL (reference range 300-1000 mg/dL)
Serum IgA (04.11.2019)	56 mg/dL (reference range 20-70 mg/dL)
Nitroblue tetrazolium (NBT) test (04.11.2019)	No reduction seen
Dihydrorhodamine 123 assay (DHR) (05.11.2019)	Δ Mean fluorescence intensity (MFI) 471.58, Stimulation index (SI) 2.75 (Δ MFI 70286, SI 272.4 in control)
b558 expression on gated neutrophils (05.11.2019)	Normal
Targeted next generation sequencing (NGS)	Homozygous mutation c.835_836delAC, p.Thr279fs in <i>Neutrophilic cytosolic factor-2 (NCF2)</i> gene encoding for p67 component of phagocyte oxidase
Plasma soluble CD25 (pg/mL)(05.11.2019)	49 670 (Normal 400-2600)

pneumonia (CAP) at this age, are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis* and *Hemophilus influenzae* [1]. Usually, CAP responds to antibiotics like amoxicillin-clavulanic acid and ceftriaxone, unless complicated with empyema or lung abscess. Since the child had an indolent course with onset of respiratory distress two months after onset of fever and did not respond to usual antibiotics, CAP is unlikely and causes of persistent pneumonia need to be considered [2]. Though *Mycobacterium tuberculosis* is an important cause of persistent pneumonia, early cavitation is extremely rare in infants [3]. This suggests possibility of infections due to unusual organisms such as opportunistic bacteria or fungi. Clinical manifestations and radiology both lack specificity for underlying organism and yield of blood culture is low at 10-30% [2]. In the absence of fine needle aspiration cytology (FNAC) from lung lesions or bronchoalveolar lavage, while alive, it is difficult to pinpoint etiologic organism for persistent pneumonia.

Recurrent/persistent infections in one lobe of lung can occur due to congenital malformations (sequestration, bronchogenic cysts, cystic adenomatoid malformation) and external or internal compression of airway by lymph nodes, foreign body, or tumours. However, these were unlikely in the index case, because he had multifocal consolidations in both lungs. Recurrent/persistent infections in bilateral lung fields occur in a setting of congenital heart disease, aspirations, impaired mucociliary clearance (ciliary dyskinesia, cystic fibrosis) and immunodeficiency. While humoral immunodeficiencies are usually associated with infections due to community acquired bacteria, which respond to usual antibiotics, pneumonia in cystic fibrosis, combined immunodeficiency and phagocytic defects may be due to opportunistic pathogens [4,5]. HIV infection was ruled out in the index case.

Normal lymphocyte count rules out severe combined immunodeficiency. As the index child had evidence of phagocytic defect documented by no reduction in NBT test and negligible stimulation index on DHR assay, CGD is likely. Further investigations showed normal b558 expression ruling out the possibility of X-linked CGD and AR-CGD due to p22 deficiency. Diagnosis was further confirmed by genetic analysis which showed a homozygous mutation (c.835_836delAC; p.Thr279fs) in *NCF2* gene which encodes for p67 component of phagocytic oxidase. Thus the index child was convincingly proven to have AR-CGD caused by p67 deficiency.

The index child succumbed to the disease during infancy. While X-linked CGD is associated with more severe disease, severity is variable in AR-CGD due to variable phagocyte oxidase activity [6, 7]. Severe disease in the index

child can be explained by near absent activity of phagocyte oxidase with SI of 2.75.

Most infections in CGD are caused by catalase positive organisms including fungi such as *Aspergillus* and bacteria such as *Staphylococci*, *Burkholderia*, *Serratia* and *Nocardia*. Enterobacteriaceae and *Candida* are other important pathogens [5,6]. After introduction of cotrimoxazole and itraconazole prophylaxis, infections with *Aspergillus*, *Burkholderia* species and *Nocardia* have been on rise [6]. Nearly 80% patients with CGD have at least one episode of pneumonia, with *Aspergillus*, *Staphylococci*, *Burkholderia*, and *Nocardia* being responsible for two-thirds of the organisms [6]. In contrast to bilateral lung involvement in the index case, *Aspergillus* pneumonia in CGD typically involves one lobe with contiguous spread to pleura, ribs and vertebrae [8].

B. cenocepacia found in post-mortem blood culture, in the index case, is a signature organism in both cystic fibrosis and CGD [4,6]. However, there are marked differences between the infection pattern in cystic fibrosis and CGD. In cystic fibrosis, this organism causes colonization of the tracheobronchial tree [9] and can rarely cause invasive cepacia syndrome. These patients are not able to clear the colonized organisms and hence, spectrum of *Burkholderia* species is narrow. Isolation from sputum helps in diagnosis.

In contrast, this organism causes bronchopneumonia with central cavitation in patients with CGD [9]. Tissue from lungs is required for isolation of organism. Antibiotics can eradicate this organism but reinfection with same or

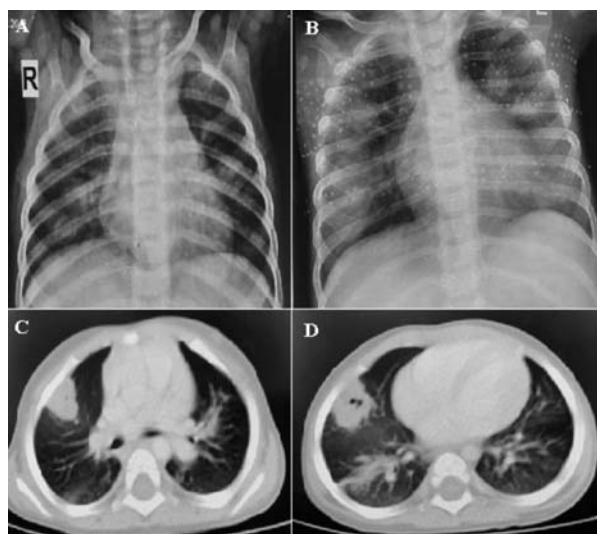


Fig. 1 A. Chest X-ray showing bilateral air space consolidations (right > left); B. Chest X-ray one month later showing progression of consolidations; C and D. PET-CT images showing pleura based cavitating nodules.

different *Burkholderia* species is common. Invasive disease with secondary bacteremia has been described with high mortality. The clinico-radiologic profile in the index child is consistent with *B. cenocepacia* infection.

Left-sided hydronephrosis, seen in this case, could be due to granulomatous inflammation, a known cause of obstruction of urinary tract in infants with CGD [5]. Anemia and thrombocytosis, early in the course were likely to be multifactorial, related to both iron deficiency anemia and chronic inflammation [5]. Preterminally, this child developed hepatosplenomegaly, bicytopenia, coagulopathy with very low fibrinogen and high d-Dimer, high serum ferritin and transaminitis with conjugated hyperbilirubinemia. All these features could be explained by secondary HLH [10], which is further supported by the high plasma soluble CD25 levels. Left-sided pneumo-thorax could be due to rupture of cavitating consolidation or as a complication of ventilation.

Gastroenterologist: The diagnosis of CGD is confirmed, though the organism causing consolidation may be debated upon.

Pulmonologist 1: Was *Mucor* considered in view of cavitary consolidations?

Clinical discussant: Though *Mucor* is an important differential in patients with cavitary consolidations, it is not a typical organism in CGD.

Pediatrician 1: Why Galactomannan elevation is not common in CGD?

Clinical discussant: In CGD, *Aspergillus* is locally invasive and hematogenous spread is rare, thus making galactomannan and β -D glucan elevations uncommon in patients with *Aspergillus* pneumonia in CGD [8].

Microbiologist 1: Galactomannan in bronchoalveolar lavage fluid may be more sensitive than serum galactomannan in CGD.

PATHOLOGY PROTOCOL

A partial autopsy was performed. All serous cavities were normal.

Both lungs together weighed 220.5 g. Pleural surface was dull and outer surface of both lungs showed multiple nodules of varying sizes with predilection towards lower lobes. Multiple lymph nodes measuring 0.5-1 cm were present in pretracheal and paratracheal regions. Tracheobronchial mucosa was congested. Cut surface of lungs showed similar nodules (**Fig. 2A**). Central area of large nodules showed necrosis with abscess formation. Some nodules showed evidence of rupture of abscess wall. Microscopy showed large irregular geographic areas of necrosis limited by interlobar septae (**Fig. 2B**). Necrosis was

palisaded by dense inflammatory infiltrate rich in epithelioid histiocytes (**Fig. 2C**), with well-formed epithelioid cell granulomas, and numerous giant cells were also noted in some places. Numerous micro-abscesses surrounded by similar inflammatory infiltrate were observed (**Fig. 2D**). No fungal profiles were identified on PAS and Grocott stains. Gram stain and Ziehl-Neelsen stain did not reveal any organisms. Adjoining alveolar spaces were densely infiltrated by neutrophils and macrophages. There was evidence of diffuse acute alveolar damage in the form of homogenous, eosinophilic hyaline membrane along the alveolar ducts and alveoli at some places (**Fig. 2E**). Other areas showed proliferative phase of diffuse alveolar damage. There was extensive fibrinous pleuritis. Lung tissue was subjected to conventional PCR targeting 16S ribosomal DNA region followed by Sanger sequencing. Nucleotide sequence obtained was matched with gene bank, which revealed presence of *Nocardia pseudobrasiliensis*. PCR for *M. tuberculosis* and non-tubercular mycobacteria was negative.

Liver and spleen weighing 490 g and 186 g, respectively, had an unremarkable capsule with mottling on the cut surface of liver and prominent white pulp and few greyish white lesions in cut surface of spleen. Peripancreatic and perisplenic lymph nodes were enlarged. Microscopic examination of liver showed preserved architecture, centrilobular hepatocyte necrosis, dense infiltration of sinusoids by histiocytes and micro-abscesses with central necrosis surrounded by palisading histiocytes (**Fig. 2F**). Microscopic examination of spleen showed similar abscesses. No organism could be identified by Gram stain, Ziehl-Neelsen stain, PAS and Grocott stains.

Both kidneys weighed 121 g with unremarkable capsule. Left ureter was grossly dilated throughout its length (**Fig. 2G**). Cut surface of left kidney showed minimally dilated pelvis, the latter showing attenuated transitional lining microscopically. No abscess or granuloma was seen in kidneys. Tubular necrosis was seen in greyish-white lesions of left kidney. Sections from vesicoureteric junction and urinary bladder showed invagination of surface mucosa into lamina propria. Lamina propria showed mild mixed inflammatory infiltrate of histiocytes. No well-formed granulomas were seen.

Small intestine showed prominent Peyer's patches. Focal loss of intestinal folds was seen in large intestine. Microscopically, granulomas were seen in lamina propria palisaded by lymphomononuclear cells. Characteristic pigmented histiocytes were seen in some of these granulomas (**Fig. 2H**). There was no evidence of cryptitis or crypt abscesses. Peyer's patches showed similar granuloma without necrosis.

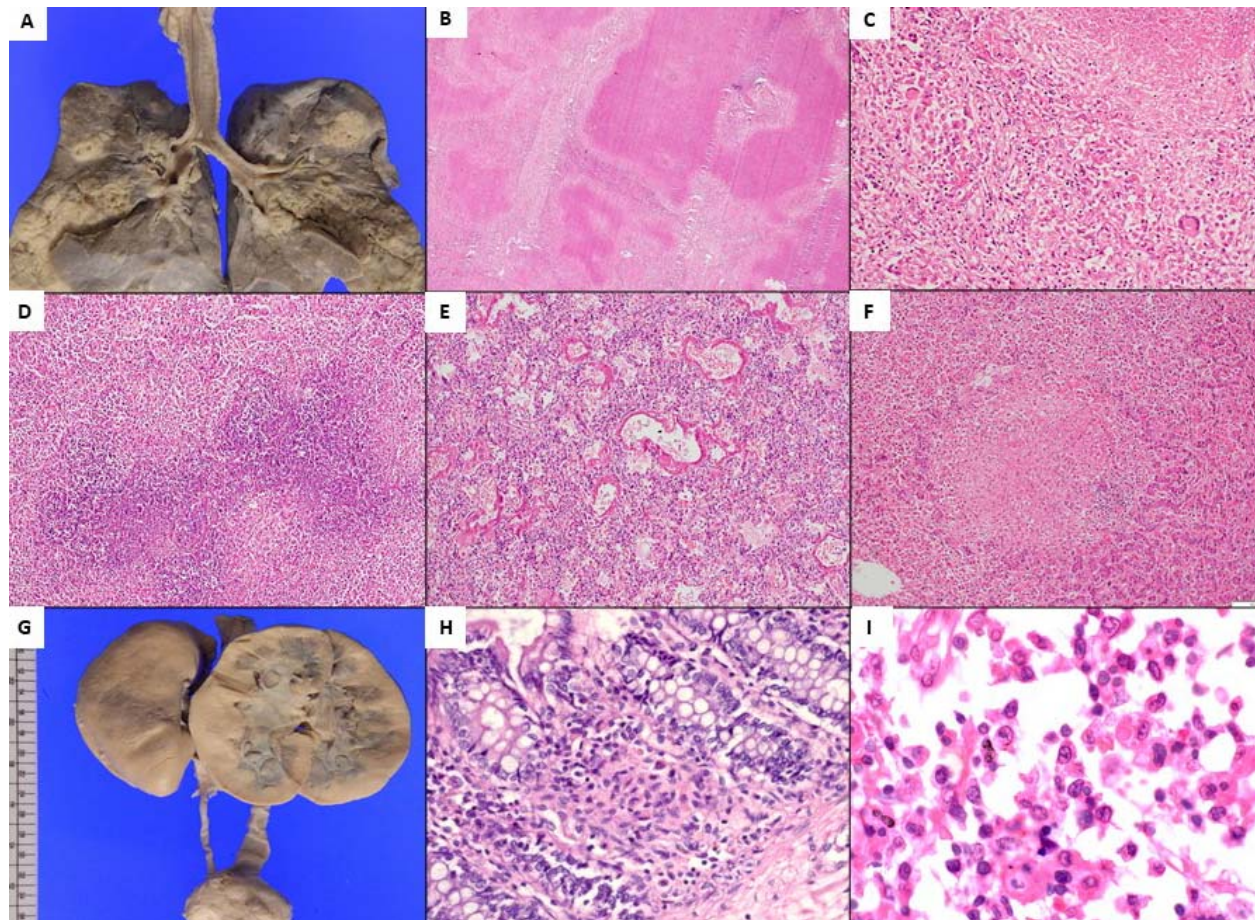


Fig. 2 A. Cut surface of both lungs shows greyish white nodules of variable size with central necrosis in larger nodules (Gross photograph); B. Large geographic type necrosis of lung parenchyma limited by interlobular septae (20X, H&E); C. Necrosis is palisaded by epithelioid cell granuloma with giant cell formation (200X, H&E); D. Abscess formation with dense neutrophils rich inflammation in adjoining alveolar spaces (200X, H&E); E. Glassy eosinophilic membrane noted along alveolar wall indicating diffuse alveolar damage (200X, H&E); F. Microscopy of liver showing necrosis with palisading epithelioid histiocytes (200X, H&E); G. Left ureter is dilated from vesico-ureteric junction to renal pelvis. Cut surface of left kidney shows mildly dilated pelvicalyceal system (Gross photograph); H. Microgranulomas with pigmented histiocytes are seen in the lamina propria of large intestine (200X, H&E); I. Bone marrow shows increase in number of histiocytes with significant hemophagocytosis (100X, H&E).

The sinus spaces of lymph nodes were markedly distended and infiltrated by benign histiocytes. Well-defined granulomas without central necrosis and occasional multinucleated giant cells were seen.

Bone marrow was hypercellular with increased histiocytes, and hemophagocytosis of neutrophils, lymphocytes and RBC in histiocytes (**Fig. 2I**). Focal hemophagocytosis was observed in liver, spleen and lymph nodes.

Other organs such as heart, thymus, testis, adrenal and skeletal muscles were grossly and microscopically normal.

Final autopsy diagnosis was necrotizing granulomatous inflammation with massive necrosis and

abscesses (*N. pseudobrasiliensis*), diffuse alveolar damage in the lungs with necrotizing granulomatous inflammation and microabscesses in liver and spleen with granulomatous colitis with left sided hydro-ureteronephrosis, granulomatous cystitis and granulomatous lymphadenitis. The overall pathologic features are consistent with a diagnosis of CGD with features of shock and HLH

OPEN FORUM

Microbiologist 1: *Nocardia pseudobrasiliensis* is usually multidrug resistant and only cotrimoxazole may work in this infection [11,12].

Pathologist 1: What is the role of FDG-PET in such a child?

Clinical discussant: FDG-PET is done in a child with prolonged fever with no obvious cause on routine investigations. The index child had evidence of bilateral consolidation during first admission. CT scan of chest may have served the purpose of delineating the consolidations better and to decide on invasive investigations for microbiologic diagnosis.

Pediatrician 2: Could the choice of antibiotics have been different?

Clinical discussant: Empiric therapy for infections in a patient with CGD includes staphylococcal cover (cloxacillin or vancomycin) and cover for gram negative bacteria (carbapenam or fluoroquinolone) [13]. Antifungal cover may be added if the patient is sick. Change in regimen may be required once an organism is isolated from clinical specimens [13].

Pharmacologist 1: Ceftriaxone and cotrimoxazole could have been good choice in this child.

Gynecologist 1: What counselling was done for the family?

Clinical discussant: Parents have been counseled about the disease, need to investigate elder sibling and risk of recurrence of 25% in any pregnancy. They have been counseled regarding need of chorionic villous sampling at 9-10 weeks of gestation for prenatal diagnosis.

DISCUSSION

Microbiological identification of organism requires invasive investigations in a child with persistent pneumonia as clinical and radiological profiles lack etiologic specificity and yield of blood culture is extremely low [2]. An early FNAC from lung lesions may have altered the outcome in the index child. Identification of organism is not only important for appropriate antimicrobials but also gives clue regarding underlying disease.

CGD is a prototype phagocytic defect due to reduced phagocyte oxidase activity. Genetic defects can cause deficiency of any of the four components namely gp91, p22, p47 and p67 of phagocyte oxidase [13]. Reduced activity of phagocyte oxidase results in defective phagocytosis and consequent infection with catalase positive bacteria and fungi. Pneumonia, lymphadenitis, subcutaneous or visceral abscesses, and osteomyelitis are frequent infections. Bacteremia and fungemia are less frequent. Initial infection with unusual organisms such as *Burkholderia*, *Nocardia*, *Serratia* and *Aspergillus* should raise the suspicion [14]. Recurrent deep staphylo-coccal infections should also warrant investigation.

