Acute Respiratory Infection and Pneumonia in India: A Systematic Review of Literature for Advocacy and Action: UNICEF-PHFI Series on Newborn and Child Health, India

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Background: Scaling up of evidence-based management of childhood acute respiratory infection/pneumonia, is a public health priority in India, and necessitates robust literature review, for advocacy and action.

Objective: To identify, synthesize and summarize current evidence to guide scaling up of management of childhood acute respiratory infection/pneumonia in India, and identify existing knowledge gaps.

Methods: A set of ten questions pertaining to the management (prevention, treatment, and control) of childhood ARI/ pneumonia was identified through a consultative process. A modified systematic review process developed *a priori* was used to identify, synthesize and summarize, research evidence and operational information, pertaining to the problem in India. Areas with limited or no evidence were identified as knowledge gaps.

Results: Childhood ARI/pneumonia is a significant public health problem in India, although robust epidemiological data is not available on its incidence. Mortality due to pneumonia accounts for approximately one-fourth of the total deaths in under five children, in India. Pneumonia affects children irrespective of socioeconomic status; with higher risk among young infants, malnourished children, non-exclusively breastfed children and those with exposure to solid fuel use. There is lack of robust nation-wide data on etiology; bacteria (including Pneumococcus, *H. influenzae*, *S. aureus* and Gram negative bacilli), viruses (especially RSV) and *Mycoplasma*, are the common organisms identified. *In-vitro* resistance to cotrimoxazole is high. Wheezing is commonly associated with ARI/pneumonia in children, but difficult to appreciate without auscultation. The current WHO guidelines as modified by IndiaCLEN Task force on Penumonia (2010), are sufficient for case-management of childhood pneumonia. Other important interventions to prevent mortality are oxygen therapy for those with severe or very severe pneumonia and measles vaccination for all infants. There is insufficient evidence for protective or curative effect of vitamin A; zinc supplementation could be beneficial to prevent pneumonia, although it has no therapeutic benefit. There is insufficient evidence on potential effectiveness and cost-effectiveness of Hib and Pneumococcal vaccines on reduction of ARI specific mortality. Case-finding and community-based management are effective management strategies, but have low coverage in India due to policy and programmatic barriers. There is a significant gap in the utilization of existing services, provider practices as well as family practices in seeking care.

Conclusion: The systematic review summarizes current evidence on childhood ARI and pneumonia management and provides evidence to inform child health programs in India

Keywords: *Action, Advocacy, ARI, Child health, Pneumonia, Systematic reviews.*

Childhood Acute Respiratory Infection (ARI) is the largest cause of morbidity among under-five children across the world. Pneumonia - the most serious presentation - is singly responsible for almost one-fifth of total mortality in this vulnerable age group. Therefore the importance of ARI and pneumonia cannot be over-emphasized. Consequently, global health-care agencies such as the World Health Organization (WHO), United Nations Children's Fund (UNICEF), national and state Governments, as well as international and local agencies involved with aid, academics, and research- have all focused on this area. In India, ARI has been given top priority in all

Government programs including the current Reproductive and Child Health Program, Phase-II (RCH-II).

The successful management of childhood pneumonia at a programmatic level revolves around four prongs *viz*. rapid and accurate detection of pneumonia in children, early treatment/management with specific therapy, management of co-morbid conditions, and efforts at primary prevention. These basic tenets are utilized to varying degrees in different programmes to manage the burden of childhood pneumonia at the national and international levels. However, there are several challenges in implementing and managing a successful program to reduce the mortality and morbidity due to childhood pneumonia, necessitating periodic review and rethinking.

This systematic review of literature was undertaken to provide evidence-based guidance for advocacy and action towards the management of childhood pneumonia in India. The specific objective was to identify, synthesize and summarize current best evidence pertaining to ARI/pneumonia. The review further aimed to identify knowledge gaps in the issues considered, with particular reference to the Indian context.

METHODS

The format for the Systematic Review Methodology has been presented earlier [1]. The search term "ARI" in Medline MeSH revealed 7 categories, none of which included acute respiratory infection. The term "acute respiratory infection" yielded no output, but the list of Suggestions included "respiratory infection". Exploding this term yielded the sub-category of "Respiratory Tract Infections" with 22 further sub-categories, one of which was "Pneumonia". Since most of the other terms did not cover acute respiratory infection, "Pneumonia" was chosen as the term for searching literature through Medline.

However, "ARI" frequently appears as a term in other documents including the World Health Organization (WHO) reports, Government of India documents, National Family Health Survey (NFHS) report, etc. Therefore, the term "ARI" also was used when searching these sources.

RESULTS

Details of the search output in terms of citations identified, titles screened, abstracts short-listed and full-text examined are shown in ***WebTable* I**. Literature searches were carried out during April 2010; and updated on15 February 2011.

1. Epidemiology

Burden of disease in India

There was no systematic review or nation-wide cohort study addressing this issue. Nation-wide data, collected prospectively from a representative sample of the Indian population, through the serial National Family Health Survey (NFHS) studies [2-4] reported an overall ARI prevalence of 6.5%, 19.0% and 5.8% among under-five children in the preceding two weeks before the survey in three surveys at three time-periods over last two decades (***Table* I**). The inexplicable three-fold higher prevalence in the second survey compared to the first is inadequately explained; it is stated that the difference is on account of different time-periods at which surveys were conducted. The National Health Profile of India report published by the Central Bureau of Health Intelligence [5] mentions 26 544 613 cases of ARI across all age groups with only 2813 deaths; although the source and methodology are not described.

TABLE I PREVALENCE AND TIME-TREND OF ARI AMONG CHILDREN [NATIONAL FAMILY HEALTH SURVEY (NFHS)]

Study	Year	Prevalence	Definition of ARI used
NFHS 1	1992-93	6.5%	children < 3y suffered from ARI (cough + fast breathing) during preceding 2 wk
NFHS 2	1998-99	19%	children <3y suffered from ARI (cough + short, rapid breathing) during preceding 2 wk
NFHS 3	2005-06	5.8%	children <5y suffered from ARI (cough + short, rapid breathing) during preceding 2 wk

A research paper reporting global estimates projected 44 million cases per year in India [6]. A previous estimate based on the same data projected 43 million *episodes* per year [7]. A recent secondary analysis pointed out that both are likely to be over-estimates based on out-dated data and/or highly sensitive diagnosis [8].

Among the small-scale primary studies, a community-based study in Udupi [9] among children less than five years old recorded overall ARI incidence of 6.42 episodes per child per year; however only 51 of 584 episodes (8.7%) were pneumonia (which works out to 0.52 episodes per child per year) and only 3 of 584 ARI episodes (0.5%) were severe pneumonia. A small ARI survey conducted in Tripura [10] among 400 rural and 400 urban slum children below five years of age, reported the incidence of ARI over 18 months as 23% in rural areas, and 17.7% in urban areas. A study from Lucknow [11] reported 17 episodes of pneumonia among 1061 children, giving an annual incidence rate of 0.096 (95% CI 0.057 to 0.16) per child year. The same study [11] also reported the annual incidence rate of respiratory disease (other than pneumonia) as 167 (95% 149-185) per 100 child-years, suggesting that just under 10% 'respiratory disease' is 'pneumonia'. A 20 year old study from AIIMS New Delhi [12] followed 5335 children in villages of Ballabhgarh block for one year and reported 834 episodes of pneumonia. The authors calculated the attack rate as 0.29/child/year among under-five children. Severe cases constituted only 0.5%.

A recent study [13] published during the process of this systematic review evaluated the incidence of hospitalised pneumonia and meningitis in infants below 2 years old. Severe pneumonia was defined to match the WHO criteria (cough or difficult breathing or tachypnea and at least one clinical sign among intercostal retractions, nasal flaring, grunting, central cyanosis, inability to feed, lethargy, unconsciousness, or head nodding). Radiographic evidence of consolidation as per the WHO criteria was labelled as Radiological pneumonia. A total of 589 episodes of pneumonia were suspected among 17951 children. The incidence of physician diagnosed pneumonia at discharge per child-year in the three study sites was 0.030 (95% CI 0.025-0.034) at Chandigarh, 0.080 (95% CI 0.071-0.091) at Kolkata and 0.037 (95% CI 0.030-0.045) at Vellore. Age-specific calculations showed that the incidence of severe clinical hospitalized pneumonia was highest in infants less than 5 months old, declining with increasing age. Only 11.3% of 434 readable radiographs were consistent with radiological pneumonia; although there was significant variation among the three study sites.