Besides infections, hyperinflammation can result in failure to thrive, hepatosplenomegaly, lymphadenopathy,

anemia, thrombocytosis, and raised inflammatory parameters [5]. Organ specific inflammation can present as colitis, granulomatous cystitis, gastric outlet obstruction, and hydronephrosis [5]. Diagnosis is clinched by demonstration of reduced phagocyte oxidase activity by NBT or DHR assays [5]. Expression of b558 helps in demonstrating gp91 and p22 components of phagocyte oxidase. While X-linked CGD due to gp91 deficiency is the commonest type in the West [6], the same is not true in other countries [7]. Owing to frequent consanguinity, AR-CGD contributes to 50-60% of all CGD patients in Asia. Severity of disease depends on residual activity of phagocyte oxidase [7]. Cotrimoxazole and itraconazole prophylaxis with or without interferon- α have resulted in significantly better outcomes [13]. Failure of the prophylaxis warrants hematopoietic stem cell transplantation.

Both *Burkholderia* and *Nocardia* are signature opportunistic organisms in CGD. Pulmonary involvement due to *Nocardia* can present with focal or multifocal consolidations with central cavitation and pleural effusions [11,12]. Most *Nocardia* species are susceptible to sulphonamides, linezolid, amikacin, imipenam, minocycline, and moxifloxacin with *Nocardia pseudobrasiliensis* being more resistant [11]. Prolonged combination therapy with 2-3 drugs is preferred for invasive disease. Steroids have been used in combination with appropriate antibiotics in CGD patients with *Nocardia* infections [15].

In conclusion, we need to be more invasive for microbiologic diagnosis when the clinical course does not suggest CAP. Isolation of organism not only provides guidance to choice of antimicrobials but also provides clue to underlying disease.

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An External Evaluation on the INCLIN Research Program to Emphasize the Public Health Significance of Childhood Pneumonia in India

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Objective: An independent external evaluation of the International Clinical Epidemiology Network (INCLIN) research program to emphasize the public health significance of childhood pneumonia in India. **Method:** An independent evaluation based on desk reviews of available documents and reports, site visits to study sites, and structured interviews with study investigators, technical advisory group (TAG) members, INCLIN staff and the donor agency. **Findings:** The program elicited responses from a range of investigators across India. The selection process was transparent and objective, and the selected projects were of public health significance. The support provided through the program strengthened research capacity and improved study outputs. However, the available expertise was not fully exploited and protocol deviations in a few studies resulted in suboptimal outputs. **Conclusions:** The program represented a new and positive paradigm for research support in India, though a few improvements may result in greater impact for future programs.

Keywords: Assessment, Child Health, Health Program, Respiratory infection.

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The International Clinical Epidemiology Network (INCLIN) established a research program to emphasize the public health significance of childhood pneumonia in India [1]. A grant from the Bill and Melinda Gates Foundation (BMGF) was used to provide catalytic funding to Indian investigators to conduct research to generate data of public health importance on childhood pneumonia in India. In addition to financial support, the program also provided technical support to improve the design, management and implementation of the research studies through two expert bodies, the Joint Working Group (JWG) and the Technical Advisory Group (TAG). The JWG consisted of 14 national and international experts who guided the development of the program evaluation framework and identified the research priorities to be supported. The TAG consisted of 32 national and international experts representing different field of research. Its role was to review and select the research projects, support capacity strengthening of the study investigators and institutes, and guide the analysis and dissemination of research outputs. The INCLIN secretariat closely monitored the implementation of each study through the review of regular progress reports and quarterly phone calls with each project team.

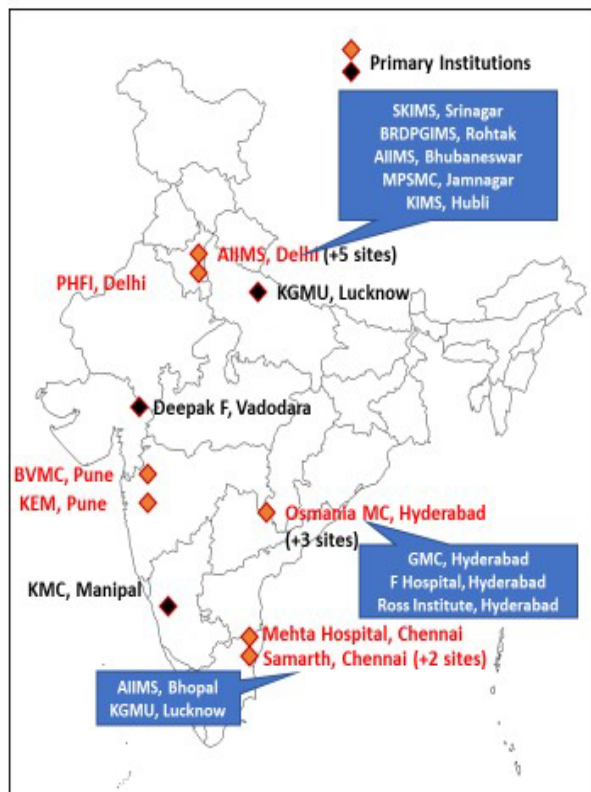
An external evaluation of the Program was conducted to obtain an independent, objective and credible assessment of the strengths and weaknesses of the

program that would help INCLIN and BMGF in making amendments to their programmatic operations, and to also enable other stakeholder and research funders to take informed decisions in supporting future research projects in India. This report briefly summarizes the methods, key findings and the recommendations from the evaluation.

METHODS

The authors of this paper were part of the three-member external evaluation team, which conducted the evaluation from 1-10 April, 2019. The evaluation focused on addressing the following four questions related to the overall program objectives: *i*) Was the research conducted under the Program of public health relevance? *ii*) Were the outputs from the Program likely to influence public health policy and programme planning and implementation? *iii*) Did the Program result in broadening of the researcher pool? *iv*) Did the Program strengthen research capacity in India?

The evaluation consisted of a desk review of all available documents and reports provided by the INCLIN secretariat, visits to seven of the ten research sites, telephone or Skype interviews with investigators at the three remaining research sites (**Fig. 1**), and interviews with a sample of TAG members, members of the INCLIN secretariat, and BMGF.



Childhood Pneumonia Program Site Visits

- 10 Projects: Combination of single site and multisite projects
- Visited 7 sites (Shown in red in the map)
- Interacted on video/teleconference with remaining 3 sites

Fig. 1 Site visits and interviews with research investigators.

FINDINGS

Based on the geographic spread and the range of investigators who responded to the Request for applications (RFA), it appears that this process was successful and achieved its objective of securing applications from around the country.

The evaluation indicated that the processes for the selection of research projects was transparent and objective for the first round of application. The choice of a single study in the second round was influenced by the funder’s priorities. The process managed to draw in less-experienced investigators and strengthened their capacity to conduct high-quality research. The provision of financial support to institutions that did not have clearance from the government under the Foreign Contribution Regulation Action (FCRA) to accept international funds was a significant achievement of this program, which enabled researchers from such institutions to carry out more substantive research projects, which they may not

otherwise have been able to conduct.

All the selected proposals were of public health relevance in India. The close engagement and support provided through the JWG and TAG resulted in improved study design and implementation of most of the studies. The program also created a new paradigm for the conduct, oversight and engagement with individual research studies in India to optimize their outputs and impact. The support from the INCLLEN secretariat, both technical and administrative, was greatly appreciated by all the investigators. The INCLLEN secretariat also conducted a Research leadership and programme management (LAMP) workshop, which benefited many of the new researchers in the program.

The program did have a few weaknesses, primarily that the expertise of the JWG and TAG was not fully exploited. Closer engagement of these two bodies during the implementation of the Program may have resulted in better outcomes for a few of the studies. While the TAG was closely involved in the process of selection of projects and in the finalization of study design, its engagement thereafter in the monitoring process was patchy. In addition, protocol deviations or changes were not always conveyed to or endorsed by the TAG as envisaged. The monitoring by the INCLLEN secretariat largely served to keep the projects on track and facilitated support for overcoming procedural bottlenecks. However, this oversight missed a few technical issues and protocol deviations that impacted the study outputs in a few projects.

Capacity strengthening was an important contribution made by the program. From all reports, the process and support provided far exceeded that provided by other national and international grant-making bodies and served in improving the design and implementation of the studies and resulted in better outputs. This was especially true for the less experienced investigators, though even the more experienced investigators reported having benefited from their participation in the program.

Of the ten research studies, seven are likely to make significant contribution to public health policy and program implementation in India. However, INCLLEN may need to play a greater role in disseminating the results to policymakers and program managers to promote the translation of the study results into public health policy and practice. Four studies evaluated care-seeking behavior for pneumonia, of which two have been published [2,3]. Two of them, which were mixed-method studies, found that knowledge about pneumonia was poor and care was mostly obtained from private service providers who were not knowledgeable about pneumonia case management. Two other studies evaluated the impact of behaviour

change communications (BCC), one which looked at its impact on the incidence of childhood diseases including pneumonia and the other that combined BCC with capacity strengthening for case management in primary care facilities in the public sector. Taken together, the findings of these studies can make important contributions to improving care-seeking and the quality of care for childhood pneumonia if it is possible to translate the findings into public health practice.

A fifth study evaluated the use of high flow nasal cannula delivery of oxygen for children with pneumonia and found that the technique and could be implemented in first referral level facilities could reduce the need for invasive ventilation, which is only available in tertiary care facilities. The sixth study used mathematical modelling to estimate the state level burden of pneumococcal disease and the cost-effectiveness of pneumococcal conjugate vaccine (PCV). The preliminary findings from this study informed the policy recommendations for the use of PCV in India. A seventh study, which is yet to be completed, is also likely to inform both global and national policies on the use of PCV.

RECOMMENDATIONS

The evaluation team made recommendation related to the current projects as well as for future projects supported by INCLEN; these are summarized below.

Recommendations for the Current Program

- a) Explore possibilities, in consultation with the JWG and TAG, to maximize returns from two studies which were not complete at the time of evaluation.
- b) The JWG/TAG should have a final closed meeting to review and score each project in terms of output and impact at the completion of the project and follow this up with a stakeholder meeting at national level to translate research to policy and practice.
- c) INCLEN secretariat should also facilitate engagement and advocate with state and district officials to promote translation of study findings to programmatic action, especially where site investigators are facing difficulties or did not have a dissemination plan.

Recommendations for Future Programs

- d) Consider higher weightage or special consideration to studies from under-researched areas/ populations on

topics that constitute important public health gaps.

- e) Provide only conditional approvals for proposals where TAG proposed major revisions, with final approval by TAG prior to study initiation.
- f) Provide greater oversight through TAG in study implementation, supplemented with mid-level researchers who can provide more regular handholding.
- g) Ensure that all changes in protocols are communicated to and approved by the TAG.
- h) Implement quarterly formal site audits to assess adherence to protocol, progress against defined milestones (e.g. enrolment rates) using structured checklists.
- i) Allow time and promote/ encourage networking at investigators' meetings to facilitate research collaborations.
- h) Make engagement with local level programme managers a requirement for studies with programmatic implications prior to study initiation.
- k) Make dissemination meetings a requirement for studies where the study results have a contribution to programme management.

Contributors: TC, PG, KT: evaluation undertaken and findings were analyzed and interpreted; TC: initial draft report was penned; KT,PG: intellectual inputs. All authors have approved the final report and take full responsibility for its contents.

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Feasibility of Pediatric Non-Invasive Respiratory Support in Low- and Middle-Income Countries

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Non-Invasive respiratory support can be viewed as mechanical respiratory support without endotracheal intubation and it includes continuous positive airway pressure, bi-level positive airway pressure, high flow nasal cannula, and non-invasive positive pressure ventilation. Over past few years, non-invasive respiratory support is getting more popular across pediatric intensive care units for acute respiratory failure as well as for long-term ventilation support at home. It reduces the need for invasive mechanical ventilation, decreases the risk of nosocomial pneumonia as well as mortality in selected pediatric and adult population. Unfortunately, majority of available studies on non-invasive respiratory support have been conducted in high-income countries, which are different from low- and middle-income countries (LMICs) in terms of resources, manpower, and the disease profile. Hence, we need to consider disease profile, severity at hospital presentation, availability of age-appropriate equipment, ability of healthcare professionals to manage patients on non-invasive respiratory support, and cost-benefit ratio. In view of the relatively high cost of equipment, there is a need to innovate to develop indigenous kits/ devices with available resources in LMICs to reduce the cost and potentially benefit health system. In this review, we highlight the role of non-invasive respiratory support in different clinical conditions, practical problems encountered in LMICs setting, and few indigenous techniques to provide non-invasive respiratory support.

Keywords: Continuous positive airway pressure, High flow nasal cannula, Low- and middle-income countries, Non-invasive ventilation.

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Non-invasive respiratory support (NRS) is defined as delivery of respiratory support without use of an invasive artificial airway such as endotracheal or tracheostomy tube. It can be delivered using negative pressure or positive pressure. In negative pressure ventilation, pressure surrounding the chest wall is lowered to decrease intrapleural pressure and thus, tidal volume is delivered to patient. Iron lung, which was used in polio epidemic six decades ago is an example of negative pressure ventilation [1]. In positive pressure non-invasive respiratory support, pressure is applied at the mouth and/or nose in spontaneously breathing patients. Continuous positive pressure ventilation (CPAP), Non-invasive positive pressure ventilation (NIPPV) and High flow nasal cannula (HFNC) are examples of positive pressure non-invasive respiratory support [2]. These modalities work by stabilizing chest wall, unloading of diaphragm and accessory muscles of respiration, increasing tidal volume/minute ventilation, maintaining functional residual capacity (FRC) to prevent atelectasis and maintaining patency of upper as well as lower airways [3]. These may also help to avoid complications associated with invasive ventilation such as infection, ventilator-induced lung injury, and airway edema [3]. Apart from supporting respiratory system, non-invasive

respiratory support also supports cardiovascular system [4]. Non-invasive respiratory support reduces the need for invasive mechanical ventilation, especially in mild to moderate cases of acute respiratory distress syndrome (ARDS) and acute lung injury [5-7]. In LMICs, cost-effective indigenously developed CPAP systems have been shown to reduce mortality and referral to tertiary care neonatal intensive care units (ICUs) in term and preterm babies with respiratory distress syndrome [8-10]. Though pediatric critical care is well developed in high-income countries, it still remains in its early stage in most LMICs due to lack of well-equipped intensive care units, trained staff, rapid access to necessary medications and supplies. Complications and mortality from high burden diseases like severe pneumonia, severe malaria and diarrhea can be reduced by training healthcare providers, selecting resource-appropriate effective indigenous equipment and co-operation from governing bodies and industry [11]. This review is aimed to address few issues relevant to the LMIC settings.

Are children from LMICs with specific respiratory problems likely to benefit from non-invasive respiratory support?

NRS can be safely used in clinical conditions such as pneumonia, bronchiolitis, asthma exacerbation, post-

extubation airway problems, acute respiratory failure in immuno-compromised children, post-operative respiratory failure (cardiac as well as non-cardiac), neuromuscular weakness, and obstructive sleep apnea [2] (**Box I**). Non-invasive respiratory support in pediatric acute respiratory failure is associated with improvement in physiological parameters such as heart rate, respiratory rate, saturation and decreased need for invasive mechanical ventilation [12]. HFNC was associated with higher ventilation free days at day 28 in children with acute hypoxemic respiratory failure [5]. Few chart reviews and proceedings from the Pediatric Acute Lung Injury Consensus Conference suggest that NRS can be safely used in children with mild to moderate- acute respiratory distress syndrome [13-15]. A recent systematic review on bubble CPAP (bCPAP) and HFNC therapy in children (day 1 to 12 years) with severe pneumonia and hypoxemia in developing countries concluded that bCPAP may be effective and the use of HFNC therapy is very limited in LMICs [16]. Non-invasive respiratory support is also commonly used in critically ill children with congenital or acquired heart disease with respiratory distress and was found to decrease both intubation re-intubation rates [17-19]. Non-invasive respiratory support is being used as first line therapy to correct hypoxemia/hypercarbia in immunocompromised children, especially those with mild to moderate ARDS and stable hemodynamic status [20-22]. In the recent past, there has been a trend towards NRS use even in obstructive lung diseases such as status asthmaticus in children [23-25].

Non-invasive respiratory support also has a role to support respiratory system in children with neuro-muscular disease (NMD). In a prospective study, where children with NMD (Duchenne muscular dystrophy, spinal muscular atrophy, limb girdle muscular dystrophy, congenital myopathy) and acute respiratory failure were treated with combination of NRS and mechanical in-exsufflator during hospital stay, physiologic indices such as PaO₂, PCO₂, pH, and PaO₂/FiO₂ improved in all patients without any mortality; this highlights the role of NRS in NMDs [26]. NRS is also commonly used in children to prevent re-intubation during post-extubation period in high-risk patients [27-30]. Summary of studies on utility of non-invasive respiratory support in pediatric respiratory failure is shown in **Web Table I**.

A recent systematic review on non-invasive ventilation in children and adults in LMICs, mostly from South Asia included 10 pediatric studies (N=1099). Pneumonia, malaria and dengue shock syndrome were the most common conditions requiring NRS. CPAP and bubble CPAP were commonly used NRS modes. Pooled risk for mortality was 9.5% (95% CI 4.6-14.5) and NRS failure was seen in 10.5% (4.6-16.5). Success rates of non-invasive respiratory support

Box I Indications of Non-Invasive Ventilation

Clinical conditions with pulmonary shunt

- Pneumonia
- Acute lung injury
- Inhalational injury
- Pulmonary edema
- Difficult intubation
- Restrictive lung diseases
- Scoliosis
- Chest wall restriction
- Interstitial lung diseases

Hypoventilation

- Weaning from anesthesia
- Neuromuscular disorders like spinal muscular atrophy and Gullian Barré syndrome

Upper airway obstruction

- Obstructive sleep apnea
- Altered mental status
- Upper airway edema

Chronic lung disorders with increase/retained secretions

- Cystic fibrosis
- Primary ciliary dyskinesia
- Palliation therapy for respiratory support

ranged from 57 to 96% and were higher in patients with acute asthma compared to pneumonia. Pooled risk of facial skin sores and pneumothorax were 2.4% (95% CI 0.8-3.9) and 1.9% (95% CI 0.1-3.9), respectively [31]. Apart from knowing the conditions where NRS can be successful, it is also equally essential to know the conditions where it is likely to fail and is contraindicated. Non invasive respiratory support is likely to fail in conditions when mean airway pressure (MAP) >11.5 cm of H₂O, FiO₂ > 0.6, there is less or minimal decrease in heart rate/respiratory rate after 1-2 hours of initiation, presence of other organ dysfunction, or presence of severe disease (high PRISM/ Pediatric logistic organ dysfunction scores) [32-35]. Absolute contraindications are respiratory arrest, facial trauma/burns, upper airway obstruction, comatose patients, intolerance, intestinal obstruction and Gullian Barré syndrome (GBS) with absent gag reflex. From the above discussion, we can say that common diseases in our settings such as pneumonia, dengue, malaria are likely to benefit from non-invasive respiratory support, particularly in areas where ICU facilities are limited/ not available. Complications related to NRS are: *Barotrauma*: can lead to tension pneumothorax, pneumomediastinum, or massive subcutaneous emphysema especially when the child is very agitated; *Aspiration*: may occur due to gastric distension and vomiting; *Skin break down*: facial skin irritation and ulceration are seen with nasal or oronasal masks; *Nasal mucosal trauma*: use of nasal masks or nasal prongs obstruct nostrils and may lead to epistaxis in case of inadequate humidification; *Gastric distension*: when inspiratory pressures exceed lower

esophageal sphincter pressure (normally 10 mmHg) or when the patient swallows air (eg, during crying), it leads to gastric distension; *Eye irritation or injury*: ocular trauma, primarily corneal abrasion or ulceration, can occur if the edge of the mask is in contact with the eye surface. A flow chart on initiation and monitoring of NRS is shown in Fig.1.