Conclusions and Comments

- The precise magnitude of childhood ARI and/or pneumonia in India is not known. ARI and pneumonia have been used interchangeably in some studies although the two are not synonymous.
- Most of the available data is based on small-scale community and hospital-based studies, and hence may not be representative of the whole population. It appears that a little less than 10% of ARI are pneumonia.
- The burden of disease in terms of episodes per child per year in small scale studies ranges from 0.03 to 0.52.

Knowledge gap

- Childhood community acquired pneumonia is an important public health problem, though the precise burden is not known.

Mortality

The Registrar General of India conducts the Sample Registration System (SRS) in randomly selected sample units all over India to calculate multiple demographic indicators. A study based [14] on a sample from the 1991 census (about 6 million people in 1.1 million households) used an enhanced format of verbal autopsy (abbreviated as RHIME for routine, reliable, representative, resampled household investigation of mortality with medical evaluation) to estimate cause specific mortality in the selected sample. Families were interviewed and cause of death assigned by physicians, providing cause-specific mortality rates for 2005. Pneumonia was identified using 32 codes of the International Classification of Diseases tenth revision (ICD-10).

Using data from this study, respiratory infection was reported as the cause of 22% mortality among 0-4 year old children for the period 2001-03. For the age group 1-4 years, respiratory infections were responsible for 22.5% deaths.

The Million Death Study [15] reported that, 27·6% (99% CI 31·8%-34·1%) deaths were attributable to pneumonia among a total of 12260 deaths in children from 1-59 months. This outweighed the deaths due to diarrhea (22·6% with 99% CI 21·5%-23·7%), making pneumonia the leading cause of childhood mortality in India. In this study, pneumonia was identified by verbal autopsy and labeled by physicians.

Using the SRS data, the Million Death Study group applied the proportions of each cause of childhood mortality to the independent UN Population Division estimate of India's total live births (27·3 million) and under-five childhood mortality (2·35 million) for the year 2005; to estimate age-specific and gender-specific mortality rates (per 1000 live births) as well as absolute number of deaths by specific causes [15]. Mortality due to pneumonia comprised 24·9% (99% CI 21·4-28·8%) of 1113 deaths in urban areas; and 28·0% (99% CI 26·8-29·2) of 11147 deaths in rural children. The proportion of deaths due to pneumonia was highest in Jammu and Kashmir, and Delhi; and lowest in Tamil Nadu. The study projected the collected data for the whole country and estimated that 13·5% (99% CI 13·0-14·1) of under five mortality is attributable to pneumonia; accounting for 369000 annual deaths. It also reported that the mortality due to pneumonia among girls was higher than boys (16.0% *vs* 11.2%) [15].

The Central Bureau of Health Intelligence of the MoHFW reported ARI mortality ranging from 3200 to 6900 each year [5], giving a mortality rate of 0.32 to 0.61 deaths per l00,000 population. The WHO-UNICEF estimated that approximately 408000 under-five deaths in India are contributed by pneumonia [6]. If this is true, it works out to a ARI case fatality rate of 0.93% [8]. A large modelling analysis of data from 193 countries calculated that pneumonia contributes 18% of a total of 8.795 million under-five deaths [16].

A recently published systematic review [17] examined causes of child deaths in India over the past 25 years. The authors included 12 data sources reporting pneumonia mortality in children beyond the neonatal age group. Although the terms ARI, respiratory infection, and pneumonia were defined differently in various studies, mortality attributable to these conditions ranged from 10 to 33%. Based on SRS data calculations, respiratory infection was listed as the leading cause in infants as well as children from 1 to 5 years of age [18].

The recently published multicentric study among hospitalized children in Chandigarh, Kolkata and Vellore reported pneumonia case fatality ratios as 1.01%, 2.35% and 0.77% respectively. The respective mortality rates in severe clinical pneumonia were 1.35%, 3.32% and 0.89% [13].

A community based study in Ballabhgarh villages [12] followed over 5000 under five children and estimated overall case fatality rate due to pneumonia as 1.26%; it also reported that mortality rate was 1% in moderate cases and 50% in severe cases, although the severity grading was not defined.

An AIIMS study [19] of hospitalized children (<5 years with WHO defined severe pneumonia) reported 21 deaths among 200 hospitalized children (10.5%). The SPEAR study [20] in children with very severe community acquired pneumonia, hospitalized across several developing countries including India, reported a mortality rate of 24 among 958 children enrolled (2.5%). Naturally, these are not necessarily representative of the mortality rate in the community.

An older study in urban slum children of Delhi (2 weeks to 5 years old) admitted in the Pediatric Emergency with ALRI reported case fatality rate by severity of pneumonia [21] as 11.1% among those with no pneumonia (n=18), 0% among those with pneumonia (n=45), 8.7% among those with severe pneumonia (n=104) and 47% in very severe pneumonia (n=9). Another study in 28 urban slums of Lucknow [22] identified 71 deaths among 2796 children (2.5%), among which pneumonia was the major cause (19.7%), followed by diarrhea (18.3%) and measles (11.4%). Yet another study in over 24000 children residing in slums, used verbal autopsy to determine cause of death and reported that among

1171 deaths, the most important cause beyond the neonatal period was pneumonia (23.4%), diarrhea (20.9%), and malnutrition and/or anaemia (11.4%) [23].

Conclusions and Comments

- In India, pneumonia is the single most important cause of death among children in the post-neonatal period, contributing as much as 27.5% of total under-five mortality according to one estimate.
- Older studies reported around 10% case fatality rate in children hospitalized with severe pneumonia and upto 50% with very severe pneumonia. Recent data in tertiary care hospitals reports lower mortality (1-3%) in severe and very severe pneumonia. Mortality calculated from hospital-based studies could be higher than community-based mortality owing to sicker children being taken to hospital; on the other hand, it is possible that very sick children die even before they reach the hospital.

Knowledge gap

- Longitudinal, community and hospital-based surveillance is required to understand the true picture of childhood pneumonia mortality in India.

Time trends

***Table* I** shows the trend in ARI prevalence over the past 1.5 decades through the NFHS series [2-4]; there is an inexplicable three-fold rise between the first and second survey, with return to baseline during the third survey. The reason(s) for this is/are not clear; although it is stated that the surveys were conducted at different times of the year. Comparison of ARI NFHS-3 data with NFHS-2 survey may not be practical also because the questions to estimate ARI changed between the two surveys, and the surveys took place at different times of the year.

Conclusion and Comment

- Identification of trend over time is fraught with the problem of diverse definitions used. Even the NFHS data using fairly similar definitions over time cannot be used to reliably assess time trends.

Risk factors for incidence and mortality

The community-based NFHS-3 survey [4] reported that ARI affects all children, irrespective of socioeconomic status; however prevalence is slightly higher among boys, in rural areas, among scheduled-tribe children, and those residing in lower standard of living households. The prevalence is lower among children of mothers who have at least completed high school and those living in households that use piped drinking water and water filter for the purification of water. A community-based study [12] among 5000 <5 children reported that infants with all forms of pneumonia had nearly twice higher attack rate (0.59/child/year), although females had higher case fatality rate than males (1.5% *vs* 1.1%). A case-control study in hospitalized children [24] reported solid fuel use (OR 3.97, CI 2.00-7.88), history of asthma (OR 5.49, CI 2.37-12.74), poor economic status (OR 4.95, CI 2.38-10.28) and keeping large animals (OR 6.03, CI 1.13-32.27) as risk factors. Subgroup analysis of the SRS data from 1.1 million households across India analyzed a total of 6790 child deaths by the household usage of solid fuel. The investigators noted that solid fuel use was associated with increased child mortality among 1-4 year old children (prevalence ratio among boys 1.30, 95% CI 1.08-1.56 and girls: 1.33, 95% CI 1.12-1.58). Solid fuel use was also associated with non-fatal pneumonia in boys (prevalence ratio 1.54 95% CI 1.01-2.35) as well as girls (prevalence ratio 1.94 95% CI 1.13-3.33) [25].