Whether suitable indigenous equipment for providing non-invasive respiratory support are available? If not, is there a need to modify existing imported design of NRS machines for their use in LMICs?

Components required for NRS are interface, ventilator/equipment and humidifier. Interfaces include nasal pillow, nasal cannula, oro-nasal mask, full-face mask, helmet (Fig. 2). In LMICs, availability and cost of interfaces are major hurdles to provide non-invasive respiratory support even in eligible children. Children with severe wasting usually have less buccal pad of fat, making fit of masks difficult. Another important equipment for non-invasive respiratory support is ventilator/specific equipment. Classical ICU ventilators or transport ventilators provide poor leak compensation and

need separate air and oxygen source. Ventilators which are designed specifically for non-invasive ventilation are usually portable, do not need separate air source and compensate well for air leak. However, the machines available in the market deliver minimum tidal volume of 100-150 mL which is much higher than tidal volume of infants and small children. Another important issue to consider is the cost of equipment. In authors' experience, cost of portable ventilators used for home ventilation in infants and children is approximately INR 400 000-500 000 (USD 5700-7200) apart from costs of the interface (e.g., mask), ventilator circuit tubing, humidifier, etc.; these costs may not be affordable by most families in a LMIC. Few BiPAP ventilator machines, which are designed for obstructive sleep apnea in adult population are available at somewhat lower costs, may be used in older children and adolescents. However, these machines have inherent problems like inability to titrate FiO_2 , lack of adequate battery backup, high inspiratory time, ineffective humidification, etc. For a PICU in a LMIC offering invasive mechanical ventilation, it may be desirable to have non-invasive modes in the same mechanical ventilator. In addition, low cost HFNC and bubble CPAP equipment may

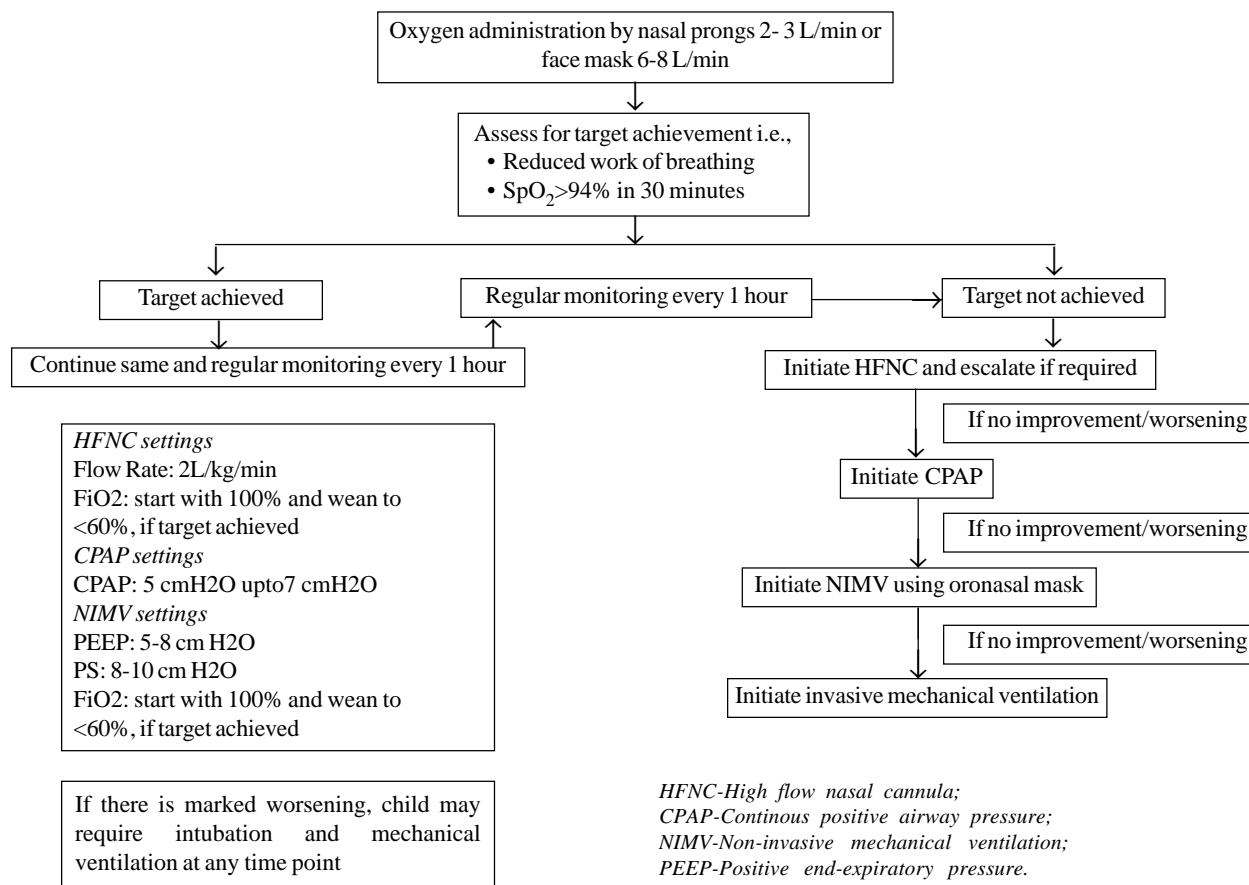


Fig.1 Flow chart of initiation and monitoring of non-invasive respiratory support.

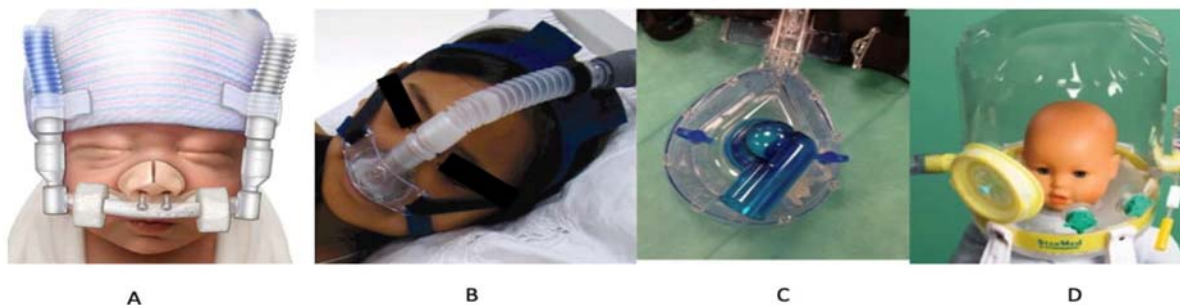


Fig. 2 Interfaces used for NIV (a-nasal cannula; b- nasal pillow; c- oronasal mask; d-helmet).

also be added. For units which do not have mechanical ventilators or inadequate numbers of ventilators, stand-alone low-cost HFNC and bubble CPAP equipment should be considered for installation.

Is there a need to have innovations in providing non-invasive respiratory support in LMICs?

In LMICs, in order to overcome the costs/availability issues, we may prepare indigenous equipment/devices to deliver NRS. Indigenously made CPAP equipment, bubble CPAP, have been used successfully in Indian PICUs. In a retrospective study from India, 60 children with acute hypoxic respiratory failure due to swine flu were treated with indigenous nasal bubble CPAP (NB-CPAP) (**Fig. 3**), which provided expiratory positive airway pressure of 5 cm H₂O and delivered FiO₂ of around 70%. All patients tolerated CPAP and none required endotracheal intubation [36].

In another study from India, indigenous CPAP was provided through flow inflating device-Jackson-Rees circuit (JR)/Bain circuit and using face mask as interface (**Fig. 4**). This study included 214 children and CPAP through flow inflating device was successful in 89.7% of cases, of which bronchiolitis accounted for 98.3%. A prolonged duration of CPAP support of >96 h was required in pneumonia. CPAP failure was noted in 10.3% of cases, the major risk factors being children <1 year and pneumonia with septic shock [37]. Jayashree, et al. [38] enrolled 330 children aged 1 month-12 years, with clinical pneumonia to bCPAP group (delivered via an underwater 'T' tube through nasal prongs) and nasal prongs group, and found that nasal CPAP is safe and effective. Indigenous HFNC circuit can also be prepared by using O₂/O₂-air mixture (blender) source, servo-control humidifier (heated wire humidifier), corrugated tubing and nasal prongs (**Fig. 5**). A blender can be used to regulate FiO₂. One has to be innovative to assemble locally available equipment in their hospitals to prepare indigenous non-invasive ventilation equipment. However, one has to remember that quality of indigenous equipment for NRS needs to be assessed by treating physician.

Training healthcare professionals to provide non-invasive respiratory support

Training of health care personnel (doctors, nursing staff, technicians) is equally important for successful outcome of non-invasive ventilation in intensive care. An important aspect of training is to choose right patient at right time for initiation. Apart from initiation, other important aspect is to closely monitor and identify early failure within 1-2 hours of initiation and step up the respiratory support in a timely fashion to improve outcome. In LMICs, where the nursing staff to patient ratio is often inadequate, early identification of failure poses an important challenge. The intensity/frequency of monitoring may actually be greater for a child undergoing non-invasive ventilation than invasive

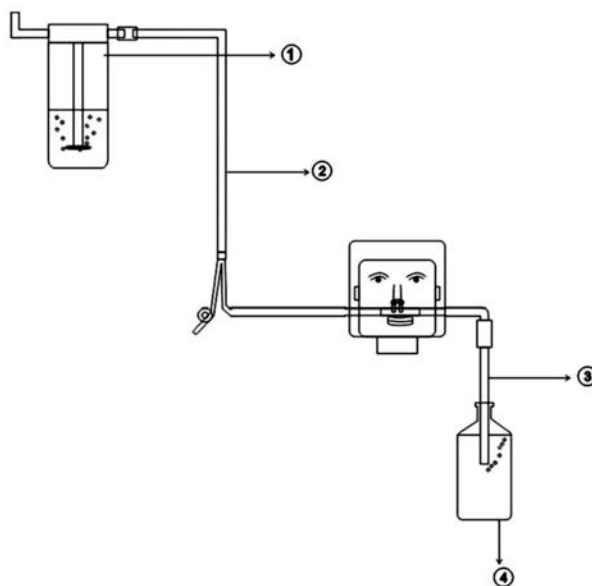


Fig. 3 Assembly of indigenous CPAP.

1- Oxygen supply through flow meter; 2- Nasal cannula; 3- Intravenous tubing cut and one end is attached to nasal cannula and other end is inserted in normal saline bottle to exert CPAP; 4- Normal saline bottle showing bubbles during exhalation.



Fig. 4 Flow inflating bag used for providing continuous positive airway pressure.

ventilation. So, having adequately trained man-power is critical for safe application of non-invasive respiratory support in critically ill children.

Will non-invasive respiratory support be cost beneficial in these countries?

A study from India [9] evaluated the cost effectiveness of

locally assembled low-cost CPAP system in neonates with respiratory distress, and found that neonatal mortality could be reduced using this CPAP system with cost of only 160 INR per one CPAP system.

In another study from Malawi [8], low-cost bubble CPAP system was used to treat neonatal respiratory distress and led to 27% absolute improvement in the survival when compared to standard care. A study on adults in India did cost-effective analysis of ward-based non-invasive respiratory support plus standard treatment with standard treatment alone in chronic obstructive pulmonary disease (COPD) with respiratory failure and found that ward-based NRS treatment increased the survival of patients with COPD respiratory failure, when ICU is not available, at a lesser cost [39]. Thus, non-invasive respiratory support in LMICs is not only cost-effective but also improves the outcome of patients requiring respiratory support.

Although India has now become a global market for many biomedical equipment and established itself as competitor for multinational counter parts, unfortunately hardly any of the NRS equipment or their parts are manufactured in India. So, there is an urgent need for establishing highly effective physician-engineer-industry collaborations for manufacturing cost effective, high quality non-invasive equipment as good as their multi-national counter parts. Often there are concerns about the quality of indigenous equipment; there has to be enough efforts put in by the manufacturers to ensure a certain level of quality of products, particularly for the safety features.

In developing countries, a child is likely to suffer around 0.3 episodes of pneumonia/year, and in developed countries it is 0.03 episodes per child/year [40]. Based on this, India is



Fig. 5 Indigenous high flow nasal cannula; a) Oxygen source and flow meter; b) Servo humidifier; c) connection of nasal prongs to corrugated tubing from humidifier; d) Nasal prongs placed in nasal cavity and should be of appropriate size to allow leak.

predicted to have about 700 million episodes of acute respiratory tract infections and about 52 million episodes of pneumonia every year [41]. For example, Broor, et al. [42] had reported 43 episodes, 536 episodes, and 2387 episodes of severe acute lower respiratory infections, acute lower respiratory infections and acute upper respiratory infections, respectively per 1000 child years from northern India. This shows that majority of children with acute respiratory tract infection need home based care or isolation, few children may need hospital care and very few of them need either high dependency unit (HDU) care or ICU care. Hence, there is a need to invest more in development and procurement of devices providing simple oxygen therapy or non-invasive respiratory support as most children with acute lower respiratory tract infection can be managed with them if intervened early and invasive ventilation is needed only in few. A pyramid depicting burden of respiratory illness and requirement of respiratory support has been shown in Fig. 5. Hence, in contrast to the usual tendency of clinicians and hospital administrations for having more high-cost equipment for invasive mechanical ventilation, there is a need to invest in procuring more of non-invasive respiratory support systems for possibly a better cost-effective solution in LMICs.

Role of non-invasive respiratory support in COVID-19 pandemic

Children of any age can be infected with COVID-19, but the severity seems to be less than that in adult population. In a systematic review, children accounted for 1-5% of total diagnosed COVID-19 cases [43]. As of April 2, 2020, among the 1,49,760 laboratory-confirmed cases reported to the US CDC (United States Centers for Disease Control and Prevention), children of less than 18 years constituted only 1.7% ($N=2572$) [44]. Among these children, 147 (range 5.7%-20%) were reported to be hospitalized, with 15 (range 0.58%-2.0%) admitted to ICU.

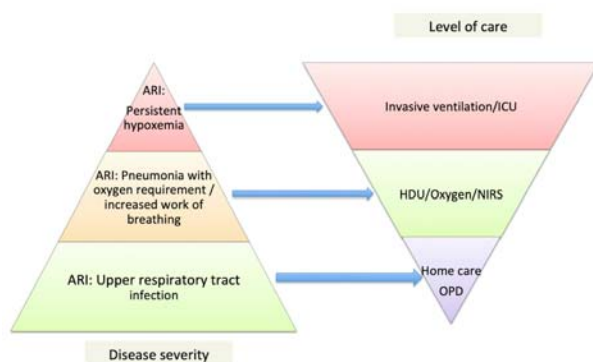


Fig. 4 Depiction of disease severity with level of care provided. ARI-acute respiratory infection; HDU-High dependency unit; ICU-Intensive care unit; NRS-Non invasive respiratory support.

In another report from China [45], out of 728 laboratory confirmed cases in children, 21 (2.9%) were either severe or critically ill. Children with severe/critical disease need respiratory support. When the respiratory status worsens in patients with non-COVID pneumonia, physicians use non-invasive ventilation without hesitation provided clinically appropriate. However, when noninvasive ventilation is considered in patients with COVID pneumonia, there are concerns about aerosol generation, which may cause contamination of ICU environment and staff. There is an ongoing debate on whether to use HFNC/NIV in patients with COVID pneumonia [46]. Appropriately fitted interfaces in HFNC/NIV may restrict direct release of air during expiration into the environment. However, in our set-up, limited availability of appropriate-sized interfaces for children, lack of negative pressure isolation rooms in all health care facilities and limited availability of high quality personal protective equipment to health care workers make pediatric intensivists not to use HFNC/non-invasive respiratory support in this scenario. Despite the apprehension associated with use of these modalities, 137 out of 1287 ICU admitted patients (11% [95% CI, 9%-12%]), were treated with non-invasive ventilation in Italy [47]. In a report from China, 61 out of 84 patients with COVID-19 ARDS received non-invasive ventilation [48]. However, there are no data describing whether these modalities were successful at avoiding intubation. Hence, the decision to initiate HFNC or NIV in COVID-19 patients should be taken by balancing the risks and benefits to the patient, the risk of exposure to healthcare workers, and availability of resources.

Monitoring on HFNC/NIV: If HFNC or NIV is administered, vigilant monitoring with frequent clinical (respiratory rates, retractions, cyanosis, sensorium) and arterial blood gas evaluation every one to two hours is needed to ensure efficacy and safety. Some physicians try HFNC/NIV while the patient is in the prone position, though there is no evidence for the same.

Precautions: Airborne precautions should be undertaken. While using HFNC, additional surgical mask can be placed on the patient face and lowest effective flow rate should be used. When NIV is initiated, a full-face mask rather than a nasal or oronasal mask is preferred to minimize particle dispersion. The mask should have a good seal and should not have an exit valve. For older children, helmet can be used as an interface. Dual limb circuit with a viral filter on the expiratory limb on routine ICU ventilator is preferred compared to single limb circuit on portable BIPAP machines. It is preferable to titrate ventilator setting to lowest effective pressures (e.g., 5-10 cm H₂O). Innovations are also being tried using a constant flow canopy over the upper part of the patient bed, thus building a restricted area around the patient where non-invasive respiratory support can be safely used.

KEY MESSAGES

- Noninvasive respiratory support is feasible in LMICs
- Clinician-industry-government collaboration is needed to design indigenous devices
- Studies on comparing indigenous devices with standard non-invasive respiratory support machines/ devices with respect to clinical outcomes are needed
- High quality of indigenous devices needs to be ensured
- Close clinical monitoring is the key for success of non-invasive respiratory support

This canopy system consists of flexible plastic canopy that covers the upper part of the body, fan filtering unit (FFU) using high efficiency particulate air (HEPA) filters and an exhaust system creating negative pressure and transferring the filtered air out to the open atmosphere [48].

India has diverse health facilities and facilities should have its own guideline whether to provide NRS to patients with COVID-19 pneumonia depending on availability of appropriate interfaces, personal protective equipment, negative pressure rooms, adequate staffing, etc. We need to strike a balance between benefit to the patient and risk to health care workers while providing NRS.

CONCLUSION

Greater use of indigenous non-invasive respiratory support equipment, adequate training of healthcare providers to use and monitor and commitment from hospital administration are important steps to improve outcomes of children in LMICs. Though HFNC is a promising therapy, it has not been adequately studied in LMICs and requires further studies prior to its widespread use. Cost-effective evaluation including assessment of optimal professional staffing levels should be addressed in future studies of non-invasive respiratory therapies in LMICs. To fill up the existing huge demand supply gap of non-invasive ventilation equipment, there is a need to develop high quality, locally manufactured, affordable non-invasive respiratory support equipment by facilitating partnership between governing agencies and industry.

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Web Table I Summary of Various Studies on Use of Non Invasive Respiratory Support in Children

Author, year	Population	Methodology	Intervention	Objectives/Outcome variables	Results	Conclusion
Yanez et al., 2008 (12) (N=50)	1month -15 years Children with respiratory failure based on FiO ₂ requirement >50% to maintain SPO ₂ >94%, with moderate to severe respiratory distress	RCT Study group (N=25): NIV plus standard therapy Control group(N=25): Standard therapy	Study group received inspiratory pressure:12-18 cm H ₂ O expiratory positive airway pressure 6- 12 cm H ₂ O Control group: mask oxygen at FIO ₂ >50% to keep saturation at >94%	Primary outcome: Need to intubate, Secondary outcome: improvement in vital signs and gas exchange for 48 hrs	Intubation rate was significantly lower in study group (28% vs 60%,p=0.045) Heart rate and respiratory rate were significantly lower after 1 hr of treatment compared with admission in study group.	NIV improves hypoxemia, signs and symptoms of acute respiratory failure and also prevents endotracheal intubation
Fortenberry et al, 1995 (13) (N=28)	Children <18 years with signs of respiratory distress who are likely to get intubated or re-intubated	Retrospective	All children received BiPAP through nasal mask		Respiratory rate decreased significantly with BiPAP(45±18 breaths per minute to 33±11, p<0.001). PaO ₂ improved (71±13 mm Hg to 115±55), PaCO ₂ , pulse oximetry saturation, and pH all improved significantly (p<0.01) Only 3 of 28 patients required intubation or re-intubation.	Non-invasive nasal positive pressure mask ventilation can be safely and effectively used in pediatric patients to improve oxygenation in mild to moderate hypoxemic respiratory insufficiency and it also avoids reintubation.
Essouri et al.,2006 (14) (N=114)	Children treated by Non invasive positive pressure ventilation(NPPV) over five consecutive years in PICU	Retrospective	Nasal or facial masks were used with dual limb circuit Mode used: Pressure support with positive end expiratory pressure	Failure of NPPV defined by the necessity of endotracheal intubation during the PICU stay	77% were successfully treated by NPPV without intubation The success rate of NPPV was significantly lower (22%) in patients with acute respiratory distress syndrome (p< 0.05) high PRISM II and PELODS at admission were associated with unsuccessful NPPV 9.6% who received NPPV died	NPPV could be proposed as a first-line treatment in children with acute respiratory distress, except in those with a diagnosis of acute respiratory distress syndrome.
Essouri et al., 2015 (15)	Children(1month – 18 years) with acute respiratory distress syndrome(ARDS)	Systematic review on non invasive ventilation in children with ARDS			NPPV can improve gas exchange and potentially prevent intubation and mechanical ventilation in some children with mild pARDS NPPV is not indicated in severe pARDS An oronasal interface provides superior support, The efficacy of high-flow nasal cannula compared with noninvasive positive pressure ventilation is unknown	NPPV can be beneficial in children with pediatric acute respiratory distress syndrome, particularly in those with milder disease.

Gupta P et al., 2012 (17)	Children between the ages 1 day and 18 years with acute respiratory failure who required NIV in a cardiovascular intensive care unit (CVICU)	Retrospective	Prophylactic group: NIV was given directly after extubation Non-prophylactic group: NIV was given after signs and symptoms of respiratory failure developed. Modes of NIV used were CPAP and BiPAP. CPAP or EPAP was initiated with 4–5 cm H ₂ O for all and maximum of 10–12 cm H ₂ O IPAP was initiated at 6–8 cm H ₂ O and maximum of 18–20cm H ₂ O was given	To identify the predictors of NIV success in preventing extubation failure in critically ill children with heart disease. To assess the efficacy of prophylactic NIV therapy To determine the characteristics, outcomes, and complications associated with NIV therapy in pediatric cardiac patients	221 events were included 172 responders (77.8 %) and 49 non-responders (22.2 %) were noted 201 events received CPAP with 156(78%) responders, 20 events received BiPAP with 16(80%) responders 58 events (26.3 %) were assigned to the prophylactic group and 163 events (73.7 %) to the nonprophylactic group. The prophylactic group experienced significantly shorter CVICU stay (median, 49 vs 88 days; p = 0.03) and hospital stay (median, 60 vs 103 days; p = 0.05)	NIV can be safely and successfully applied in critically ill children with cardiac disease to prevent extubation failure
Fernandez, et al.,2016 (18) (N=200)	Children 3days – 16 years age requiring NIV after heart surgery in a PICU over 12 years	Retrospective observational study comparing the first 6 years of the study with the last 6 years.	Physician driven use of NIV (CPAP/BiPAP)		Duration of NIV was 3 days (median) Mortality rate was 3.9%. The use of NIV was increased from 13.2% in first 6 years to 29.2% in the second 6 years (p <0.001). CPAP was the most common modality of NIV (65.5%). The use of BiPAP increased from 15% in first 6 years 42.9% in the second 6 years period (p < 0.001) NIV failed in 15% of patients. The mortality rate did not change between the two periods	NIV is increasingly being used in the postoperative period of heart surgery It is associated with a lesser need for invasive mechanical ventilation CPAP was the most common modality and in the in the latter years, the use of BIPAP has increased significantly
Kovacikova L et al, 2013 (19) (N=82)	Children 1day – 18 years age with congenital heart disease (post operative)	Prospective observational study	NPPV with pressure support and/or pressure control mode was applied Median PEEP used 10 cm H ₂ O (4–12) Median maximum IPAP used was 21 cm H ₂ O (10–28) Interfaces used were Naso-pharyngeal tube, Oro-nasal mask, or helmet	NPPV was used (1) in patients with hypoxemic or hypercarbic respiratory failure or those who were likely to require intubation based on clinical signs; (2) as a preventive measure in patients with high risk for extubation failure	Within the first hour of NPPV, partial pressure PaO ₂ /FiO ₂ was increased, and pCO ₂ , RR were decreased. In 59.8 % of cases, NPPV prevented tracheal intubation The Aristotle Basic Complexity score, presence of infection, residual cardiac defect, and pH <7.36 in the first hour were independent predictors of NPPV failure	NPPV improved oxygenation and decreased respiratory effort in pediatric cardiac patients, A high-complexity surgical score, presence of infection, residual cardiac defect, and pH <7.36 in the first hour are predictors of NPPV failure
Pancera CF et al. 2008 (20) (N =239)	Immunocompromised children with acute respiratory failure	Retrospective Two groups 1. NIV group (N=120), defined as children who received NPPV as the first choice for at least 24 hours 2. Invasive	The NIV mode used was pressure support with positive end-expiratory pressure. Nasal mask was used Decision to initiate NIV was by the	To evaluate the feasibility of NPPV in PICU To assess the clinical efficacy of NPPV To identify predictive factors	1/4 th of the patients from the NIV group subsequently required intubation. Independent predictive factors for intubation were solid tumors cardiovascular dysfunction and	NIV can be used as first-line treatment in children with malignancies who develop acute respiratory failure, except those with severe hemodynamic compromise

		ventilation group(N=119) defined as children who received conventional MV as the first choice ^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100}	physician	for endotracheal intubation	therapeutic intervention scoring system score (TISS) >40 points	
Piastra et al., 2009 (22) (N=23)	Immunocompromised children with acute respiratory distress syndrome (ARDS)	Retrospective	Mode: pressure support mode or pressure controlled Interface: face mask/helmet	To evaluate the feasibility of non-invasive ventilation (NIV) in immunocompromised children with ARDS	Early and sustained improvement in P/F ratio were observed in 82 and 74% of cases, respectively. 13 out of 23 (54.5%) avoided intubation and were discharged from the PICU. PICU and intra-hospital mortality was higher for NIV-non responders (p <0.001). PICU stay was shorter for NIV responders (p = 0.03).	NIV administration is feasible and well tolerated in immunocompromised children with ARDS. A short NIV trial can be used to verify the usefulness of the technique.
Basnet et al., 2012, (23) (N=20)	Children age 1-18 years admitted to PICU with status asthmaticus with a clinical asthma score 3-8 after receiving one dose of methylprednisolone, 1 hr of continuous albuterol (SABA), and three doses of ipratropium bromide	RCT NPPV plus standard treatment versus standard treatment alone	BiPAP mode with face mask/nasal mask was used Inspiratory positive airway pressure was gradually increased to 8 cm H ₂ O to achieve a tidal volume of 6–9 mL/kg and end-expiratory positive airway pressure to 5 cm H ₂ O	Improvement in the clinical asthma scores	Improvement in clinical asthma score was significantly greater in non invasive positive pressure ventilation group compared to standard group at 2 hrs, 4–8 hrs, 12–16 hrs, and 24 hrs after initiation of interventions (p<0.01). There were no major adverse events related to NPPV. 9 out of 10 patients tolerated NPPV through the duration of the study	Early initiation of non invasive positive pressure ventilation, along with short acting β-agonists and systemic steroids, can be safe, well-tolerated, and effective in the management of children with status asthmaticus
Thill et al., 2004 (24) (N=20)	Children admitted to the pediatric intensive care unit with acute lower airway obstruction	RCT, cross over	Group 1: 2 hrs of NIV followed by crossover to 2 hrs of standard therapy Group 2: 2 hrs of standard therapy followed by 2 hrs of NIV BiPAP was used using nasal mask IPAP of 10 cm H ₂ O and an EPAP 5 cm H ₂ O, were used	Improvement in clinical asthma severity (CAS) score	Non invasive ventilation decreased signs of work of breathing compared with standard therapy There was no serious morbidity associated with noninvasive ventilation.	Non invasive ventilation can be an effective treatment for children with acute lower airway obstruction
Pilar et al., 2017 (25) (N=42)	Children (1.5 – 14 years) with acute severe asthma admitted to PICU	Retrospective Patients were given high flow nasal cannula (HFNC) or non invasive ventilation (NIV) as per physician discretion	For NIV, BiPAP mode was used with full face masks or oronasal masks as interface IPAP of 8 cmH ₂ O and EPAP of 4 cmH ₂ O were used to achieve a tidal volume of 6-9 ml/kg. IPAP and EPAP were titrated based on tidal volume, saturation and clinical signs For HFNC, flow rates: 2 L/kg/min for the first 10 kg plus 0.5 L/kg/min for each kg above that (maximum	Primary outcome measure was failure of initial respiratory support (need to escalate from HFNC to NIV or from NIV to invasive ventilation). Secondary outcome measures were the duration of respiratory support and PICU length of stay (LOS)	22 received NIV 20 received HFNC The mean EPAP was 5cmH ₂ O (4-7) and the mean IPAP was 12cmH ₂ O (8-17) No treatment failure in NIV group 8 children (40%) in the HFNC group required escalation to NIV. The PICU length of stay was similar in both the groups. HFNC failure subgroup had longer respiratory support duration and longer PICU stay compared to HFNC success subgroup.	Early initiation of NIV is a safe and feasible initial alternative for the treatment of severe asthma exacerbation. HFNC could potentially delay the initiation of NIV in severe cases and result in longer PICU stay, and the consequent morbidity and cost

			flow 50 L/min)			
Fioretto et al., 2015 (27) (N=108)	Children aged 1 month to 3 years who were intubated and mechanically ventilated for 48 hours	RCT	NIV group(N=55): NIV was provided using conventional ventilator with PC-SIMC-PS mode. Initial PEEP of 5 cm H ₂ O, IPAP of 15 cm H ₂ O, PS of 10 cm H ₂ O, and FiO ₂ of 50% Maximum PEEP of 10cmH ₂ O Maximum IPAP of 20cmH ₂ O and maximum PS of 15cm H ₂ O were used A nasal or facial mask was used as interface. Standard group (N=53): Oxygen by nasal cannula		Reintubation rates in NIV group was 9.1% and in standard group was 11.3%(p=>0.05) No difference in length of PICU stay or hospital stay	No differences were seen between groups. The number of excluded patients was high
Juan P. Bonora et al., 2018 (29) (N=255)	Children aged 1 month to 18 years old who required post extubation NIV	Retrospective multicenter Rescue NIV (N=112): implementation of NIV within 48 hours of extubation due to respiratory failure Elective NIV (N=143): implementation of NIV prophylactically after extubation	NIV modes included pressure support ventilation, pressure-assist/control ventilation, bi-level pressure support, continuous positive airway pressure	To determine the rate of post-extubation NIV success and the factors associated with failure or success	The rates of success in rescue and elective NIV were 68.8% and 72.7%, respectively Mortality was higher among patients in whom rescue NIV failed	The use of post-extubation NIV may be a useful to prevent re-intubation
Mayordomo-Colunga J et al., 2010 (30)	Children admitted to PICU who had invasive ventilation for at least 12 hours and then extubated	Prospective observational study Types of NIV elective NIV: when the patient was extubated directly to NIV rescue NIV: when the child developed respiratory failure within 48 hours of extubation	BiPAP was used Nasal mask, facial mask/helmet were used as interface In elective NIV, EPAP was set at 1-2 cmH ₂ O higher than previous PEEP during invasive ventilation. In rescue NIV, initial EPAP was 4-5 cmH ₂ O IPAP was started at 6-8 cmH ₂ O in both	To determine post-extubation NIV characteristics and to identify risk factors of postextubation NIV failure.	rescue and elective NIV had success rate of 50% 81% respectively(p = 0.037).	Post-extubation NIV seems to be useful in avoiding reintubation when applied immediately after extubation

Sleep Studies in Children

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Sleep-related breathing disorders (SRBD), also referred to as sleep-disordered breathing (SDB), are common sleep disorders in children. They can be broadly divided between central and obstructive sleep-disordered breathing with or without associated hypoventilation. In most cases, SRBD are associated with adenotonsillar hypertrophy (obstructive SDB) which are classified as simple. SRBD can co-exist with an underlying condition like obesity, genetic syndromes or neuromuscular disorders which are classified as complex. Polysomnography (PSG) is the gold standard for diagnosing sleep disorders. However, it is time-consuming and requires trained technician to acquire and interpret signals. Attended in-lab respiratory polygraphies are easier to conduct and provide respiratory data equivalent to a PSG. Similar to adult sleep services, overnight unattended home respiratory polygraphies are becoming more widely used. These require careful patient selection and good parental education programs to be most successful in children. Overnight oximetry has limitations but can be a useful tool for screening children with obstructive sleep apnea and prioritizing treatment. This review aims to discuss these various diagnostic methods to assess sleep disorders in children.

Keywords: Adenotonsillar hypertrophy, Diagnosis, Polysomnography Sleep-related breathing disorders.

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The International Classification of Sleep Disorders 3 (ICSD-3) broadly classifies sleep disorders into insomnia, sleep-related breathing disorders (SRBD), central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders and other sleep disorders [1].

Sleep-related breathing disorders (SRBD) commonly referred to as sleep disordered breathing (SDB) is an umbrella term for chronic conditions with partial or complete cessation of breathing occurs many times throughout the night. This leads to sleep fragmentation and impacts gas exchange with night-time symptoms, daytime symptoms and long-term deleterious health effects. SDB is divided into obstructive sleep disordered breathing and central sleep disordered breathing with or without hypoventilation. The subtypes of SDB are not exclusive and several subtypes can be present in a child depending on the clinical situation.

The commonest type of SDB is obstructive sleep apneas/hypopneas syndrome (OSAHS). OSAHS is a disease spectrum varying from prolonged partial airway obstruction (snoring and upper airway resistance) to intermittent complete upper airway obstruction (obstructive sleep apnoea or OSA). OSAHS can be classified as simple or uncomplicated when it occurs only in association with adenotonsillar hypertrophy. It can be classified as complex or

complicated when it is associated with other medical disorders (e.g., neuromuscular diseases, chronic lung diseases, sickle cell disease), genetic syndromes (e.g., Down syndrome, obesity syndromes, craniofacial anomalies, Pierre Robin sequence) and other high risk comorbidities such as obesity.

Children with complex OSAHS often have multilevel airway obstruction related to their craniofacial morphology and upper airway tone. Morphological features include midface hypoplasia, flat nasal bridge, retrognathia, glossoptosis amongst others. In this complex group, it is not unusual to have a multifactorial complex SDB picture with a combination of obstructive, central and hypo-ventilation components [2].

Sleep negatively affects control of breathing, lung mechanics and respiratory muscle contractility with reduction in functional residual capacity and minute ventilation. Upper airway resistance also increases during sleep. Hence, SDB is seen in many chronic illnesses where detailed sleep evaluation and management should be considered. These include intrinsic cardiopulmonary disorders (advanced cystic fibrosis, bronchiectasis, bronchiolitis obliterans etc), chest wall abnormalities like kyphoscoliosis or thoracic dystrophy, neuromuscular diseases, spinal cord injury or genetic disorders like Prader Willi syndrome [3,4].

EVALUATION

Evaluation and diagnosis of childhood sleep disorders may include sleep questionnaires, sleep diaries, actigraphies and sleep studies. This review will detail these with an emphasis on pragmatic sleep diagnostic tools for developing countries.

Sleep Questionnaire

Many questionnaires have been used for diagnosis of simple OSAS, with pediatric sleep questionnaires (PSQ) by Chervin, et al. [5], being used most widely. PSQ has a sensitivity of 0.85 and specificity of 0.87 in otherwise well children aged 2-18 years for identifying SDB confirmed by polysomnography. Others have shown a moderate sensitivity and specificity to diagnose SDB. As such, they are useful as a screening tool in primary care. However, it is not a good screening tool for OSAS in children with complex underlying disorders e.g., neuromuscular disorders, cranio-facial anomalies and Down's syndrome [8].