The WHO 2008 report [6] cited and categorized risk factors as: (i) *Definite* risk factors: malnutrition (weight-for-age *z*-score < -2), low birth weight, lack of exclusive breastfeeding during first 4 months, lack of measles immunization, indoor air pollution, crowding; (ii) *Likely* risk factors: parental smoking, zinc deficiency, maternal inexperience, co-morbidities; and (iii) *Possible* risk factors: maternal illiteracy, day-care attendance, rainfall (humidity), high altitude (cold air), vitamin A deficiency, higher birth order, outdoor air pollution.

A systematic review of mortality risk in pneumonia identified 16 studies across several countries and reported that malnourished children

had higher mortality; RR 2.9-121.2 with severe malnutrition, and 1.2-36.5 with moderate malnutrition [26].

Among Indian studies, risk factors of mortality in children with severe pneumonia [19] were reported as presence of head nodding (RR 8.34, 95% CI 2.71-12.77), altered sensorium (RR 5.44, 95% CI 1.34-17.56), abnormal leukocyte counts (RR 5.85, 95% CI 1.36-17.14), and pallor (RR 10.88, 95% CI 2.95-20.40). Among children with pneumonia (severe and very severe cases) admitted in the Emergency department of a teaching hospital in Delhi [21], risk factors for mortality included age less than 1 year (OR 23.1, 95% CI 2.7-197.5), inability to feed (OR 6.2, 95% CI 1.3-30.7), malnutrition defined by weight for age Z score <-3.0 (OR 3.9, 95%CI 1.01-9.7), and presence of bandemia on peripheral smear (OR 1.1, 95% CI 1.05-1.2). The presence of concomitant diarrhea was also an independent predictor of mortality (OR 5.1, 95% CI 1.2-27.3).

A hospital-based case control study [27] identified severe pneumonia (OR 4.2; CI 1.2-14.4), marasmic status (OR 2.9, CI 1.5-5.7), age under 6 months (OR 2.8, CI 1.3-5.7), and associated illnesses, as risk factors for death.

Conclusions and Comments

- ARI (and therefore pneumonia) in India affects children irrespective of socioeconomic status.
- Malnourished state, younger age and concomitant illnesses are associated with higher mortality.
- Lack of breast feeding, younger age (less than one year), lack of measles immunization, and solid fuel use are additional risk factors for pneumonia morbidity and/or mortality.

Knowledge gaps

- The net effect/impact of a set of multiple risk factors, for an individual child to develop ARI/ pneumonia and/or response to treatment, is not known.
- Feasibility and effectiveness of interventions to reduce exposure to some of the risk factors is not known.

2. Etiology

Etiology of Childhood Pneumonia in India

There is no systematic review or nation-wide study of etiology in India. A prospective study [28] of microbiology of nasopharyngeal aspirates and, serology in children with severe ALRI (*n*=95) reported viruses from NP aspirate in 38%, bacterial isolates from blood cultures in only 16%, *Mycoplasma* in 24%, *Chlamydia* in 11% by serological testing, and mixed infections in 9%.

Additional tests like latex agglutination test (LA) for *H. influenzae* and *S. pneumoniae*; immunofluorescent technique (IFAT) and enzyme immunoassay (EIA) for respiratory syncytial virus (RSV) in another study [29] isolated *Haemophilus influenzae* in 15%, RSV in 14%, *Klebsiella* in 13%, and *S. pneumoniae* in 12%. Among young infants < 3 months, *E. coli* was the commonest organism, followed by RSV. In older infants (7-24 months), RSV and *H. influenzae* were relatively more common. Among those older than five years, *S. aureus* and *S. pneumoniae* were isolated in 40% and 20% respectively by culture.

In the ISCAP trial [30], among 2188 under-five children with non-severe pneumonia there were 878 isolates of *S. pneumoniae* and 496 isolates of *H. influenzae* at enrollment. A total of 513 samples (23%) tested positive for RSV.

A serotyping study [31] reported that among 150 clinical isolates from invasive and other clinically significant pneumococcal infections, 59.3% belonged to serotypes 1, 6, 19, 5, 23 and 7. Serotype 1 was the commonest isolate in meningitis and empyema. In another study [32], among 42 pneumococcal strains, over one-third in children and nearly half in adults were serotypes 5, 6 and 7. The remaining 11 of 14 strains in children and 20 of 28 strains in adults belonged to 8 serogroups/types, namely 3, 4, 10, 11, 12, 13, 19 and 20.

The IBIS study [33,34] was a prospective hospital-based surveillance for *H. influenzae* and invasive pneumococcal disease (IPD) in 6 teaching/ referral hospitals across India. Children (1mo-12y) as well as older patients with radiologic or clinical

pneumonia, fever, suspected meningitis or suspected sepsis; underwent microbial culture. Among a total of 3441 patients, the majority were children and 2324 had pneumonia. A total of 182 *S. pneumoniae* and 58 *H. influenzae* were isolated. Of the 58 *H. influenzae* isolated, 96% were serotype b. Among patients with *H. influenzae* infection 40 had meningitis, and only 11 had pneumonia; whereas patients with *S. pneumoniae* on culture had pneumonia and meningitis in almost equal proportions (about one-third). Nearly all isolates were from children <5 years old, majority from <1 yr. It is believed that the true prevalence of Hib disease may not be identified by culture; antigen testing and PCR increase yield in CSF by 1.3-5.5-fold, compared with culture alone [35]; this suggests that the prevalence of Hib disease is significantly higher than that reported by studies isolating the organism by culture methods.

Studies targeted towards isolation of atypical organisms by serological tests or indirect immunofluorescence identified *M. pneumoniae* in 17 of 62 children and *C. pneumoniae* in 4 [36]. A recent study identified RSV in 29 of 67 (43.3%) children with clinically defined pneumonia, although the age range was not restricted to under-five children [37]. A hospital-based study [38] applied viral culture and immunofluorescence techniques in 736 children <5 years of age with ARI (pneumonia 39%, upper respiratory infection 38%, croup or bronchiolitis 23%). Among those with pneumonia, viruses were detected in 66 of 287 (23%) cases. The isolates included measles (33%), adenovirus (18%), RSV (14%), influenza (18%) and parainfluenza (17%). In contrast, among children hospitalized with very severe pneumonia, the SPEAR study [20] reported RSV positive in only 47 of 724 (6.4%) samples, suggesting that severe disease is less likely to be viral.

The WHO Bulletin 2008 report [6] identified *Streptococcus pneumoniae* and *Haemophilus influenzae*, *Staphylococcus aureus* and *Klebsiella pneumoniae* as the major bacterial causes of childhood pneumonia. It also mentioned *H. influenzae* as an important cause in developing countries. The report cited older data to show that Pneumococcus is responsible for 30–50% cases, *H. influenzae* type b for 10–30% cases, followed by *S. aureus* and *K. pneumoniae*.

A systematic review [26] of mortality risk in children with pneumonia identified 16 studies, and reported that among severely malnourished children, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Haemophilus influenzae* are the common organisms in that order.

Conclusions and Comments

- Most studies are not designed to identify the etiology of pneumonia, but restricted to detection of one or more micro-organisms through non-invasive methods; hence may not reflect true etiology.
- Childhood pneumonia in India is caused by bacteria, viruses, atypical organisms like Chlamydia and *Mycoplasma*, although the precise proportions in community and hospital-based studies is not clear. However, it appears that about 10-15% of childhood pneumonias are caused by H. *influenzae* and RSV each; and 12-35% by pneumococcus. Other important causes include *S. aureus*, Gram negative organisms (especially in younger infants), *Mycoplasma* and *Chlamydia*.
- Serotypes of *S. pneumoniae* causing childhood pneumonia are also not well identified; limited data suggests that around 50% are covered by the 7-valent Pneumococcal conjugate vaccine.

Knowledge gap

- India's large size and diverse socio-economic, cultural, climatic influences and variable service delivery systems; mandate that surveillance systems are set up for identifying etiology of childhood pneumonia at the community and health facility levels.

Antimicrobial resistance pattern

This section includes data on antimicrobial susceptibility of organisms that are responsible for pneumonia, but not necessarily isolated from children with pneumonia.

The IBIS study [33,34] reported that more than 50% of 57 *H. infleunzae* isolates were intermediately or fully resistant to chloramphenicol, and 38 to 41%

were resistant to cotrimoxazole, ampicillin or erythromycin. None of the isolates showed resistance to a third generation cephalosporin. Among *S. pneumoniae*, there was 56% cotrimoxazole resistance. However, resistance to penicillin was rare (1.3%), and none of the isolates was resistant to injectable third generation cephalosporins. Amongst *H. influenzae*, resistance was common both to co-trimoxazole (45%) and ampicillin (38%) [34].