Sleep Diary

Sleep diary is a simple and inexpensive screening tool where parents make a two week daily record of the child's daily sleep routine and sleep related activity. This is done by shading times where child is asleep including during the day and adding visual aids to see when the child went to sleep or woke up. This provides interesting and useful visual representation of sleep. Any additional information provides a useful complement e.g., how refreshing the night sleep was, the amount of exercise or medications and caffeine/food intake particularly in the period before bedtime. Sleep diary is also a useful tool to measure treatment outcomes. However, sleep diaries have their limitations as self-reporting has a subjective element prone to systematic biases. For example, parents had reported total sleep times (TSTs) that were significantly higher (by an average of 1-2 hours) than those reflected in actigraphy recordings of their child [7]. They are; however, easy to implement and can be useful in understanding sleeping patterns. Salient points to be noted on a pediatric sleep diary are shown in **Web Fig. 1**.

Actigraphy

Actigraphy devices are worn on the wrist and record movements (movements and light exposure both in the more modern devices) that can be used to estimate sleep parameters (sleep onset, sleep duration, wake time) with specialized algorithms in computer software programs. It has the advantage of providing objective information on sleep habits in the patient's natural sleep environment.

Actigraphy is well validated for the estimation of night-time sleep parameters across age groups. In patients reporting significant sleep disruption, it can objectively document sleep patterns and evaluate treatment outcomes.

They provide a visual map of a child's sleep and are less biased than the sleep diary. Typically two weeks of recording is recommended; however, this may vary depending upon the sleep parameters to be evaluated. Once the monitoring period is over the device is removed and data downloaded for evaluation. Actigraphy can be quite useful in evaluating hypersomnias, insomnias and circadian rhythm disorders [8].

SLEEP STUDY

A sleep study is a test that records physiological parameters while the child is asleep. It is usually done in a special sleep laboratory with the equipment to measure all the various physiological parameters including good video and audio recording. Ideally, a trained sleep physiologist sets up the study and monitors the child during the complete study. A good sleep study should have a total sleep time of at least six hours [9]. Sleep study using a non-standard equipment or untrained technicians have poorer data quality and are not routinely recommended. Unobserved studies currently have poorer data quality which may be overcome with the development of trained home sleep services. Recommendations for pediatric sleep investigations are currently the subject of British Thoracic Society guidelines with release expected in the near future.

Broadly, sleep studies can be classified as diagnostic or ventilation titration studies [non-invasive (NIV) or invasive via tracheostomy (long term ventilation or LTV)]. Diagnostic studies include simple overnight oximetry, oxycapnography, cardiorespiratory polygraphy (RPG) or a complete polysomnography (PSG). Details of how these studies are performed, scored and interpreted are available from the American Academy of Sleep Medicine (AASM) [10].

Diagnostic Sleep Studies

Oximetry: Overnight oximetry studies are unobserved downloadable studies done using a timed pulse oximeter. These studies might be domiciliary or in-hospital. The use of an appropriate oximeter is paramount for accurate data interpretation. For example, averaging time is a crucial setting in assessing the diagnostic efficiency of the oximeter. Longer averaging times (8-16s) may reduce signal artefact (e.g. from motion) but also reduce the ability to detect the rapid change in saturation (SpO₂) often seen with central or obstructive events (apnea/hypopnea). Therefore, a pulse oximeter with an averaging time of 2-3 seconds should be used to maximize diagnosis efficiency rather than the routine ICU pulse oximeters with usually longer averaging times. The oximeters should have the facility to download and review data in a way that is useful for interpretation of SDB. These studies are easy to perform and cost effective. They are useful in evaluating oxygenation in children on domiciliary

oxygen and help with weaning supplemental oxygen. Recent technical guidelines are available on overnight oximetry in children [1]. Overnight oximetry can also be useful to screen children with non-complex OSAHS for moderate to severe disease and help prioritize treatment. McGill's scoring [12], is done using the pulse oximetry trace. At least three clusters of desaturation events, and at least three SpO₂ drops below 90% in a nocturnal oximetry recording are indicative of moderate-to-severe OSAHS [12]. Abnormal oximetry had 97% positive predictive value to detect OSAHS diagnosed by in-laboratory PSG; however, sensitivity was 43%, indicating that patients with an inconclusive oximetry could still have OSA. Therefore, in the context of significant symptoms, an inconclusive oximetry is not enough to rule out OSA [13]. In children with OSAHS and co-morbidities, positive predictive value of the McGill score is significantly lower. The higher number of false positives in children with medical comorbidities may be due, to central apneas.

Cardiorespiratory sleep studies or respiratory polygraphy (RPG): This is a limited channel study involving respiratory channels (nasal airflow, thoraco-abdominal movements, oximetry, end-tidal or transcutaneous CO₂), cardiac channels (ECG, pulse oximetry) and body position channel. These studies are technician attended in-lab studies with a full audio and video recording and scored manually. Since the number of channels in a cardiorespiratory study are reduced [electroencephalogram (EEG), electro-oculogram (EOG), chin electromyogram (EMG)] it makes the set up and scoring less complex, less time consuming and provides almost the same respiratory information as a complete PSG. RPG can be scored using adapted rules as per the AASM 2012 guidelines for the scoring of sleep and associated events [10]. RPG have previously been demonstrated to be an accurate tool for the detection of SDB [14]. Sleep stages are scored as either wake, active sleep or quiet sleep in 30 second epochs by visual

analysis of the cardiorespiratory parameters based on heart rate and respiratory rate variability and amplitude of breathing patterns [15]. It however, provides limited information on sleep architecture. Recent evidence suggests that unattended respiratory polygraphy after being set up in doctor's clinic is feasible, technically acceptable and interpretable in between 81-87% of pediatric patients [16]. However, drawbacks from these particular studies were the absence of audio, video recording, technician monitoring and carbon-dioxide channel. More evidence is currently being collected about home respiratory polygraphies and many centers, following the lead of adult sleep specialists, are now gathering experience [17,18].

Polysomnography (PSG): This is a complete study involving the respiratory and cardiac channels previously described for RPG with additional neurological channels (EEG, EOG, chin EMG, leg EMG). Other channels like extended montage EEG, 24h esophageal ph/impedance, diaphragmatic EMG can be added as per clinical need. The details of the channels used in both types of studies are shown in **Table I**.

Scoring a sleep study involves scoring sleep stages and then scoring respiratory events. Sleep staging involves identification of REM and NREM stages (N1, N2, N3) and arousals based on EEG, EOG and chin EMG. Respiratory scoring involves identification of apneas, hypopneas, and hypoventilation as per the AASM guidelines definitions [10]. Apnea is defined as cessation of flow >90% of the baseline for >2 breaths or >10 seconds while hypopnea is defined as flow reduction by $\geq 30\%$ for >2 breaths or >10 seconds with either a $\geq 3\%$ oxygen desaturation or an arousal (on EEG). If the events are associated with snoring, flattening of nasal flows or thoraco-abdominal paradox they are classified as obstructive events. Central, obstructive or unclassified events are scored separately.

Table I Channels Used in Polysomnography and Cardiorespiratory Sleep Study or Respiratory Polygraphy

<i>Channel</i>	<i>Purpose</i>	<i>Cardiorespiratory sleep study^a</i>	<i>Polysomnography</i>
Nasal cannula or thermistor or both	Detects apnea and hypopnea	Yes	Yes
Thoracic and abdominal belts	Respiratory effort	Yes	Yes
Body position sensor	Body position	Yes	Yes
Microphone	Snoring	Yes	Yes
Video recording	Body movements, position, etc	Yes	Yes
Electrocardiogram	Cardiac rhythm	Yes	Yes
Oxygen saturation	Desaturations	Yes	Yes
CO ₂ : Transcutaneous or end tidal	Hypoventilation	Optional	Optional
EEG, EOG and chin EMG	Presence and stage of sleep	No	Yes
Leg EMG	Periodic limb movement	No	Yes

^aor respiratory polygraphy. CO₂-carbon dioxide; EEG-electroencephalogram; EOG-electro-oculogram; EMG-electromyogram.

The most important parameter defining SDB in a sleep study (PSG or RPG) is the apnea hypopnea index (AHI) which is defined as number of apneas and hypopneas per hour of total sleep time [10]. The AHI can be further subdivided in OAH (obstructive apnea-hypopnea index), CAHI (central apnea-hypopnea index) and UAH (unspecified apnea-hypopnea index for events difficult to characterize). An AHI < 1 is considered normal, an OAH between 1-5 represents mild OSA, 5-10 moderate OSA, and > 10 severe OSA. This classification only applies to OAH and OSA and cannot be extrapolated to central SDB. Additional information is available from video and audio like snoring, gasps, pauses, apneas, work of breathing and sleep posture. **Web Figs. 2-4** shows respiratory poly-graphy epochs of obstructive apnea, obstructive hypopnea and central apnea, respectively. **Web Fig. 5** shows a polysomnography epoch.

Non-Invasive Ventilation Titration Studies

Children deemed to require CPAP or a Bi-level PAP require a ventilation titration study to ascertain the adequacy of ventilation (and optimize the CPAP or bilevel PAP support (determination of optimal pressure settings and assessment of synchronization with the ventilator). During the sleep study, mask fitting and unintentional leak can also be assessed. NIV titration studies are ideally preceded by a phase of mask fitting and acclimatization. Split night studies are not usually done in children for initiating NIV. They can be done in children when improvement of underlying SDB is suspected and removal of NIV is being considered. Most NIV titration studies can be done as RPG or even oxycapnography in compliant patients.

Multiple Sleep Latency Test (MSLT)

MSLT is another type of sleep study performed to evaluate children with excessive daytime sleepiness (EDS) and are often diagnostic for narcolepsy. It measures how quickly a child falls asleep in a quiet and dark environment during the day (over 5 naps of 20 minutes separated by 2 hours break) and how often and quickly they enter into REM sleep during those naps. This is usually done after a diagnostic overnight PSG to confirm the absence of OSA as a cause of EDS and to ensure the quality of sleep the night before was decent and will not influence the result of the MSLT [20].

INDICATIONS

Currently, the majority of care givers make a diagnosis of SDB or OSAHS on clinical parameters that include night-time and daytime symptoms of OSAHS in the presence of a predisposing clinical condition like adenotonsillar hypertrophy, obesity, craniofacial syndromes etc. In this context, sleep studies are seldom used as they are deemed expensive, burdensome and are often unavailable for children.

However, contrary to the general belief, the correlation between clinical symptoms and severity of OSA is poor. A meta-analysis on seven models of OSA questionnaires presented moderate sensitivity (0.04-0.94) and specificity (0.28-0.99). Some clinical features such as excessive daytime somnolence and observed apneas had a better specificity but have poor specificity unlike snoring and tonsillar hypertrophy, which had poor specificity [21]. The gold standard for diagnosing SDB and OSAHS is a sleep study. Delayed diagnosis of SDB and OSAHS can significantly lead to increased morbidity. The clinical signs and symptoms further, have poorer sensitivity and specificity in children with complex disorders.

The American Academy of Pediatrics recommends a sleep study in children having regular snoring and any of the additional complaints or findings suggestive of OSA like laboured breathing during sleep with gasps/snorting noises/observed episodes of apnea, sleep enuresis, sleeping in a seated position or hyperextended neck posture, morning headaches, excessive daytime somnolence, attention-deficit/hyperactivity disorder and any learning problems. Examination findings include being underweight or obese, having tonsillar hypertrophy or adenoidal facies, micrognathia/retrognathia, high-arched palate and/or hypertension [22]. The size of tonsils poorly correlates with SDB severity [23]. A sleep study in such situations clarifies the severity of SDB and assists therapeutic decision making [24]. The indications for sleep study are detailed in **Box I** and conditions with complex sleep apneas are detailed in **Web Table I**.

Symptoms of OSAHS in children with genetic syndrome can often be subtle and non-specific. These children often have multifactorial SDB and multilevel airway obstruction indicative of need for an in-lab cardiorespiratory study (RPG) or a PSG is recommended [25]. Children with neuromuscular disorders will often develop nocturnal hypoventilation early which can eventually progress to diurnal hypoventilation. Sleep study is an important component of their evaluation and follow up [26-28].

Most typical parasomnias like confusional arousals, sleep walking and night terrors can be diagnosed based on clinical presentation ideally supplemented with a good video recording of the event. Sleep study is not necessary for diagnosis. A comprehensive in-laboratory video-PSG is recommended to evaluate parasomnias which are: *i*) unusual or atypical because of the patient's age at onset; the time, duration, or frequency of occurrence of the behaviour; or the specifics of the particular motor patterns in question (e.g., stereotypical, repetitive, or focal); *ii*) potentially injurious or have caused injury to the patient or others; and/or *iii*) potentially seizure-related but the initial clinical evaluation and a standard EEG are inconclusive.

Box 1 Indications of a Diagnostic Sleep Study*Respiratory indications of a sleep study (respiratory polygraphy or complete polysomnography)*

Suspected sleep disordered breathing in association with adenotonsillar hypertrophy

Complicated sleep disordered breathing in the setting of:

- Genetic syndromes like Craniofacial syndromes (Apert, Crouzon, Pfeiffer), achondroplasia, Down syndrome, Obesity syndromes (e.g., Prader Willi), Mucopolysaccharidoses, Pierre Robin sequence etc.
- High risk groups like chronic lung diseases (eg CLD of prematurity, bronchiectasis, CF), obesity, Chiari malformation, sickle cell disease, airway disease (vocal cord palsy, tracheo-bronchomalacia)

Neuromuscular disorders with suspected nocturnal hypoventilation

- Spinal muscular atrophy (SMA) Type 1, 2, 3, SMA with respiratory distress (SMARD)
- Duchenne muscular dystrophy (after loss of ambulation)
- Congenital muscular dystrophy: Ulrich, Rigid spine
- Congenital myopathies: minicore, nemaline rod, myotubular
- Myotonic dystrophy type I
- Congenital myasthenic syndromes
- Hereditary sensory motor neuropathy (HSMN)
- Mitochondrial myopathy

Non-respiratory indications of a sleep study (complete polysomnography)

- Atypical or potentially harmful parasomnia vs nocturnal seizures when the initial clinical evaluation and standard EEG are inconclusive (expanded EEG montage)
- Periodic limb movement disorder (PLMD)
- Children suspected of having restless legs syndrome (RLS) who require supportive data for diagnosing RLS
- Hypersomnolence (suspected narcolepsy) (PSG followed by a MSLT)
- Insomnias and circadian rhythm disorders to confirm an underlying SDB, RLS or PLMD

Restless legs syndrome in children can be diagnosed on clinical presentation and a sleep study is usually not necessary. Sleep study might be required to assess sleep quality (including apnea) which may worsen RLS or to assess periodic limb movements in sleep as a supportive tool for making a diagnosis of RLS [29,30]. Most children with insomnias and circadian rhythm disorders can be diagnosed with a sleep diary supplemented with an actigraphy. PSG might be required to confirm an underlying SDB, RLS or PLMD. Children with excessive daytime somnolence and suspected narcolepsy require a PSG to rule out a SRDB and ensure quality of sleep prior to a MSLT the day after.

LIMITATIONS OF A SLEEP STUDY

Often the sleep study result of a single night is taken into account for decision making. However, this may not be reliable as the patient's sleep can be affected by the unfamiliar surroundings leading to a poor night sleep. This often requires a second sleep study. Sporadic events like parasomnias and seizures can also be missed on a single night study. The family and the child undergoing a sleep study have to remain in a sleep laboratory hooked up on sleep study equipment that can sometimes affect sleep quality. Sleep studies also require laboratory set up, training of sleep technologists and adequate staffing to conduct, score and report sleep studies.

Pediatric sleep centers require multi-disciplinary involvement with a pediatric pulmonologist and sleep

specialist and ideally, a pediatric neurologist, a craniofacial surgeon, a pediatric ENT surgeon, a pediatric endocrinologist and a pediatric cardiologist. It also requires well trained paraclinical team of sleep physiologists, child psychologists and play therapists. The diagnostic options need to be prioritized in clinical context for the best outcome of a sleep study.

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Note: Additional material related to this study is available with the online version at www.indianpediatrics.net

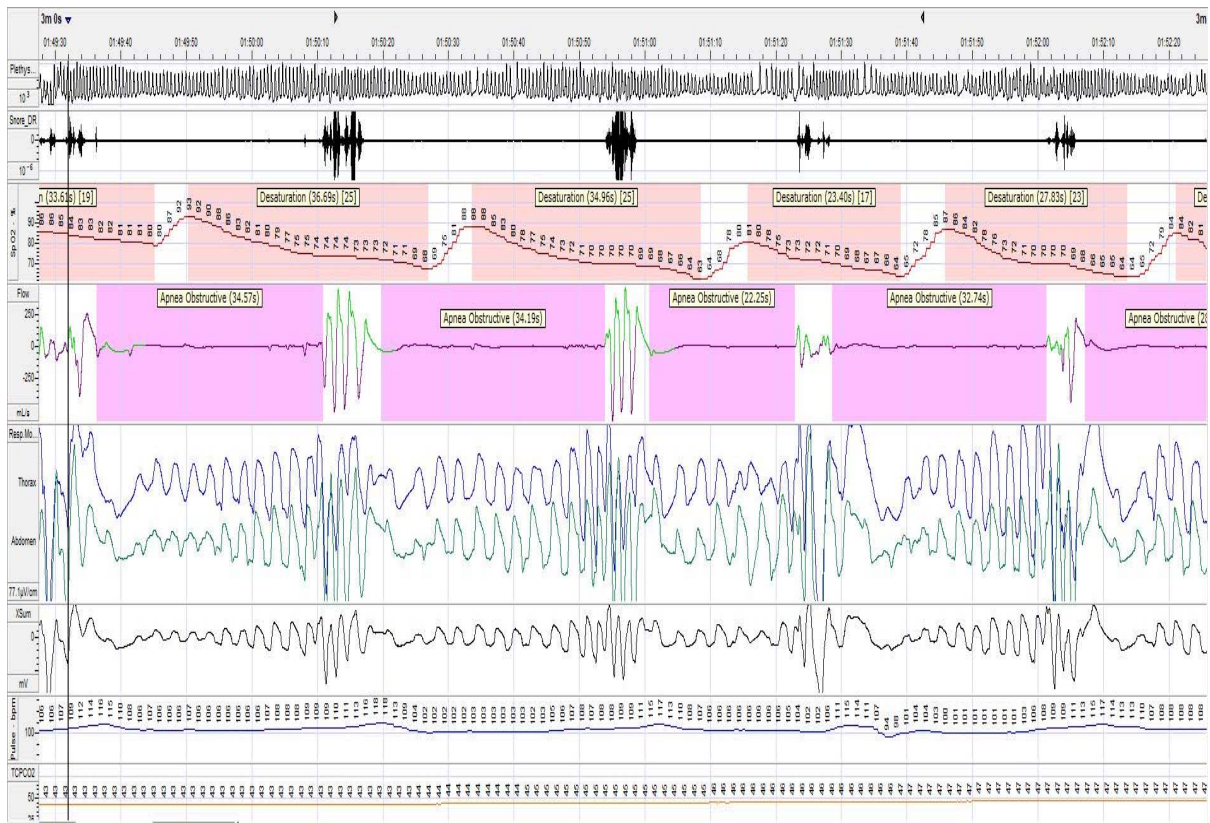
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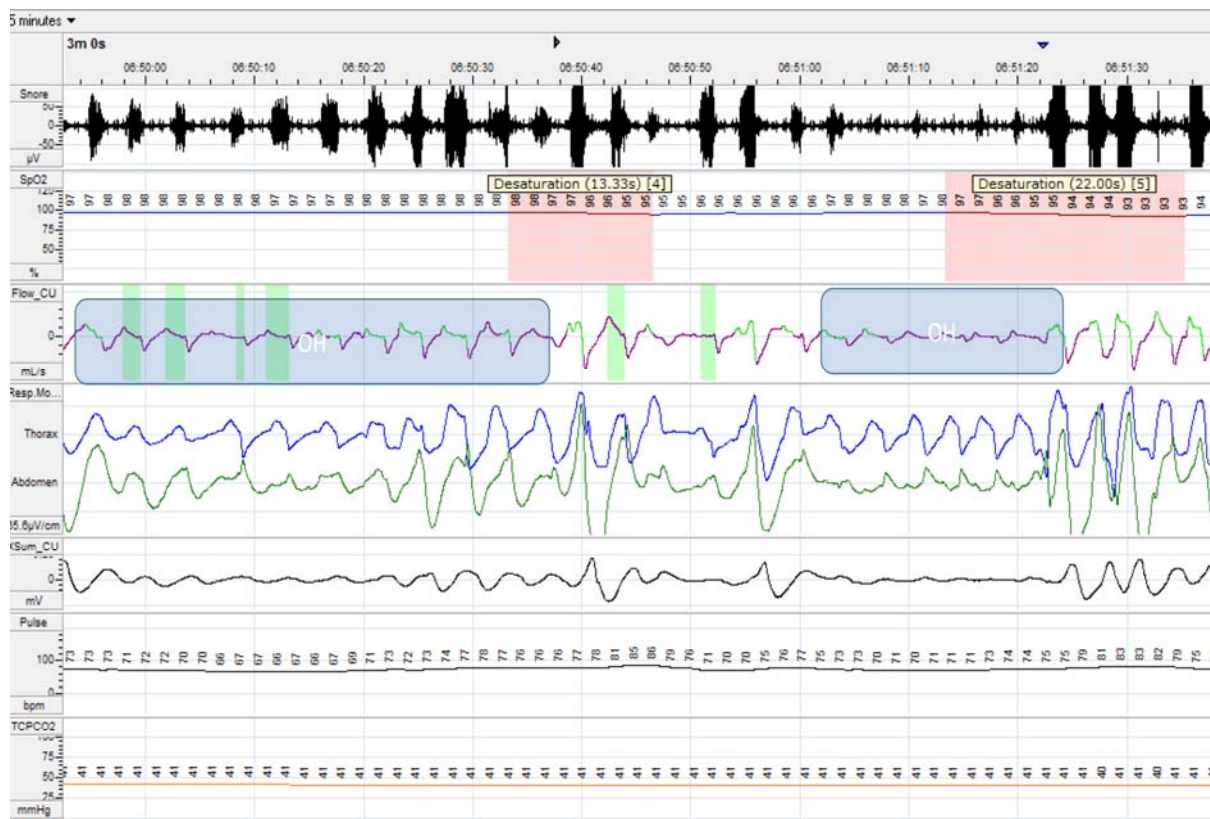
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Web Table I Complex Sleep Disordered Breathing in Children

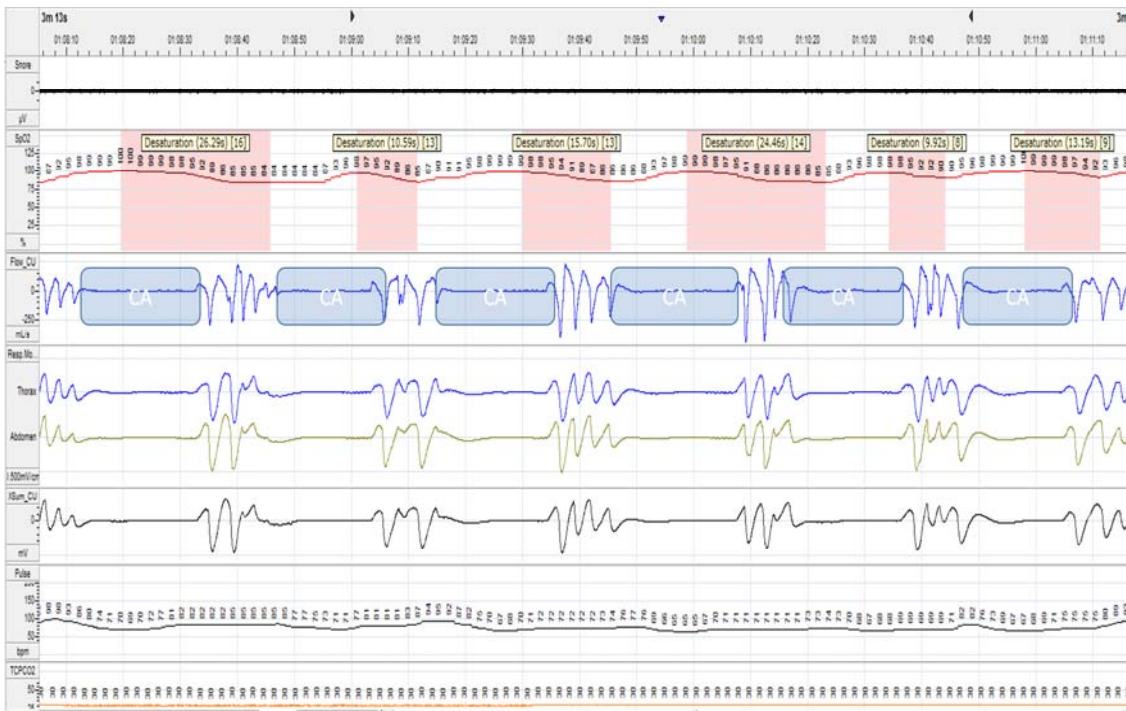
<i>Condition</i>	<i>Factors predisposing to SDB</i>	<i>Recommendation for testing</i>
Craniosynostosis and Craniofacial syndromes (Apert, Crouzon, Pfeiffer, Muenke and Saethre Chotzen)	Midface hypoplasia. Chiari malformation is a frequent finding in Crouzon (70%) & Pfeiffer (50%) syndromes and can have associated central sleep apnea	Yearly screening in patient with Apert, Crouzon and Pfeiffer syndromes. Muenke and Saethre Chotzen syndromes evaluate only if they become symptomatic
Down's syndrome	Relative macroglossia, midface hypoplasia, reduced muscle tone, small upper airway, adeno-tonsillar hypertrophy, obesity	All children before age of 4 years. In all children pre adenotonsillectomy
Cleft lip/palate	Small size of pharyngeal airways & craniofacial dimensions. Oropharyngeal musculature is disrupted by the cleft, which impacts on speech and swallow, as well as adversely affects maintenance of airway patency during sleep.	Sleep study is recommended if child is symptomatic, in the presence of syndromic cleft lip/palate or pre pharyngoplasty and pharyngeal flap surgery.
Syndromic micrognathia (i.e. Pierre Robin Sequence, Stickler syndrome, etc)	Micrognathia, glossoptosis, midface hypoplasia	All children should be screened
Obesity syndromes (eg Prader Willi, Bardet Biedl)	Obesity, hypotonia, micrognathia, small naso and oropharynx, scoliosis leading to OSA. Central sleep apneas, nocturnal hypoventilation, hypersomnolence/cataplexy also seen	Yearly sleep studies are recommended. Sleep study pre growth hormone therapy & post 3-6 m post therapy & afterwards if symptoms of SDB reappear. MSLT if hypersomnolence
Mucopolysaccharidosis	Cranial and spinal abnormalities (e.g., flattened nasal bridge, short neck, mandibular abnormalities) and glycosaminoglycans deposition in the mouth, nose, throat	All patients should be evaluated at diagnosis
Achondroplasia	OSA: Facial hypoplasia, retruded position of chin, adeno-tonsillar hypertrophy. Central sleep apneas also seen.	Should be screened at least once from 1 yr and then subsequently (or prior) if symptoms develop
Duchenne muscular dystrophy, limb-girdle muscular dystrophy, fascio-scapulo-humeral	Decreased respiratory drive, muscle weakness; pharyngeal muscle weakness, scoliosis, obesity, recurrent lung infections. OSA, central apneas & hypoventilation seen	FVC <60% predicted, symptoms of nocturnal hypoventilation or when children become non-ambulatory. Follow up annually.
Spinal Muscular Atrophy Congenital Myopathies Congenital Muscular Dystrophies Myotonic Dystrophy Congenital myasthenic syndromes	Same as above. OSA, central apneas & hypoventilation seen	Sleep study advised if: profound weakness with non ambulation, weak cry, ineffective cough, swallowing difficulties, repeated chest infections, poor lung function, scoliosis & chest wall deformity
Hereditary Motor Sensory Neuropathy		Episodic apnoea of infancy and childhood (sometimes life-threatening) described in CHAT and RAPSN mutations. Progressive respiratory muscle weakness in COLQ and DOK7 mutations. Sleep Study recommended if these mutations present and symptoms suggestive of SDB. Required if weakness is severe and persistent or if symptoms suggestive of SDB



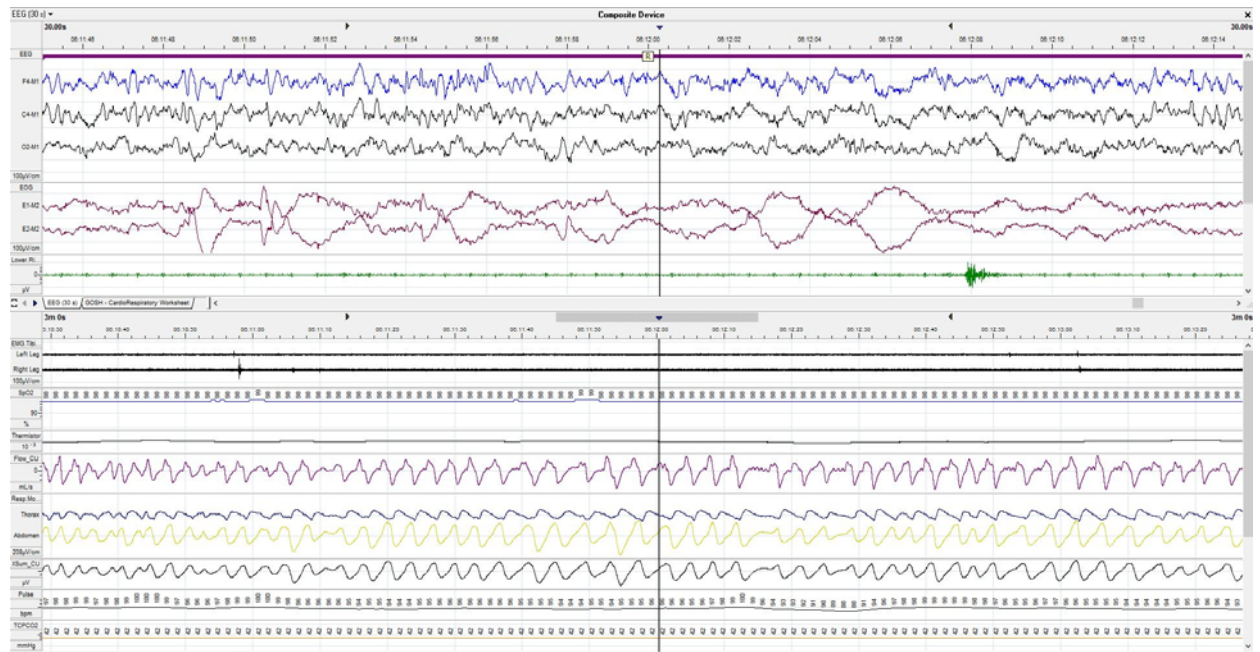
Web Fig. 2 A 3 minute epoch of a Cardiorespiratory Sleep study showing multiple Obstructive Apneas (scored on the nasal flow trace). Note the accompanying desaturations and paradoxical breathing in the thoraco-abdominal bands.



Web Fig. 3 A 3 minute epoch of a Cardiorespiratory Sleep study showing obstructive Hypopnea. Note that the flow is reduced >30% associated with desaturation and the thoraco-abdominal bands show paradoxical efforts.



Web Fig. 4 A 3 minute epoch of a Cardiorespiratory Sleep study showing multiple Central Apneas. Note that the thoraco-abdominal bands show no efforts compared to paradoxical efforts in obstructive apneas.



Web Fig. 5 A 30 s epoch of a Polysomnography. Note the additional neurological channels (EEG, EOG and chin EMG)

Clinical Manifestations and Outcomes of Respiratory Syncytial Virus Infection in Children Less Than Two Years in Colombia

This retrospective study describes the epidemiology and risk factors associated with severe complications in lower respiratory tract infection (LRTI) due to respiratory syncytial virus (RSV) in a population of infants hospitalized in a tertiary care hospital in a tropical region of Colombia. RSV was detected in 193 (46.3%) of 417 patients with LRTI. The average hospital stay lasted for 5.9 days. Severe hypoxemia (SpO₂ ≤90% in the emergency department) was present in 57.5% of the patients. After controlling for potential confounders, comorbidities bronchopulmonary dysplasia, congenital heart disease, length of hospital stay, and alveolar infiltrates in X-ray were independent predictors of severe complications in RSV LRTI.

Keywords: *Complications, Outcome, Predictors.*

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The epidemiology and severity of lower respiratory tract (LRTI) due to respiratory syncytial virus (RSV) in tropical regions may differ from that in other climates [1]. This study aims to describe the epidemiology and identify risk factors associated with severe complications in RSV LRTI in a population of infants hospitalized in a tertiary care hospital in a tropical region of Colombia.

This review of medical records included all infants under two years of age in tertiary centers, in Rionegro, Colombia admitted with RSV LRTI (ICD-10 code: J21.0) according to the National clinical guideline of bronchiolitis (first wheezing episode younger than 24 months of age) [5] from January, 2015 to December, 2016. Inclusion criteria were defined as children younger than two years of age admitted to the pediatric ward with a diagnosis of RSV confirmed using direct immuno-fluorescence (Light Diagnostics Respiratory Panel 1 DFA, Merck-Millipore Laboratory). Patients without lower respiratory compromise, with positive bacterial cultures on admission, confirmed whooping cough (culture or PCR), referred from another hospital center were excluded. The study protocol was reviewed and approved by the institutional review board.

We collected the following variables: age, sex, weight, height, signs and symptoms on admission (including fever, chest in drawing, chest auscultation, oxygen saturation, respiratory rate), history of prematurity, comorbidities [congenital heart disease (CHD), neurological disease, bronchopulmonary dysplasia (BPD)], results of chest X-rays and other medical test, drugs and other treatments, adverse drug reactions, and complications, (pneumonia (5), atelectasis, sepsis, respiratory failure/ICU).

A composite outcome was used to define severe complications associated with RSV (SCRSV). This composite outcome was defined as the presence of oxygen saturation (SpO₂)

≤90% in the emergency room and/or pneumonia and/or atelectasis and/or sepsis and/or respiratory failure during hospitalization.

A sample size of 123 patients was estimated to find an OR of at least 1.5 between the presence of complicated RSV and the history of comorbidities with a 95% confidence level, 90% accuracy, and a minimum comorbidity frequency in patients without complicated RSV of 1% [3].

To identify factors independently associated with SCRSV, we used ordered logistic regression models to adjust for potential confounding variables. All statistical tests were two-tailed, and the significance level used was $P < 0.05$. The data were analyzed with Statistical Package Stata 15.0 (Stata Corporation).

RSV was detected in 193 (46.3%) of 417 patients with LRTI and 16% patients were younger than 6 months of age. Only 1 patient (with a history of congenital heart disease) had received palivizumab. The majority (92%) required oxygen, and more than half had chest retractions in the emergency department. A third of all patients had a radiological abnormality (**Table I**). On analyzing the data about seasonal distribution of RSV infections, there was two peaks of cases, the first between April and August, and the

Table I Characteristics of Children with Respiratory Syncytial Virus Pneumonia (N=193)

<i>Variable</i>	<i>Frequency</i>
Age (mo) , median (IQR)	5.66 (6)
Male	113 (58.55)
Premature birth	28 (14.51)
Comorbidities (CHD or neurological)	11 (5.71)
BPD	7 (3.6)
Atopy	21 (10.88)
SpO ₂ %, median (IQR)	88 (0.93)
O ₂ support	178 (92.33)
<i>Clinical and laboratory parameters</i>	
Fever	53 (27.46)
Chest indrawing	102 (52.85)
Tachypnea	30 (15.54)
Rhonchi	78 (40.41)
Crepitation	36 (18.65)
Leucocytosis (>15000/mm ³)	31 (16.76)
Increased CRP (>4 mg/L)	59 (44.81)
<i>Chest X-ray</i>	
Normal	22 (12.36)
Peribronchial thickening	63 (35.39)
Hyperinflation	33 (18.54)
Atelectasis	5 (2.81)
Bilateral interstitial infiltrates	33 (18.54)
Alveolar infiltrates	22 (12.36)

All values in no(%) or as stated. CRP: C-reactive protein.

second between November to January; corresponding to the two rainy season in this region.

The median hospital stay was 5.88 days [6]. Severe hypoxemia (SpO₂ ≤90% in the emergency department) was present in 57.5% of the patients. Twenty three patients (11.9%) had pneumonia, and 9 (4.7%) patients experienced sepsis, 5 (2.6%) had atelectasis and 3 (1.5%) had respiratory failure. No patient had pneumothorax or died.

On bivariate analysis, the following variables presented a significant association with SCRSV: age (OR 1.06, 95%CI 1.08-1.13), O₂ support (OR 22.6, 95% CI 2.91-176.12), chest in drawing (OR 2.43, 95% CI 1.35-4.37), crackles in lung auscultation (OR 8.78, 95% CI 2.51-30.70), and alveolar infiltrates in X-ray (OR 8.78, 95% CI 2.51-30.70), length of hospital stay (OR 1.19, 95% CI 1.06-1.33), comorbidities (BPD, CHD, neurological) (OR 0.59, 95% CI 0.59-1.77). After controlling for these potential confounders, comorbidities (BPD, CHD, neurological), length of hospital stay, and alveolar infiltrates in X-ray were independent predictors of SCRSV in our patients (**Table II**).