In the ISCAP trial [30] the resistance pattern of *S.pneumoniae* to various antibiotics was: cotrimoxazole 66.3%, chloramphenicol 9.0%, oxacillin 15.9% and erythromycin 2.8%. The respective resistance rates among *H. influenzae* were 57.7%, 24.7%, 29.0% and 18.2%.

Among 150 clinical isolates from invasive and other clinically significant pneumococcal infections, only 11 (7.3%) isolates were relatively resistant to penicillin, although 64 were resistant to one or more antibiotics especially cotrimoxazole, tetracycline and chloramphenicol [31]. In 464 South Indian infants (2-6 months) [39], pneumococci isolated from nasopharynx were tested for resistance to three common antibiotics (penicillin, cotrimoxazole and erythromycin). When tested individually, there was no resistance to penicillin. However, when tested together, overall resistance to penicillin was 3.4%, cotrimoxazole 81% and erythromycin 37%. Serotypes most frequently resistant were 6, 9, 14, 19 and 23; although less than 1% isolates were multi-drug resistant. A similar study [40] in 100 infants detected colonization with Pneumococcus on at least one occasion in 81 infants. Resistance to penicillin, chloramphenicol, cotrimoxazole and erythromycin was observed in 0%, 6% and 3% isolates, respectively.

The IBIS study [34] reported 60% resistance to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, or erythromycin; with 32% isolates resistant to more than 3 antimicrobial drugs; among 125 isolates. None were resistant to third-generation cephalosporins. Another study from Lucknow [41] reported the resistance pattern of 90 *Haemophilus* isolates among patients with ARI of all age groups as: cotrimoxazole 33.3%, ampicillin 21.1%, cephalexin 7.8%, chloramphenicol 7.8%, ciprofloxacin 2.5% erythromycin and tetracycline 5% each. In a limited study [42] with 12 Hib isolates, 8 (67%) were multiply resistant to ampicillin, chloramphenicol and cotrimoxazole, but all were susceptible to cefotaxime and erythromycin.

Among older children, a study [43] in 5-10 year old school children identified 1001 *H. influenzae* isolates from 2400 nasopharyngeal swabs; Hib constituted 316 (31.6 %). Of these, 44.0 % were ampicillin resistant, although only 13.1 % non-type b *H. influenzae* isolates were ampicillin resistant. 196 of 229 ampicillin resistant isolates were positive for beta-lactamase. This suggests that these antibiotics may not be the most appropriate first choice in this age group.

Among Gram negative organisms, tertiary-care center hospital data from Lucknow [44] reported resistance patterns of *E. coli* and *Klebsiella* from various body fluids of patients with septicaemia in all age groups as amikacin 15%, gentamicin 67%, trimethoprim/sulphamethoxazole 79% and ciprofloxacin 94%. Extended spectrum beta-lactamases (ESBL) were found in 64% of 143 *E. coli* isolates and 67% of 57 *K. pneumoniae* isolates. In a study [45] of 100 clinical isolates of *Klebsiella* spp. from cases of neonatal septicaemia, 58 were reported to be ESBL positive. In a retrospective study of community acquired as well as nosocomial septicemia [46], a total of 4027 samples were obtained from children less than 15 years of age. Among 736 positive cultures, Gram negative organisms predominated (66%) followed by Gram positive (33.5%) and fungi (1%). Among the Gram negative bacteria, *Klebsiella pneumoniae* (22.4%) and *E. coli* (12.6%) predominated followed by *Acinetobacter* (9.3%) and *Salmonella typhi* (5.4%). Both *Klebsiella* and *E. coli* showed 70-80% resistance to amoxicillin and cephalexin, and minimum resistance to cefotaxime (23%) and ciprofloxacin (12%).

Conclusions and Comments

- There is variable *in-vitro* resistance to common antibiotics among organisms implicated in childhood pneumonia; however penicillin resistance is uniformly low and cotrimoxazole resistance high.

- Research studies published after 2000 show higher resistance to cotrimoxazole among Pneumococci and *H. influenzae*, than earlier studies.
- Gram negative organisms are also showing increasing resistance to common antibiotics; this needs to be factored in as they are implicated in childhood pneumonia in India.
- The use of antibiotics is recommended for all children with Acute Lower Respiratory Infection (ALRI) based on fast breathing. On one hand, this guideline results in early treatment (and recovery) of pneumonia; on the other hand it may result in overtreatment increasing antibiotic resistance.
- In view of increasing reports of *in-vitro* cotrimoxazole resistance it may be prudent to use amoxicillin as the first-line antibiotic, monitor the sensitivity patterns, and use an antibiotic rotation policy, in tune with surveillance data.

Knowledge gaps

- An antibiotic surveillance system is required to identify the antimicrobial sensitivity patterns (*in vitro* and *in vivo*), and modify recommendations for public health programs based on changing patterns.
- The degree of match between *in vitro* and *in vivo* results; and data from large hospitals versus the spectrum within the community, are not clear.
- The level of resistance at which, one antibiotic should be abandoned in favor of another (in a national program) is not known.

3. Management

Chest radiography is not routinely indicated for children with community acquired pneumonia. Hence data pertaining to radiography has not been included in this review.

Antibiotic therapy

As it is inappropriate to examine data comparing antibiotic versus placebo/no treatment in childhood pneumonia, such studies are not included.

Choice of antibiotic: A recent Cochrane review [47] updated an older Cochrane review [48] on antibiotic therapy for childhood pneumonia. The latest conclusions are that for non-severe pneumonia, cotrimoxazole and amoxicillin have comparable treatment failure rate (OR 0.92, 95% CI 0.58-1.47) and cure rate (OR 1.12, 95% CI 0.61-2.03). The two antibiotics appear to have similar failure rate for severe pneumonia diagnosed clinically (OR 1.71, 95% CI 0.94-3.11) or radiologically (OR 2.14, 95% CI 0.96-4.78). Mortality with the two antibiotics is also comparable (OR 2.08, 95% CI 0.22-20.06). These findings are in line with data from an effectiveness study [49] that reported no difference in effectiveness of oral cotrimoxazole versus amoxicillin for (non-severe) pneumonia.

The Cochrane review [47] reported cotrimoxazole to be comparable to procaine penicillin in terms of cure rate (OR 1.58, 95% CI 0.26-9.69), hospitalization rate (OR 2.52, 95% CI 0.88-7.25) and mortality (OR 3.09, 95% CI 0.13-76.13). Coamoxiclav is reported to be comparable to amoxicillin for multiple outcomes including cure rate (OR 10.44, 95% CI 2.85-38.21), complications (OR 5.21, 95% CI 0.24-111.24) and side effects (OR 5.21, 95% CI 0.24-111.24).

In severe pneumonia, the Cochrane review [47] reported that chloramphenicol resulted in greater treatment failure rate on multiple days of treatment as compared to a combination of ampicillin and gentamicin (OR 1.51, 95% CI 1.04-2.19 on day 5, OR 1.46, 95% CI 1.04-2.06 on day 10, and OR 1.43, 95% CI 1.03-1.98 on day 21). The necessity to change antibiotics was also higher with chloramphenicol than the combination. Mortality showed a trend of being higher with chloramphenicol (OR 1.65, 95% CI 0.99-2.77). In very severe pneumonia, chloramphenicol was reported to be comparable to penicillin plus gentamicin in terms of mortality (OR 1.25, 95% CI 0,76-2.07), need to change antibiotics (OR 0.80, 95% CI 0.54-1.18) and adverse events (OR 1.26, 95% CI 0.96-1.66). However odds of treatment failure were higher with chloramphenicol (OR 1.61, 95% CI 1.02-2.55).

The multi-nation SPEAR trial [20] comparing 5 day treatment with injectable ampicillin plus gentamicin *vs* chloramphenicol in children aged 2-59

months with very severe pneumonia reported greater treatment failure with chloramphenicol at day 5 (RR 1.43, 95% CI 1.03-1.97) and also by days 10 and 21.

Another multi-center study [50] in eight developing countries in Africa, Asia, and South America, among children aged 3-59 months with severe pneumonia, evaluated 48 hour hospitalization followed by 5-day course of oral amoxicillin at home. In-hospital treatment was either oral amoxicillin (*n*=857) or parenteral penicillin (*n*=845). Treatment failure (persistence of lower chest indrawing or new danger signs) was 19% in each group. Age <12 months (OR 2.72, 95% CI 1.95-3.79), very fast breathing (OR 1.94, 95% CI 1.42-2.65), and hypoxia at baseline (OR 1.95, 95% CI 1.34-2.82) predicted treatment failure by multivariate analysis. An older randomized-controlled trial [51] compared 10 days of treatment with penicillin G and chloramphenicol *vs* ceftriaxone and found similar cure rates.

A 2003 WHO meeting [52] concluded that for (non-severe) pneumonia, three days therapy with oral antibiotics is sufficient in countries where HIV is not a major public health problem. Oral amoxicillin is a superior choice in countries where cotrimoxazole resistance is high. Oral amoxicillin can be used twice daily instead of thrice. Children presenting with wheeze and pneumonia should be given a trial of rapid acting bronchodilator (where feasible) before an antibiotic is prescribed. For severe pneumonia, if HIV infection is clinically suspected or confirmed, routine WHO ARI case-management should not be used.

A recent Cochrane review [53] extracted data pertaining to children with *Mycoplasma* pneumonia to evaluate whether macrolides are superior to other antibiotics (especially coamoxyclav). In most trials, clinical response was comparable with macrolide and non-macrolide antibiotic.

In older children and adolescents, for non severe cases, oral amoxicillin or coamoxyclav are the first choices; severe cases require injectable antibiotics. Crystalline penicillin is an appropriate starting choice. Cloxacillin should be added if Staphylococcal disease is suspected clinically. Atypical organisms such as *Mycoplasma* are fairly common in this age group and treatment is with macrolide [54]. The current guideline for patients ≥18 years of age with community acquired pneumonia [55] also recommends beta-lactams as the first line, since it covers the most common pathogens responsible; however the resistance rate is reportedly higher than in children. It is not clear whether such guidelines can be extrapolated to adolescents.

In a recent trial in Bangladesh [56], children (2-59 months old) with severe pneumonia (WHO criteria) but without severe malnutrition and/or other complications, were randomized to be treated with injectable ceftriaxone either as 'day-care' or hospitalized. After treatment, both groups had comparable duration of symptoms, oxygen therapy and duration of stay; suggesting that severe pneumonia without malnutrition could be managed as day-care without admission.

Route of antibiotic: A Cochrane review [57] compared effectiveness and safety of oral *versus* parenteral antibiotics for treatment of severe pneumonia in children (3mo-5y), although meta-analysis was not performed owing to limited data. One of the trials found similar treatment failure rate with oral cotrimoxazole *vs* intramuscular procaine penicillin followed by oral ampicillin in 134 children. Another larger trial (*n*=1702) reported similar results. A recent cost-minimisation economic analysis [58] among children hospitalized with CAP who were randomized to receive either oral amoxicillin or i.v. benzyl penicillin; reported that parenteral treatment was significantly more expensive than oral owing to cost of therapy and greater length of stay. Unfortunately the equivalent costs in a developing country setting are not mentioned.

Dose of antibiotic: A RCT in Pakistan [59] compared 45 mg/kg/day versus 90 mg/kg/day oral amoxicillin for 3 days, among children aged 2-59 months with non-severe pneumonia. There was no significant difference in treatment failure between the groups. The COMET study [60] reported that treatment failure rate in children with non-severe pneumonia receiving double dose of cotrimoxazole (8 mg trimethoprim plus 40 mg sulfamethoxazole/kg) was comparable (RR 1.10; 95% CI 0.87–1.37) to those receiving standard dose (4 mg trimethoprim plus 20 mg sulfamethoxazole/kg).

Duration of therapy: A Cochrane review [61] comparing short versus standard duration of therapy identified 3 trials (5763 children) and showed no significant difference in clinical cure, treatment failure and relapse rate after seven days of clinical cure with shorter durations of therapy. A meta-analysis [62] comparing short (≤7 days) versus long (≥2 days difference) course therapy for CAP in children 2-59 month old did not find any differences. The MASCOT trial [63] compared 3-day *vs* 5-day oral amoxicillin in (non-severe) pneumonia among 2000, 2-59 month old children. Treatment failure was similar: 209 (21%) with 3-day *vs* 202 (20%) with 5-day treatment. Relapse rate also was similar between the groups (1% in each group).

Prophylactic antibiotics following measles: A Cochrane review [64] with 7 trials (1385 children) reported no difference in the incidence of pneumonia with antibiotics (OR 0.28; 95% CI 0.06-1.25) when all trials were compared. Removing an outdated trial (1942) that showed increase in pneumonia, resulted in strong evidence of reduction in incidence (OR 0.17; 95% CI 0.05-0.65; NNT 24). The incidence of complications was lower with antibiotics: purulent otitis media (OR 0.34; 95% CI 0.16-0.73) and tonsillitis (OR 0.08; 95% CI 0.01-0.72), although there was no difference in conjunctivitis (OR 0.39; 95% CI 0.15-1.0), diarrhea (OR 0.53; 95% CI 0.23-1.22) or croup (OR 0.16; 95% CI 0.01-4.06).

Conclusions and Comments

- There is adequate data to support the choice of antibiotics recommended in the IAP-IndiaCLEN 2010 guideline.
- Oral route can be used for most childhood pneumonia in the community; severe and very severe cases require injectable antibiotics. Successful trials of oral therapy in severe pneumonia may not give similar results unless research setting level of follow-up/monitoring can be maintained.
- For (non-severe) pneumonia, 3 days therapy appears sufficient.
- Children with measles can be offered antibiotics to prevent pneumonia and/or complications.

Knowledge gap

- Treating all children with rapid breathing (pneumonia as per the WHO criteria) can result in antibiotic over-use and its consequences; however the short and long term impacts of this are not known.

Oxygen therapy

Prevalence of hypoxemia in pneumonia: A systematic review [65] reported the median prevalence of hypoxemia among studies in children with severe pneumonia as 9.4% (IQR 7.5-18.5%); it was 13% for combined severe and very severe pneumonia defined by the WHO criteria. Another older systematic review [66] to determine the prevalence of hypoxemia in under-five children with ALRI (17 cohort studies, 4021 children) reported low risk (6-9%) of hypoxemia among out-patient children and those with upper respiratory infection. The prevalence was 31-43% in emergency departments; and 47% among hospitalized children and highest (72%) in those with radiographically confirmed pneumonia.

Prospective data from Papua New Guinea in hospitalized children (including pneumonia) [67], reported hypoxemia in 384 of 1313 children (29.25%, 95% CI 26.8-31.8); oxygen was not available on the day of admission for 22% of children including 13% of all children with hypoxemia. Oxygen was less available in remote rural district hospitals than in provincial hospitals in regional towns. Clinical signs proposed by WHO as indicators for oxygen would miss 29% of children with hypoxemia and using the signs, 30% of non-hypoxemic children would receive oxygen. In a Nepal study [68], the prevalence of hypoxemia (SpO2 <90%) in 150 children with pneumonia was 38.7%. Of them 100% of very severe pneumonia, 80% of severe and 17% of pneumonia patients were hypoxic. Clinical predictors significantly associated with hypoxemia on univariate analysis were lethargy, grunting, nasal flaring, cyanosis, and complaint of inability to breastfeed or drink. Chest indrawing with 68.9% sensitivity and 82.6% specificity was the best predictor of hypoxemia. An older prospective Kenyan study [69] described the prevalence of

hypoxemia in children admitted to hospital as 977 of 15289 (6.4%) admissions (5-19% depending on age group) and was strongly associated with inpatient mortality. Only 215 of 693 (31%) hypoxemic children had a final diagnosis of lower respiratory tract infection (LRTI). The most predictive signs for hypoxemia included shock, heart rate <80/minute, irregular breathing, respiratory rate >60/ minute and impaired consciousness. However, 5-15% of the children who had hypoxemia on admission were missed, and 18% of the children were incorrectly identified as hypoxemic, suggesting that clinical signs are poor predictors of hypoxemia.

Clinical markers of hypoxemia: A recent Cochrane review [70] reported that cyanosis, grunting, difficulty in feeding and mental alertness have better specificity in predicting hypoxemia; however there is no single clinical sign or symptom that accurately identifies hypoxemia. Another review [71] reported that very fast breathing (>60-70 breaths per minute), cyanosis, grunting, nasal flaring, chest retractions, head nodding and auscultatory signs, as well as inability to feed or lethargy; all correlated with hypoxemia to varying degrees. The sensitivity and specificity of these signs are highly variable, but can be taught to mothers and care-givers to predict hypoxemia with reasonable accuracy.