In our study, the clinical characteristics and seasonal distribution was similar to previous reports from tropical regions [1,7,9]. Risk factors, including prematurity and underlying chronic illness were similar to those observed in others populations [8-12]. The reported complications were similar to those in previous studies ranging between 6.5-23% [3, 9-11].

Since this study was based on medical records review, we cannot included others variables such as passive smoking, maternal breastfeeding, environmental pollution. The study was conducted in a tertiary referral hospital and therefore the patients included represent the high severity, limiting the generalization of results to other contexts. However, the similarity of our population in term of clinical characteristics, risk factors and seasonality of RSV with previous reports suggest strength and consistency in our results.

RSV is an important cause of morbidity in children with bronchiolitis in tropical areas during the rainy season. Identifying groups at high-risk for severe complications, such patients with underlying chronic illnesses are essential to plan future interventions to reduce the burden of disease in these regions.

Table II Independent Predictors of Severe Complications Associated With RSV

Variable	OR (95% CI)	P value
Age (mo)	0.91 (0.76-1.08)	0.340
Comorbidities (CHD, neurological)	21.45 (1.80-254)	0.015
Length of hospital stay	1.57 (1.26-1.94)	0.001
O ₂ supportive	0.72 (0.38-13.77)	0.832
Chest indrawing	1.07 (0.26-4.43)	0.918
Alveolar infiltrates	12.93 (8.93-18.76)	0.001

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The Long-Term Effect of a Quality Improvement Intervention in the Management of Bronchiolitis

Quality improvement interventions have been shown to improve adherence with bronchiolitis treatment guidelines; however, the long-term effect of these interventions is unclear. We show that while such an intervention led to a long-lasting change, this was attenuated with time. Repeated interventions are required to maintain guideline adherence.

Keywords: *Emergency department, Management, Radiography.*

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Bronchiolitis has a broad differential diagnosis but alternate diagnoses can be distinguished by history and physical examination alone [1]. Guidelines therefore state that clinicians should not routinely order chest X-rays for the diagnosis of bronchiolitis as findings have no effect on patient management or outcomes [2]. We previously conducted a successful quality improvement (QI) intervention to decrease the use of chest X-ray in bronchiolitis at two medical centers, also showing a reduction in hospitalization and use of unnecessary medication [3]. However, as the long-term effects of QI are unclear, and prior studies were mostly limited to one season [4,5], we conducted the current study to assess the long-term outcomes.

This was a retrospective cohort study at the Hadassah EinKerem and Mount Scopus Medical Centers in Jerusalem, Israel. In November, 2015 the pediatric and emergency department (ED) staff participated in formal educational sessions led by pediatric pulmonologists that focused on the guidelines, emphasizing those sections on chest X-ray. Guideline cards were positioned throughout the ED physician stations, with routine follow-up during the 2015-16 bronchiolitis season [3]. The study was approved by the institutional review board.

The current study compared patients with bronchiolitis seen in the ED during three time periods. The historical group (prior to the intervention) the early group (seen during the year of the intervention) and the late group (comprised of patients seen the following two bronchiolitis seasons). A total of 1,115 cases were included in the final analysis: 207 in the historical group, 298 in the early group and a sample of 610 in the late group. The groups were similar in terms of gender, vaccination status, background diseases and family history of asthma. Patients were younger in the early and late groups, with mean (SD) age of 5.7 (4.9) and 6.2 (5.4) month, respectively, compared with the historical group, 7.9 (5.4) month ($P<0.0001$). Symptoms and physical examination findings were similar throughout the three periods.

The rate of chest X-ray use decreased from 58.3% in the historical group to 36.6% ($P<0.001$) in the early group but increased to 44.6% ($P<0.001$) in the late group. There were no significant differences between the two seasons included in the late group, or the two centers. On multivariate analysis, only belonging to the historical group predicted getting a chest X-ray (OR=1.6, 95%CI 1.1-2.3; $P<0.013$). The proportion of abnormal

chest X-rays increased from 28.4% in the historical group to 48.1% in the early group and slightly decreased to 31.5% in the late group ($P<0.001$).

Analysis of secondary outcomes showed a decrease in the hospitalization rate from 76.8% to 69.8% ($P=0.05$) in the early group and 57.7% in the late group ($P<0.001$). The length of stay was unchanged. The readmission rate was 2.9% and 2.7% in the historical and early groups, respectively ($P=0.89$), but 8.4% in the late group ($P=0.008$). However, this was not correlated with chest X-ray use ($P=0.34$). Use of supplemental oxygen in the ED increased over the study period. There was a downtrend in the use of antibiotics, bronchodilators, and hypertonic saline with no change in corticosteroids. Fewer laboratory tests were performed; 71.7% in the historical group to 64.1% in the late group ($P=0.047$).

Nose swab samples were drawn from 55.8% of the historical group, 47% of the early group, and 40.7% of the late group. Respiratory syncytial virus (RSV) decreased from 80.2% to 59.7% ($P<0.001$) and adenovirus from 21.6% to 10.9% ($P=0.007$); human metapneumovirus (hMPV) increased from 6.9% to 14.1% ($P=0.047$). Having had a chest X-ray correlated with positive findings on the nose swab ($P<0.001$), but not specific pathogens.

We have shown that a focused intervention may lead to a persistent effect; however, this is attenuated with time. While chest X-ray rate remained lower than it was before the intervention (44.6% vs. 58.3%), it increased by 22% compared with the year of the intervention. Few studies have investigated the long-term effects of QI in bronchiolitis. Perlstein, et al. [6] showed partial adherence over three years in their study, while Tejedor-Sojo, et al. [7] utilized periodic feedbacks to sustain momentum, and showed improvement with time.

The most plausible reason for the increase in the rate of chest X-ray in our study is the time lapse from the intervention. However, our findings were suggestive of a more severe bronchiolitis season during the study period, with an increase in ED visits, an increase in hMPV that may cause a worse illness [8,9] and a decrease in RSV. Furthermore, oxygen supplementation rates increased as did re-admission rates. One may argue that the increase in re-admissions reflects an undesired effect of the QI intervention. However, there was no statistical association between the decrease in chest X-ray and the increase in re-admissions.

To conclude, we have shown that a QI intervention led to long-lasting change in management practices; however, the improvement attenuated with time. We therefore recommend conducting repeat interventions at the beginning of each bronchiolitis season to maintain adherence.

Ethics approval: Hadassah-Hebrew University institutional review board; 008-16-HMO, dated April 14, 2016.

Contributors: JR, MCC: conceptualized and designed the study, analyzed and interpreted the data, reviewed and revised the manuscript; AB, AB: designed the data collection instruments, collected data, carried out the initial analyses, and drafted the initial manuscript; SH, DR: participated in the study design, data

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Vitamin A Supplementation in Children in Guédiawaye Health District, Senegal

To assess the coverage rate of routine vitamin A supplementation, a descriptive study was carried out in the Guédiawaye Health District. The coverage rate for vitamin A supplementation was 48.6%. Age over 24 months, uneducated father, maternal age over 25, and lack of disease-related knowledge were factors associated with delayed vitamin A supplementation.

Keywords: Coverage, Health program, Under-5 children.

Vitamin A deficiency remains a public health problem in developing countries, particularly in Africa and the Indian subcontinent. It affects young children, often associated with protein-energy malnutrition, and pregnant women [1]. Vitamin A supplementation is recommended in infants and children aged 6-59 months as a public health intervention to reduce child morbidity and mortality [2]. In accordance with this guideline, Senegal adopted vitamin A supplementation as a strategy during routine immunization activities and mass campaigns, since 2013. The objective of this study was to determine the coverage rate for vitamin A supplementation among children 6-59 months of age in the Guédiawaye Health District.

This community-based descriptive study was conducted from 1 June to 30 November, 2018 in the Guédiawaye district. The surveys relating to the characteristics of the child, the family and knowledge about vitamin A supplementation concerned the households drawn at the level

of each stratum, using a systematic two-stage cluster random sampling. The first stage consisted in selecting neighborhoods within the geographical area of the district, and the second stage in selecting households within the drawn neighborhoods. In each selected household, all children aged 6-59 months were included in the survey. Data collection was carried out by two trained investigators. Each investigator was accompanied by a *bajenou ngox*, a neighborhood godmother, to facilitate the interview. The parameters studied were: the individual characteristics of the child (age, sex, position within sibling, spacing interval between births), household characteristics, and knowledge about vitamin A supplementation. A written informed consent was obtained from the individual parent prior to the survey.

The median age of fathers was 38 and that of mothers 28 years. The average household size was 7 people. Out of 366 children aged 6-59 months surveyed, 188 (51.4%) had not received vitamin A. The coverage rate was higher for children over 23 months of age (65.6%). Before 12 months, coverage rate was 36.8% and between 12 and 23 months 64.6%. The characteristics of the households surveyed are summarized in **Table I**. Age over 24 months [OR (95% CI) 3.41 (1.87-6.19); $P<0.001$], father's lack of education [OR (95% CI) 1.49 (0.91-2.44); $P=0.11$], maternal age over 25 year [OR (95% CI) 1.74 (1.01-3.02); $P=0.04$], and lack of knowledge of means of protection against diseases [OR (95% CI) 1.43 (0.83-2.44); $P=0.19$] were factors associated with delayed vitamin A supplementation.

Improving the vitamin A status of under-5 children increases their chance of survival by reducing mortality by 25% from childhood illnesses such as malaria, diarrhea, acute

Table 1 Household Characteristics

<i>Characteristics</i>	<i>No. (%)</i>
Interviewee:	
Mother	182 (96.8)
Married	176 (93.6)
Educated father	139 (73.9)
Educated mother	90 (47.9)
Mother employed	66 (35.1)
Fathers occupation	
Liberal profession	129 (68.6)
Civil servant	31 (16.5)
Worker	18 (9.6)
Housing occupancy status	
Tenant	109 (58.0)
Family property	47 (25.0)
Owner	31 (16.5)
Free accommodation	1 (0.5)
Main source of income	
Trade	146 (77.7)
Salary	35 (18.6)
Other source	7 (3.7)
Main source of stable income	35 (18.6)
Main source of regular income	35 (18.6)
Income amount per mo^a	
36000 – 72000 XOF	2 (1.1)
Over 72 000 XOF	3 (1.6)
Does not know	178 (94.7)

^arefused to answer. XOF – West African CFA Franc.

respiratory infections and measles [3]. Therefore, evaluating the coverage rate for vitamin A supplementation and knowing the factors associated with delayed supplementation help reduce under-5 morbidity and mortality. A vitamin A supplementation coverage rate of 48.6% was found in this study. This rate is lower than that found in the 2017 demographic and health survey (57.4%) [7] and that of the local vitamin A supplementation days (90.4% in June, 2011 and 93.5% in December, 2011) [8]. In Mali, Sangho, et al. [9] found a 90% vitamin A supplementation coverage rate in children. These higher coverage rates than that found in this study do not reflect the results associated with routine vitamin A supplementation because in these studies the surveys were carried out immediately after supplementation campaigns. This proves that routine vitamin A supplementation activities alone do not achieve the expected coverage rates, hence the need to couple them with mass campaigns. According to WHO, vitamin A supplements should be given to children 6 to 59 months of age twice a year, during contact with the health system [2].

Children between 12 and 23 months of age and those between 24 and 59 months of age were 3.53 times and 3.41 times, more likely respectively to receive vitamin A than infants between 6 and 12 months of age, in this study. This could be due to vitamin A supplementation being integrated into

immunization activities in Senegal, and that the older the child the more contact he has with these services. Likewise, fathers' lack of education and knowledge of protective measures against diseases were associated with no vitamin A supplementation. Fathers' education was previously also reported to be associated with vitamin A coverage of children in Mali [10]. Possibly the role of fathers in healthcare decisions, and parental education promoting better adherence to interventions are the reasons for these findings.

This study reveals that vitamin A supplementation coverage in routine activity seems low in the study area. Educating parents and organizing mass campaigns could help improve coverage rates.

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Ethics clearance: Research Ethics Committees, Cheikh Anta Diop University of Dakar; No. 0260/2017/CER/UCAD dated May 22, 2017.

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Congenital Diarrheal Disorders in Neonates: A Single-Center Experience

Congenital diarrheal disorders (CDDs) are a group of inherited diarrheas with typical onset in the early neonatal period [1,2], with most being gene specific [3]. There is limited literature on the clinical spectrum and outcome of CDDs from India. Molecular genetic analysis has become the preferred diagnostic modality in recent years [4,5]. Here we report a case series of six cases of neonatal-onset chronic diarrhea (>14 days) with their outcomes over a 3-year period (2017- 2020) (Table I) [6].

Cases No. 1, 3 and 4: These patients were diagnosed with congenital glucose-galactose malabsorption (CGGM). All three developed diarrhea on exclusive breast feeds during the first week of life. Case No. 1 presented with osmotic diarrhea, hypoglycemia, hypernatremia and metabolic acidosis and septicemia. There was no evidence of immune deficiency. There was no improvement on hypoallergenic formula and total parenteral nutrition (TPN). The child eventually succumbed to fungal sepsis without a diagnosis. Next generation sequencing (NGS) sent 3 weeks prior to death provided the diagnosis of CGGM posthumously. Parents were advised prenatal counseling for the next pregnancy. Case No. 3 and 4 with CGGM had a very similar presentation. Oral rehydration solution (ORS) glucose challenge [8] was positive in both the cases. Endoscopic biopsy and electron microscopy were unremarkable. In view of history of consanguinity, lack of response to amino acid-based formula (AAF) and a clinical picture that resembled CGGM, they were commenced empirically on fructose-based special formula (FBF) pending the final reports of NGS (Next generation sequencing). There was dramatic clinical recovery with complete resolution of

diarrhea within 48 hours and TPN was discontinued. Optimal and consistent weight gain was achieved prior to discharge. Molecular genetic analysis by NGS confirmed the diagnosis during follow-up. Both children, when last assessed at 2 years of age, were found to be thriving well and had achieved age-appropriate developmental and social milestones.

Case No. 2 and 5: These two patients were diagnosed with diacylglycerol acyltransferase (DGAT-1) deficiency. They presented during the second week of life with feed refusal and failure to thrive on exclusive breastfeeds. Formula feed supplementation also resulted in vomiting, dehydrating diarrhea and hypoalbuminemia. Continuous nasogastric infusion of AAF did not resolve the symptoms. Investigations did not reveal any evidence of sepsis or immune deficiency. Oral glucose challenge was negative. Endoscopic biopsies appeared to show nonspecific patchy villous atrophy with no viral inclusion bodies. Electron microscopy was normal. They were started on TPN while awaiting a genetic diagnosis. NGS confirmed DGAT-1 deficiency and they were treated with a special custom-made fat free infant formula, fat soluble vitamins and MCT oil. These children, in addition to dehydrating diarrhea and FTT, had recurrent vomiting, hypoalbuminemia, hypertriglyceridemia and occasional bulky/greasy stool classical of DGAT -1 deficiency. Case No. 2 is currently aged 18 months and has motor developmental delay. The child continues to fail to thrive on the fat-free specially formulated diet. Case No. 5 also responded to fat-free diet and showed slow weight gain, but is now lost to follow-up.

Case 6: This patient presented with neonatal cholestatic jaundice, osmotic diarrhea on exclusive breastfeeds and failure to thrive. The jaundice disappeared gradually but diarrhea and failure to thrive persisted despite adequate breastfeeds. The child continued to remain symptomatic even on supplemental

Table I Characteristics of Infants With Congenital Diarrheal Disorders

Case No.	I	II	III	IV	V	VI
Age (wk)	6	3	4	3	6	3
Age of onset (wk)	1st	2nd	1st	1st	1st	1st
Gender	F	M	F	F	M	M
Consanguinity	2 nd degree	3 rd degree	2 nd degree	3 rd degree	2 nd degree	3 rd degree
Birth weight (kg)	3.12	3.00	3.00	3.25	3.70	2.90
Weight at admission (kg)	2.37	1.99	2.22	2.10	3.78	2.60
Discharge weight (kg)	NA	3.34	2.65	2.99	3.98	3.57
TPN/PPN (d)	48	68	10	22	20	7
Hospital stay (d)	122	104	21	42	45	14
Diagnosis	Glucose galactose malabsorption	DGAT1 deficiency-fat malabsorption	Glucose galactose malabsorption	Glucose galactose malabsorption	DGAT1 deficiency-fat malabsorption	Congenital lactase deficiency
Treatment	Carbohydrate free, fructose-based formula	Fat free, protein rich formula	Carbohydrate free, fructose-based formula	Carbohydrate free, fructose-based formula	Fat free, protein rich formula	Hypoallergenic formula rich in MCT

All children survived except the first case.

infant formula. Serum total IgE levels were elevated, suggesting atopy. The child improved dramatically on a trial of hypoallergenic formula rich in MCT. NGS revealed an eventual diagnosis of congenital lactase deficiency. The baby is growing well and is now able to tolerate lactose-free cow milk protein containing infant formula at 9 months of age.

We, herein, describe the clinical spectrum of genetically confirmed CDDs; though electron microscopy aided diagnosis of MVID has previously been reported [9]. Our case series showed that congenital brush border enzyme deficiencies are the most common form of CDDs rather than congenital enteropathies or ion channelopathies. CGGM has autosomal recessive inheritance with classical triad of hypernatremia, hypoglycemia and metabolic acidosis [4,7]. All children with CDDs were born of consanguinity and diarrheal onset was within the first 2 weeks with classical triad. For DGAT-1 deficiency, literature cites resolution of diarrhea with fat free formula and a possible need for fat soluble vitamin supplementation and intra lipid infusions [10]. Both the neonates in our case series had resolution of diarrhea; however, had slow weight gain on fat free formula.

NGS has revolutionized the diagnostic approach to CDDs; however, it is expensive and turnaround time is late (4 weeks). It is more precise and is reliable than stool microscopy and stool electrolytes. The triad of clinical presentation, tissue electron microscopy and NGS form the cornerstone for apt diagnosis of CDDs. The management is individualized based on the molecular and tissue diagnosis and ranges from simple change to specialized specific diet to complex lifelong TPN.

Contributions: SSS,VHK: responsible for patient management, data collection and manuscript writing; NCK,SS: responsible for drafting the paper; NCK will act as guarantor of the study; CSS: helped in manuscript writing. The final manuscript was approved by all authors. *Funding:* None; *Competing interest:* None stated.

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EVENTS

□ December 4-5, 2021

East Zone PEDICON, Jamshedpur, Ranchi
at Wave International NH 33, Jamshedpur

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OBITUARY

Dr Gadadhar Sarangi



(1st April, 1949 - 8th September, 2021)

The sad demise of Dr. Gadadhar Sarangi is a great loss to the Indian pediatric fraternity as well as the state of Odisha.

Born on 1st April, 1949 in Odisha, he did MBBS from Hamirpur (Odisha) in 1973; MD Pediatrics from PGIMER, Chandigarh, in June, 1976; MNAMS in 1979; Fellow in MCH (Liverpool) 1990; FICMCH 1998; FIAP in 2005; FPAI in 2015. He joined Odisha Medical Services in August, 77; Teaching faculty at Institute of Pediatrics, Cuttack; MKCG Medical College, Berhampur (1978 to 1999); Professor Pediatrics, Jagannath Institute of Medical Sciences, Bhubaneswar (1999 - 2000). He was Chairman - Medical Director, Baidyanath Memorial Hospital Bhubaneswar till the end.

He contributed sixty nine scientific papers in Indian Journals and presented forty seven papers in various national and state conferences. He received many state level recognitions for child welfare activities.

He was advisory member of Indian Pediatrics and Indian Journal of Pediatrics; Chief Editor of Pediatric Journal of Odisha; Single author books on Childhood Immunisation, Diarrhoeal diseases. Kidney diseases, ABC of Neonatology & Practice of ECG. He had a good knowledge of Hindu mythology and religious sermons.

He was EB member two times. He had organized two state and two national conferences. He was Organising Secretary of most successful Pedicon 2008 at Bhubaneswar and contributed a highest sum to IAP CO at that time. He is the founder of Pediatric Association of India.

He was a perfect amalgam of knowledge, simplicity, humane nature and excellent teaching qualities. A great, honest and bold administrator, and a firebrand teacher, he taught and created a generation of Pediatricians for Odisha. He was always available for service to the children in resource restrained situations.

He breathed his last on 8th September, 2021 with a short illness of three days. He was clear hearted, lovable, selfless and well wishing person. He will always be remembered and his memories would be cherished as pride possession in our hearts. May his soul rest in eternal peace and family be able to bear this loss.

Protocol for Infant Massage in Home Settings

Traditional infant care and child rearing practices are known to be important determinants of child health. While some practices are known to be beneficial or harmful, for some there is less scientific knowledge. Infant oil massage is highly prevalent traditional practice in India [1] and several developing countries [2]. Recent evidence suggests beneficial effects of topical application of vegetable oils in preterm infants in preventing invasive infections [3]. It is often administered in neonatal intensive care units for improved growth, hypothermia prevention and reduced hospital stay. Massage in term infants seems to improve physical and mental health; however, much remains to be known about this [4]. Although considerable variations exist in practice of infant massage at homes, which may affect potential for gain/harm, massage being a cultural practice is 'normalized' and seldom receives professional attention [1].

We recently conducted an e-Delphi study and developed a protocol for massage in healthy infants at homes [5]. The protocol provides a step-by-step guide for home care givers of infants born beyond 37 weeks of gestation. It details aspects such as when should massage be done or not, how to determine that the infant is fit for massage, how to ensure the environment and time is appropriate for massage, who should perform the infant massage, how often should massage be performed, what are the appropriate techniques for infant massage, and what are the recommended substances/appropriate oil for infant massage.

The seventeen experts involved in the three round Delphi study included neonatologists, general pediatricians, developmental pediatricians, pediatric occupational therapist, naturopathy expert, ayurvedic pediatricians and specialists in

Panchakarma (includes massage therapy). The paper not only reports consensus but also non-consensus and stable disagreement that are informative and highlight differences in perspectives [5]. We feel that it would be a useful guide for academicians and clinicians for teaching and patient education, and as a standard protocol for use by researchers.

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First Aid Training to School Students: Should Younger Children Be Trained?

We read with interest the recent article by Mehreen, et al. [1] on the effectiveness of an educational school-based intervention on injury prevention and first aid. The educational intervention significantly increased the knowledge on the prevention of unintentional injuries and first aid among students (mean age 15.9 years) [1]. In order for first-aid to be effective, continuous training, practice and several trainees are required. Research has demonstrated the ability of children to provide first aid after receiving appropriate education [2]. Specialists or certified

teachers are capable of teaching first aid and many countries have introduced first aid training programs in schools [3]. However, most programs including the present study, focus mainly on children aged 10-18 year, while younger ages receive much less attention [4]. We systematically reviewed the literature and found only three studies of first aid programs being delivered to children at preschool. Results showed that the interventions improved preschool students' knowledge and skills of first aid.

It is important to educate children from an early age. Early age training cultivates skills that are retained for almost a lifetime and can be easily retrieved from memory. Furthermore, young children function as multipliers because their knowledge is disseminated in the family and in their friend-circle. Finally, it

cultivates social responsibility to the trainees, which is necessary for the progress of the society. We strongly believe that first aid training shall be included as part of basic education as a compulsory module, that can be taught by trained school teachers.

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Safety: A Primary Concern in Thalidomide Use in Thalassemia

I read with interest the article by Chandra, et al. [1] published in the journal recently. Authors have presented their data on the efficacy and safety of thalidomide in adolescents with transfusion dependent thalassemia (TDT). It is an excellent effort and much awaited publication keeping in view the quantum of thalassemia in India, the high cost of bone marrow transplant (BMT), and the scarce data on use of thalidomide in TDT. However, I would like to highlight a few issues in the study.

The primary concern with use of thalidomide in TDT remains safety rather than efficacy. A study period of six months is too short for a disease requiring long-term therapy with thalidomide. During a study of any new drug for a disease, the criteria for stoppage of trial are pre-defined for ensuring safety [2]. In their study, 8/37 developed infection with one death (due to unrelated causes), and 10/37 developed neutropenia (one severe grade-III neutropenia) and one grade-IV renal injury. Such a high incidence of neutropenia is unexplained by co-administration of deferiprone alone [3]. Considering the small sample size, continuing the trial despite severe adverse reactions may warrant more details.

The very low baseline mean hemoglobin F (HbF) and the steep rise in the study [1] is not supported by the literature. Mean baseline HbF levels were 2.95% and have risen to 49.2% after six months of thalidomide therapy. The baseline levels are generally higher (10-60%) in adolescents in the studies of HbF inducers in thalassemia [4]. Also in clinical studies, on an average, a 20% rise is seen in responders of HbF-inducer agents in thalassemia [5].

The baseline mean packed cell received in the study cohort was 75 mL/kg in last 6 months, which seems quite modest for adolescent children with thalassemia (12-18 years) as their requirement is high due to growth and pubertal spurt. Even the sample size calculation in the study was based on assumption of 220 mL/kg/year. Therefore, was there a selection bias as the cases were randomly enrolled?

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Presuming the mean hemoglobin (Hb) depicted in comparative table II are mean pre-transfusion Hb (not mentioned in methodology); mean Hb at baseline was 9.45 g/dL and at end of study was 8.89 g/dL. Were study children under-transfused during study period of 6 months? Also, mean thalidomide dose in baseline table I is 2.05 mg/kg/day, which is well below the mean daily dose of thalidomide in three response groups as depicted in Table III.

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REPLY

We are thankful to the reader for appreciating the need for developing drugs for thalassemia. The learned reader has reiterated the same safety issues which we had already mentioned in the last paragraph of our paper, including the need for larger studies addressing safety of thalidomide [1]. We restricted the study for 6 months on account of financial reasons.

As regards adverse effects (AEs), reader's attention is drawn to a recent study on another fetal haemoglobin (HbF) inducer—luspaterecept. In this study, 96% patients had one or more AE with 29% having AE grade 3 or more, 15% having serious AE with

several having infections. Even patients in placebo group had several infections [2]. High incidence of neutropenia is an important finding and it was rightly documented. The reader has quoted our previous work, which looked at deferiprone safety in young children. This study had children on deferiprone monotherapy [3].

The very low baseline mean HbF were on account of the fact that the patients were on regular transfusion at 2-3 weeks interval, with mean pre-transfusion Hb of 9-10.5 g/dL, which is expected to keep patients' erythropoiesis under check. The study by Ren, et al. [4] was in patients with thalassemia intermedia, where higher baseline HbF are noted as these patients are not regularly transfused [4]. A good pre-transfusion Hb is also the reason for lower requirement of packed cell. Hb during the study is slightly lower than baseline Hb but the difference is statistically not significant. The dose of thalidomide in Table I is the starting dose.

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Sensing temperature and touch

The Nobel Prize 2021 in physiology or medicine has been jointly awarded to David Julius and Ardem Patapoutian for the discovery of novel receptors involved in sensing temperature and touch by the human body, respectively. Dr Julius, from the department of physiology at the university of California, USA, while trying to find out how we perceive pain on coming in contact with capsaicin a compound present in chili peppers discovered a gene which encodes a novel ion channel named as TRPV1, heat sensing receptor which gets activated at temperatures perceived as painful. Later, histeam discovered another receptor TRPM8, which gets activated by cold.

Ardem Patapoutian, molecular biologist at Scripps Research in La Jolla, California studied how mechanical stimuli get converted into an electrical impulse responsible for sensing touch and proprioception. Patapoutian and his team discovered novel ion channels named as Piezo1 and Piezo2, which gets directly activated by the exertion of pressure on cell membranes. Both these channels are involved in the regulation of blood pressure, respiration and urinary bladder. Their findings also showed that Piezo2 is critically important in proprioception.

(Nobelprize.org 4 October 2021)

The malaria vaccine

Almost a decade after the beginning of the trial RTS, S/AS01 (RTS,S) - Malaria vaccine recently got the WHO's recommendation for its widespread use among children living in the sub-Saharan Africa and other regions with moderate to high prevalence of *P.falciparum* malaria. RTS,S is not only the first antimalarial vaccine but also the first vaccine developed against any parasite.

The pilot program, which was started in 2019 in three African countries – Ghana, Kenya and Malawi, had vaccinated almost 800,000 children by administering 2.3 million doses leading to a significant (30%) reduction in the severe malaria in high *P. falciparum* prevalence areas. Apart from this, the introduction of RTS, S has been proven to be feasible through the routine vaccination program with documented safety, efficacy and without any compromise of the other routine malaria control interventions. In areas of moderate to high transmissions of *P. falciparum*, it has been proven cost-effective by significant reduction in hospital admission for severe malaria or severe anemia due to malaria. A four dose schedule has been recommended for children aged 5 months or above, with 4 weeks gap between the first three doses and last dose to be taken after two years.

(who.int 6 October 2021)

Impact of COVID-19 – Do adults transmit influenza and RSV?

Since the recognition as a human respiratory pathogens, the seasonal occurrence of epidemics of influenza and respiratory syncytial virus (RSV) in children are causing significant morbidity and mortality. Studies over the years have described the role of children, especially the elder siblings, in the transmission of these two. But recently, the incidence of the respiratory infections and

the role of children and adults have been reviewed. The results showed a significant decline (94-99%) in the incidence of RSV and influenza cases compared to last few years (2012-2019) in the winter months in Western Australia, New Zealand, Chile, European and South African region. Initially this was thought to be an indirect consequence of various measures taken to control COVID-19. However, around September 2020, despite the reopening of schools with the return of children including younger ones (<5 years) to schools, sustained low incidence of these pathogens have highlighted a probable role of adults in transmission. The change in adult behavior like social distancing, use of mask and hand hygiene; due to current pandemic supports the role played by adults in the occurrence of these illnesses in children, which has to be looked into actively.

(Pediatric Pulmonology 14 October 2021)

Vaccination for children

The subject expert committee has forwarded its recommendations to the Drug Controller General of India (DCGI) for the use of Bharat Biotech's COVID-19 vaccine- "Covaxin" for use in the children aged 2-18 years. After DCGI's approval this will be the first COVID-19 vaccine worldwide, approved for the use in children aged 2-18 years. Recently ZydusCadila's DNA vaccine ZyCoV-D was approved for the emergency use in children aged 12-18 years. Though the results of the clinical trial by Bharat Biotech have not been disclosed publically, but the documented efficacy in adults is 77.8% against symptomatic infection. The availability of these vaccines will likely pave the way for the reopening of schools and return to normal life for children – full of outdoor activities and social interaction.

(Print 12 October 2021)

Mask - the savior!

During the current pandemic, use of face mask along with social distancing and hand hygiene have been suggested as the best methods to avoid the virus. There have been news reports on cautioning against the use of N95 mask while doing exercise in adults, but what about children? Parents are worried that the use of N95 mask can cause breathing difficulty or low oxygen levels in children.

An Italian study divided children into two groups to use N95 masks with and without exhalation valve, while being monitored over 72 minutes initially without wearing a mask after that with wearing a mask followed by a 12 minute walk. The use of masks did not affect the oxygen saturation or pulse rate significantly in the two groups, but the use of N95 mask without exhalation valve was associated with the significant increase in P_{ETCO_2} and respiratory rate even without walking test. Thus, surgical mask is believed to be the best option as for use in children as the use of N95 mask could potentially cause breathing difficulty, especially if the child is doing physical activity and the mask does not have an exhalation valve.

(Journal of Pediatrics October 2021)

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Congenital Milium of the Nipple

A 13-month-old girl, born of non-consanguineous marriage, presented with complaints of pearl like lesion on right nipple since birth. The lesion had slowly increased to size of a pea, but was not associated with any pain or itching. Growth and development were normal. Examination showed 5×5 mm pearly white nodule involving right nipple, with normal surrounding skin (**Fig. 1**). There was no erythema, induration or tenderness around the lesion. Left nipple was normal. A diagnosis of congenital milium of nipple was made, and parents were counselled about the benign and self-limiting nature of the lesion.

Milia (singular, milium) are inclusion cysts in the epidermis. The lesion develops due to entrapment of keratin. It appears as yellow to pearly white papule on the skin. It can be primary that arise spontaneously or secondary resulting from trauma such as sunburns or bullous skin disorder. Primary congenital milia are common in neonate and may be seen in almost 40% of full-term neonate. They generally appear over the cheeks, nose or eyelids. Solitary and large milium is seen over areola, scrotum or vulva. Solitary milium should be differentiated from the other lesions like syringoma, calcinosis cutis, trichoepithelioma and fibroma. Milium of the nipple should also be differentiated from witch's milk seen in some neonates due to maternal hormones, and galactorrhea due to excessive secretion of prolactin. Congenital milia resolve spontaneously but rarely may persist



Fig. 1 Pearly white nodule involving right nipple, with normal surrounding skin.

for a long duration. Excision of the lesion in the nipple area should be avoided as it can lead to functional and aesthetic complications, especially in a female child.

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Cutaneous Pili Migrans

A 2-year-old girl presented with a black linear elevation of the skin on the sole of the left foot. The child had no pain, itching discomfort, and had no history of trauma. On examination, a thin black line of about 1.8 cm was observed on the sole of the left foot without erythema or papules on the periphery (**Fig. 1**). After local skin disinfection, we used a sterile needle in combination with forceps to extract it. It was observed under a microscope as a hair structure with no hair follicles at either end. A diagnosis of cutaneous pili migrans was made. There was no recurrence on follow-up.

Cutaneous pili migrans is a rare skin condition characterized by a fragment of hair embedded in the epidermis or dermis layers of the skin. Differential diagnosis includes cutaneous larva migrans. If there is a hair follicle at one end of the hair, it may be necessary to destroy the hair follicle completely to prevent recurrence.

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Fig. 1 A distinct, S-shaped black line on the sole of the left foot with no signs of inflammation in the surrounding skin.

Genital Bullous Impetigo in a Child

A 6-year-old girl presented to us with a 7-day history of genital eruption. She was initially diagnosed with eczema herpeticum and treated with systemic acyclovir without any improvement. On dermatologic examination, there were erosions and hematic crusts on the peri-nasal area, the chin, and the vulva. The vulvar area was erythematous with vesicles and crusted and eroded erythematous plaques surrounded by a collarette of blister roof (Fig. 1). The patient was afebrile and the remaining physical examination, including lymph nodes, was normal. Bacterial culture of vesicle fluid was positive for methicillin-sensitive *Staphylococcus aureus*. A diagnosis of bullous impetigo was made. The patient was treated with oral amoxicillin-clavulanic acid along with chlorhexidine body wash. The lesions fully resolved within four days.

Genital bullous impetigo is an uncommon form of impetigo. It can be misdiagnosed for other vesiculating rashes such as varicella, eczema herpeticum, and linear IgA bullous dermatosis. However, it is distinguished clinically from these conditions by the presence of vesicles, flaccid blisters scaling in collarette, and children are well-appearing even in case of widespread bullous impetigo. Topical antibiotics are the first-choice treatment, and systemic antibiotic therapy is required in disseminated cases.



Fig. 1 Vesicles, hematic crusts and scaling in a collarette over the genital area.

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Infantile Digital Fibromatosis

A 6-month-old female patient presented with swelling in a finger of the left hand. Physical examination revealed a 1x1 cm firm, painless, nodular mass on the medial aspect of the distal phalanx of the fourth finger. On pathological examination of the excised mass, the patient was diagnosed as infantile digital fibromatosis (IDF). Nine months later, soft tissue masses of 1x1 cm formed at the operation site and also on the posterolateral surface of the distal phalanx of the third finger (Fig. 1). No treatment was administered since the tumor had a benign character, recurred after surgical treatment, and did not cause pain or loss of function.

Skin and subcutaneous nodules that occur among infants are typically benign, but malignant lesions like rhabdomyosarcoma, fibrosarcoma, neuroblastoma and congenital leukemia, may occur as well. IDF is a rare benign childhood tumor that presents almost exclusively in the fingers or toes. The lesion is typically firm and painless and presents on the dorsal, lateral, or ventral aspect of a finger as an erythematous or skin-colored, solitary papule less than 2 cm in diameter. Medical or surgical treatment may be required for lesions causing functional impairment. In medical treatment, topical steroids, intralesional steroids and topical tacrolimus treatment are applied. Recurrence occurs in 60-75% following surgical excision. As the lesions regress



Fig. 1 Skin-colored firm nodules on the distal phalanx of the third and fourth fingers.

spontaneously over several months to years, observation is recommended in cases without pain or dysfunction.

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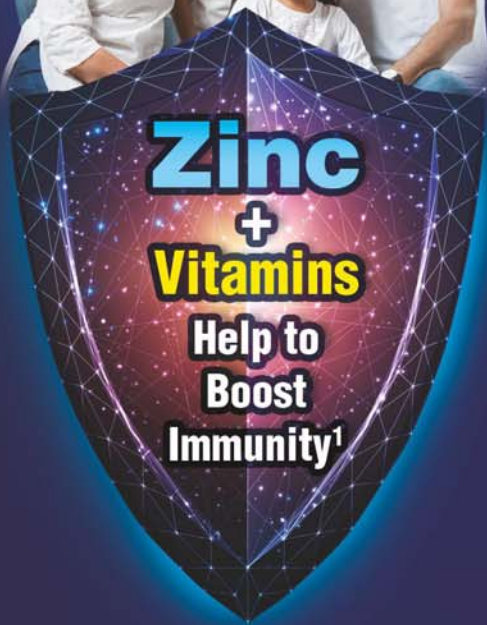
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