Although cyanosis, head nodding and drowsiness are good predictors of hypoxia, they lack sensitivity. Decisions based on these signs result in oxygen under-use. Pulse oximetry is the best indicator of hypoxemia and, although relatively expensive, its use might be cost-effective in controlling oxygen requirements [72]. In Zambia [73], of 158 under-five ALRI children, 55 (35%) were hypoxemic. For children under 1 year of age, respiratory rate of > 70 was the only significant predictor of hypoxemia (P <0.001, sensitivity 63%, specificity 89%).

Delivery of oxygen: A Cochrane review [70] comparing oxygen delivery methods (3 studies); showed no differences in treatment failure (OR 0.96; 95% CI 0.48-1.93) between nasal prongs (NP) *vs* nasopharyngeal catheters (NPC). A detailed review summarizing methods of oxygen delivery concluded that all low-flow methods, i.e., NPC, NC, NP are effective in severe pneumonia or bronchiolitis. Nasal prongs are the safest and most preferred method in small hospitals in developing countries [74].

In Papua New Guinea [75], an improved oxygen system (oxygen concentrators, pulse oximeters, and management protocol) led to a drop in pneumonia case fatality from 4.97% (95% CI 4.5-5.5%) to 3.22% (95% CI 2.7-3.8%). The estimated costs of this system were US$51 per patient treated, US$1673 per life saved, and US$50 per disability-adjusted life-year (DALY) averted. In Malawi [76] five key steps enabled introduction of concentrators: (1) develop a curriculum and training materials; (2) train staff on use and maintenance; (3) retrain electromedical departments on maintenance and repair; (4) conduct training once concentrators arrived in the country; and (5) distribute concentrators once staff had been trained.

Conclusions and Comments

- Hypoxemia is a relatively common occurrence in pneumonia, especially severe and very severe pneumonia.
- Clinical signs often do not accurately predict presence and/or absence of hypoxemia.
- Pulse oximetry is the only reliable, non-invasive method to confirm hypoxemia.
- Oxygen delivery improves outcome and all low-flow methods are safe and effective.
- Use of oxygen concentrators improves oxygenation in small hospitals.

Zinc supplements

A systematic review published in early 2010 [77] included 11 community-based RCTs of zinc supplementation for preventing pneumonia in children Although pneumonia and lower respiratory tract infection were defined differently in different trials, the study definitions were consistent with the WHO criteria. The balance of evidence (8 trials, 11701 participants) suggested that zinc supplementation does not prevent the occurrence of pneumonia. A more recent systematic review [78] (10 trials, 49450 children) also reported a similar finding that zinc supplementation had no effect on preventing pneumonia defined by the WHO criteria

(incidence rate ratio 0.96, 95% CI 0.86-1.08) or ALRI defined by less specific criteria or reports by caregivers (incidence rate ratio 1.01, 95% CI 0.91-1.12). However, when trials with specific definitions of pneumonia (tachypnea plus one or more of retractions, bronchial breathing, crackles, nasal flaring, danger signs were considered), zinc supplementation reduced the incidence of ALRI (incidence rate ratio 0.65, 95% CI 0.52-0.82).

As recently as December 2010; a Cochrane review [79] with 6 trials (7850 children) reported that zinc supplementation reduced the incidence of pneumonia (RR) 0.87; 95% CI 0.81-0.94). One trial included in the review reported that supplementation reduces the prevalence of pneumonia (RR 0.59; 95% CI 0.35-0.99). In this review also, the authors reported that zinc supplementation was effective when pneumonia was defined by specific criteria (i.e clinical with radiological confirmation) and not in trials using the lower specificity WHO case definition. One randomized trial [80] was published after the inclusion date in the Cochrane review; it reported that zinc supplementation did not reduce the incidence of pneumonia or severe pneumonia.

A systematic review [77] evaluated whether zinc has a possible therapeutic role when given with antibiotics in children with severe pneumonia . The 4 included trials used various definitions for pneumonia, but all were consistent with the WHO criteria. The balance of evidence suggests that there is no therapeutic benefit of adding zinc to antibiotic therapy. Since then, two more trials [81,82] have confirmed the absence of benefit in pneumonia as well as severe pneumonia.

Conclusions and Comments

- Zinc supplementation for at least three months duration could be useful to prevent pneumonia (defined by specific criteria).
- Zinc does not have therapeutic value in childhood pneumonia.

Knowledge gap

- It is not clear if zinc supplementation would be useful if it is used only in a sub-group of children with clinical deficiency.

Vitamin A supplementation

A recent systematic review [83] on vitamin A identified 11 trials exploring prophylactic role of vitamin A, and 9 trials examining therapeutic role. There was no difference between vitamin A and placebo for any of the outcomes in the prophylaxis trials. In the therapy trials, five outcomes viz. mortality, duration of hospitalization, duration of illness, complications, and side effects; were not significantly different with vitamin A or placebo. An even more recent Cochrane review [84] confirmed these findings. Vitamin A supplementation did not have beneficial effect on lower respiratory tract infection mortality (RR 0.78; 95% CI 0.54-1.14), LRTI incidence (RR 1.14, 95% CI 0.95-1.37), LRTI prevalence (RR 0.46, 95% CI 0.21-1.03) or hospitalization (RR 0.11, 95% CI 0.01-2.06).

An older Cochrane review on vitamin A in measles [85] showed that there was no significant reduction in mortality with 1 dose (RR 0.70; 95% CI 0.42-1.15; but mortality declined with two doses (RR 0.18; 95% CI 0.03-0.61). Likewise with two doses, pneumonia-specific mortality (RR 0.33; 95% CI 0.08-0.92), incidence of pneumonia (RR 0.92, 95% CI 0.69-1.22) and diarrhea (RR 0.80; 95% CI 0.27-2.34) declined significantly.

Conclusions and Comments

- Vitamin A has neither therapeutic nor prophylactic value in childhood pneumonia.
- Two doses of vitamin A appear to be beneficial in children who develop measles.

Knowledge gap

- It is not clear if vitamin A supplementation would be useful in a sub-group of children with clinical deficiency.

Routine immunization and pneumonia

A detailed review of observational studies [86] examined the mortality reduction with childhood vaccines. A total of 24 studies on measles vaccine were included; the authors reported that relative risk of mortality was reduced by 62-86%. Even when methodologically lower quality data was eliminated,

there was a 31-46% relative reduction in mortality. This reduction is a consequence of reduction of measles disease and attendant complications (among which pneumonia is the most significant). Another systematic review [87] identified 10 cohort and 2 case-control studies reported a similar 38-86% reduction in mortality with measles vaccine when children from the same community were compared. When immunized children were compared with unimmunized children from different communities, mortality reduction was estimated to be 30%-67%. In this review, vaccine efficacy was reportedly far greater than could be attributed to reduction in measles deaths; confirming that the benefit extended to reduced complications.

A systematic review [88] of published RCTs and quasi-experimental studies identified three measles vaccine RCTs and two studies with data on prevention of measles disease. Meta-analysis showed 85% (CI 83-87%) efficacy in preventing measles disease. The review also suggested that 95% effect estimate is reasonable when vaccinating at 1 year or later and 98% for two doses of vaccine based on serology reviews.

Conclusion and Comment

- Measles immunization leads to significant decline in child mortality, at least partly mediated by its impact on reduction of complications, including pneumonia.

Hib vaccine

A systematic review [89] on Hib vaccine efficacy showed that there was decline in invasive Hib disease (OR 0.16; 95% CI 0.08-0.30), meningitis (OR 0.25; 95% CI 0.08-0.84) and pneumonia (OR 0.31; 95% CI 0.10-0.97). Another systematic review of RCTs [90] in developing countries reported the effect of Hib conjugate vaccines as follows: pneumonia mortality RR 0.93 (95% CI 0.81-1.07), all-cause mortality RR 0.95 (95% CI 0.86-1.04), radiologically confirmed pneumonia RR 0.82 (95% CI 0.67-1.02), clinically defined severe pneumonia RR 0.94 (95% CI 0.89-0.99) and clinical pneumonia RR 0.96 (95% CI 0.94-0.97). This corresponds to effect on all clinical severe pneumonia as 6% reduction (95% CI 1-11%) and clinical pneumonia as 4% reduction (95% CI 3-6%). These findings suggest a marginal unequivocal benefit on clinical pneumonia and clinical severe pneumonia. A Cochrane review on Hib vaccine published in October 2009 [91] has since been withdrawn; hence is not discussed further.

Yet another systematic review of the effectiveness of Hib vaccine reported that conjugate vaccines are highly effective in reducing the incidence of invasive Hib disease, with similar efficacy across geographical regions and different levels of socioeconomic development [92]. Indirect benefits of vaccination even in countries with poor immunization coverage due to reported herd effect [93] has also been reported. However, some recent publications from India have challenged the data regarding Hib incidence, prevalence and beneficial effect of routine Hib vaccine in Indian children [94,95].

A Cochrane review [96] compared the efficacy of DTP-HBV-Hib combination versus DTP-HBV and Hib separately. However, none of the included trials reported clinical outcomes; all reported surrogate outcomes, especially immunogenicity. Children receiving the combination achieved lower antibody responses than the separate vaccines for Hib and HBV. Serious and minor adverse events were comparable.

Conclusion and Comment

- The exact burden of Hib pneumonia in India is not clear. The vaccine is efficacious in reducing invasive Hib disease and Hib pneumonia and meningitis in research trials; however the overall effectiveness depends on the proportion of childhood pneumonia caused by Hib.

Knowledge gap

- Public health impact and cost-effectiveness of Hib vaccination in India.

Role of Pneumococcal conjugate vaccine

An updated Cochrane review [97] included 11 publications from six RCTs conducted in Africa, US, Philippines and Finland where 57015 children received PCV and 56029 received placebo or another vaccine. Pooled vaccine efficacy (VE) for invasive

pneumococcal disease (IPD) caused by vaccine serotypes was 80% (95% CI 58%-90%); for IPD caused by any serotype 58% (95% CI 29%-75%); for radiological pneumonia (defined as per WHO criteria) 27% (95% CI 15%-36%); for clinical pneumonia 6% (95% CI 2%-9%); and for all-cause mortality 11% (95% CI -1%-21%). Another systematic review of RCTs (in developing countries) [90] evaluated 9 and 11 valent Pneumococcal conjugate vaccines (PCV) and reported the effect of vaccination on various outcomes as follows: clinical pneumonia 7% (95% CI –2 to, 15%), clinical severe pneumonia 7% (95% CI –1 to 14%), radiologically confirmed pneumonia 26% (95% CI 12-37%), and all-cause mortality 15% (95% CI 2-26%). This suggests that the vaccine has limited efficacy against pneumonia identified by less specific definitions.

A 2009 systematic review [98] included trials of PCV in children and reported the vaccine efficacy as 89% for vaccine-serotype invasive pneumococcal disease (IPD); and 63% to 74% for all serotypes. Vaccine efficacy to prevent clinical pneumonia was 6% and 29% for radiologically confirmed pneumonia. In yet another systematic review [99], 42 studies were included to review safety of PCV. Reacto-genicity data from some trials suggested that PCV-7 may result in more mild, self-limiting local reactions and fever than control vaccines; although severe adverse events were not increased. Two of the largest trials reported a statistically significant increased risk of hospitalization for reactive airway disease, including asthma; this was true for 7 as well as 9 valent vaccine. However, a third trial did not substantiate this observation.

A Cochrane review of pneumococcal vaccination during pregnancy [100] to prevent pneumococcal disease during the first months of life, included three trials and reported the absence of benefit for reducing neonatal infection (RR 0.51; 95% CI 0.18-1.41). However, there was reduction in neonatal colonization (RR 0.33; 95% CI 0.11-0.98), though this was not sustained at 2 months (RR 0.28; 95% CI 0.02-5.11) or 7 months of age (RR 0.32; 95% CI 0.08-1.29).

In India, limited data [31,32] suggests that the 7-valent PCV covers a little over 50% of the serotypes responsible for invasive disease; based on this a recent analysis [8] reported that the limited efficacy of the vaccine is further diminished in the Indian context. The recently introduced 13-valent PCV is expected to cover about three quarters of the serotypes responsible for invasive disease in India, and is expected to be slightly more efficacious than PCV-7.

Conclusions and Comments

- The exact burden of Pneumococcal pneumonia and the serotypes responsible for invasive disease in India are not clear. PCV are efficacious in reducing disease caused by vaccine-serotypes, however the overall effectiveness against childhood pneumonia is dependent on the relative burden of Pneumococcal pneumonia and the serotype coverage of the vaccine.

Knowledge gaps

- Serotypes of Pneumococci responsible for significant clinical disease in India need further exploration.
- Public health impact and cost-effectiveness of Pneumococcal vaccination in India are not known.

Current guidelines for treatment of childhood pneumonia

The current treatment guidelines of the national program (RCH-II) are concordant with the guidelines of Integrated Management of Newborn and Childhood Illnesses (IMNCI) for children under five years [101]. According to IMNCI, all children classified as pneumonia (based on rapid breathing and absence of danger signs) should receive oral antibiotics. Cotrimoxazole is proposed as the drug of first choice, and amoxicillin is proposed as the second line drug if there is no improvement. Children with danger signs or those with chest indrawing and/or stridor are classified as severe pneumonia; they require referral for admission and management after an initial dose of chloramphenicol. Where referral is not possible, continued intramuscular chloramphenicol is recommended.

The recent IAP-IndiaCLEN 2010 paper [102] further reviewed the evidence on antibiotic treatment

of pneumonia and made the following additional observations and recommendations:

(*i*) *Assessment of need for antibiotics*: Although fast breathing is used for identifying children requiring antibiotics at the community level, at the facility level auscultation should be used to identify and exclude other causes of fast breathing. It is especially important to identify wheezing, which may improve with bronchodilators without requiring antibiotics.

(*ii*) *Selection of appropriate antibiotic:* In view of increasing resistance of *S. pneumoniae* and *H. influenzae* to cotrimoxazole, amoxicillin is recommended as the first line antibiotic for non-severe pneumonia, at both community level and in clinic settings.

(*iii*) *Treatment of severe or very severe pneumonia:* All children with severe pneumonia should be admitted and given injectable antibiotics and supportive care including oxygen, intravenous fluids and close monitoring.

While there is some evidence of efficacy of oral amoxicillin for children with severe pneumonia [103], application in program guidelines does not appear justified at this moment. The research trial excluded children with very severe disease (cyanosis, lethargy, recurrent vomiting, unable to feed), severe malnutrition, and those who received prior antibiotic therapy.

For hospital treatment, a combination of injectable ampicillin and gentamicin is superior to Injection chloramphenicol, in view of equal efficacy and lower adverse effects. Parenteral third generation cephalosporins (cefotaxime, ceftriaxone) should not be used routinely but serve as reserve drugs for those who fail to respond to first-line therapy or have associated complications (septicemia and meningitis). Staphylococcal infection should be suspected in children with skin boils, abscesses or having rapid progression/ deterioration; and Cloxacillin added.

Subsequently, the above recommendations have been included in the Facility based IMNCI training modules (F-IMNCI) [104].

In India, under the RCH-II program, community based workers (ANM and Anganwadi workers; and in some states ASHA) are trained in IMNCI, including management of pneumonia. However, there are several gaps in the current policy regarding community based management of pneumonia in India. Firstly, there is no clear policy on whether the community health workers (especially ASHAs and AWWs) can use antibiotics for treatment of childhood pneumonia. Secondly, antibiotics are not included in the drug kits of either ASHAs or AWWs [105]. Thirdly, drug kits for ANMs that do include antibiotics have had erratic supply for many years, though is more streamlined now [106].

No treatment guidelines applicable to older children and adolescents were found. The WHO IMCI strategy is also designed for under-five children, hence not applicable to older children.

Conclusions and Comments

- The existing guidelines and programs for management of childhood pneumonia are widely applicable.
- The mandate of the community health workers to manage childhood pneumonia is unclear; deficiencies in antibiotic supplies can adversely affect the scale-up of community based management of pneumonia in India.
- The applicability of individual (even multi-centric) research studies on alternative treatment strategies, such as community management of severe pneumonia, requires careful evaluation in non-research settings, before considering universal implementation.

Knowledge gap

The individual and community impact of empiric antibiotic therapy to all children with WHO-defined pneumonia, in terms of increased antibiotic resistance is not known.

Adherence to clinical guidelines

A systematic review of interventions [107] to encourage adherence to community-acquired pneumonia guidelines showed that they are safe and improve patient and process outcomes. The review included 6 studies (31618 children) including 2

cluster RCTs (*n*=2351), 2 before-and-after studies with concurrent controls (n=28840) and 2 time series (*n*=427). One cluster RCT, 1 before-and-after study and 1 time series reported statistically significant reductions in length of stay and 1 before-and-after study reported statistically significant reductions in mortality with CAP treatment according to the guidelines; other studies reported no significant differences. All 6 studies reported significant improvements in at least one process measure with guideline adherence.

Conclusions and Knowledge gaps

- Adhering to guidelines appears to improve clinical and process outcomes.
- Effectiveness in the Indian context is not known.

Case-finding and/or community-based management

A systematic review of 9 studies [108] (7 of which were controlled trials) on the mortality impact of WHO case-management showed reduction in total mortality of 27% (95% CI 18-35%), 20% (95% CI 11-28%), and 24% (95% CI 14-33%) among neonates, infants, and children 0-4 years of age, respectively. In the same three groups, pneumonia mortality was reduced by 42% (95% CI 22-57%), 36% (95% CI 20-48%), and 36% (95% CI 20-49%). Meta-analysis of community-based trials of case management of pneumonia included seven concurrent trials from Bangladesh, India (2 trials), Nepal, Pakistan, Philippines and Tanzania. Mortality surveillance and verbal autopsy reported odds ratio for mortality as 0.70 (95% CI 0.59-0.84), 0.74 (95% CI 0.63-0.87) and 0.74 (95% CI 0.64-0.86) among children <1 month, <1 year and 0 to 4 years. The odds ratio for pneumonia-specific mortality, was 0.56 (95% CI 0.37-0.83), 0.63 (95% CI 0.46-0.86) and 0.63 (95% CI 0.47-0.86) among children <1 month, <1 year and 0 to 4 years respectively. This translates to child mortality reduction of 26% and a 37% reduction in pneumonia mortality.

The Gadchiroli field trial [109] involved training of paramedical workers, village health workers and traditional birth attendants to diagnose and treat childhood pneumonia. Over 3.5 years, a total of 2568 episodes of childhood pneumonia were managed. The case fatality rate in the area of active intervention was far lower than the control areas (0.9% *vs* 13.5%) [110]. The case fatality rates for the three types of worker were similar.

A systematic review [90] of the effect of pneumonia case management on mortality from childhood pneumonia estimated that community-based management could result in 70% mortality reduction among under-5 children. However, there is insufficient evidence for quantitative estimates of the effect of hospital case management pneumonia mortality. A 2009 review [111] reported that community management of neonatal infections, including pneumonia in neonates in a developing country setting resulted in significant reduction in mortality.

Although case finding and management are reported to be immensly beneficial, there is controversy about the most appropriate tools for detecting cases accurately. A recent review [112] enumerating clinical signs predictive of pneumonia listed fever, tachypnea, nasal flaring and reduced oxygen saturation to have high specificity in infants suspected to have pneumonia. However, the negative predictive value of all of them is low; hence absence of these features does not rule out pneumonia. An older review [113] identified fever, decreased breath sounds, crackles, and tachypnea as independent predictors of pneumonia in children 1-16 years of age. Fever plus diminished breath sounds, crackles, or tachypnea; or fever, crackles, and tachypnea had high sensitivity (93-97%) but poor specificity (11-19%). Another study [114] confirmed that the absence of fever and presence of hypoxemia in children with cough was highly predictive of pneumonia.

Conclusions and Comments

- Research studies and real-world experiences show that community based case detection and management can lead to significant improvements in pneumonia specific mortality and overall child mortality.
- The reduction in mortality depends on the rigour with which community workers are trained, supervised and monitored.

- In India, the policies and programs lack adequate clarity and emphasis on involvement of community health workers for management of childhood pneumonia.

Knowledge gaps

- It is not clear as to what systemic factors affect performance of the community health workers in management of childhood pneumonia. It is not clear as to what content of training, supervision structure and monitoring protocol are required for optimal performance and at what cost.
- There is need to evaluate the effectiveness, feasibility and cost of delivering single interventions (such as management of childhood pneumonia) compared to delivering integrated interventions.

4. Wheezing in ARI

The WHO strategy focuses on reducing mortality due to pneumonia and hence includes a very sensitive but less specific definition. This has resulted in many children without pneumonia (but another diagnosis) being treated for pneumonia, with consequent overuse of antibiotics and underuse of bronchodilator therapy in children with wheezing.

Frequency of wheezing

There is no systematic review reporting the prevalence of wheezing among children with WHO-defined pneumonia. The recent review [115] on the subject quoted older reports [116] and estimated that up to 75% of children with 'pneumonia' or 'severe pneumonia' classified on the basis of WHO criteria have associated wheezing in hospital-based studies. Likewise these studies generally report asthma to be a more frequent diagnosis among children with cough or difficult breathing than pneumonia [117,118].

The multicentric ISCAP trial [30] reported wheezing in 287 of 2188 (13%) children 2-59 months of age enrolled with non-severe pneumonia, despite excluding children with recurrent respiratory distress, and those responding to bronchodilators. Similarly, a cluster randomized multicentric study [49] with over 2000 children (2-59 months) with WHO defined non-severe pneumonia reported wheezing in 22%, despite excluding recurrent respiratory distress. The CATCHUP multicentric RCT [119] in Pakistan recorded wheezing in 10.9% children (2-59 months) with non-severe pneumonia. The investigators analyzed children less than 1 year and older than one year separately and reported comparable wheezing frequency (11.4% *vs* 10.3%) in both age groups. However, the COMET trial [60] in 2-59 month old children with non severe pneumonia reported wheezing to be far more prevalent among infants less than 12 months than older children (31.5% *vs* 19.9%). A multicentric trial in Pakistan [103] in children (3-59 months) with severe pneumonia documented wheezing at enrolment in 499 of 2100 (23.8%), despite excluding known asthmatics (those with >3 episodes of wheezing in 1 year) and those with lower chest indrawing that responded to bronchodilators alone. Wheezing was much more common in infants than those over one year.

Diagnosing wheeze in ARI

Although a large proportion of children have wheeze, it is audible without aid in less than one-third, making it difficult to diagnose in a field setting [115]. Therefore the standard case management of ARI (two doses of rapid acting inhaled bronchodilator at 15 minute intervals to children with audible wheeze and fast breathing and/or lower chest indrawing) misses a number of children with treatable wheeze. In a significant proportion of children, the respiratory rate comes back to normal and the chest indrawing disappear after two to three cycles of inhaled bronchodilator medications.

Distinguishing pneumonia and wheezing disorders in children

A study in children 2-59 months old with radiologic pneumonia and wheezing [120] re-examined the validity of the WHO criteria for diagnosis. The WHO criteria used alone had sensitivity 84% (95% CI 73-92%) and specificity 14% (95% CI 8-24%); WHO criteria plus fever had sensitivity 81% (95% CI 70-90%) and specificity 33% (95% CI 23-45%). The higher specificity of including fever with the WHO criteria was valid in infants below as well as above 2 years of age.

A history of previous episode(s) of wheezing in the setting of WHO pneumonia appears to be a strong predictor of the diagnosis being non-pneumonia. A prospective study in India [117] reported that history of previous episode of cough and difficult breathing, and history of fever in the WHO case management algorithm can identify more specific diagnoses. A way out could be to assess the response to inhaled bronchodilator before assigning the diagnosis of pneumonia or severe pneumonia in all children with 'fast breathing' or 'chest indrawing.' However, such a strategy would result in considerable overuse of bronchodilators and potentially delay the management/referral of children. Perhaps the ideal approach would be the appropriate assessment by auscultation [115]. It may be possible to train health workers to do this efficiently in the field itself.

Management of children with (WHO) pneumonia and wheezing

In a large, multi-centric trial across 8 public sector hospitals in India [121], 3487 children (2-59 months) with non-severe pneumonia were first nebulized with salbutamol to assess response to bronchodilator. Among them, 46% responded in terms of normalization of respiratory rate, suggesting that a large proportion of children who have non-severe pneumonia (by the WHO criteria) do not require antibiotic therapy. From the remainder, those who did not have radiological signs of pneumonia were randomized to receive either amoxicillin or placebo in addition to bronchodilators. It was noted that treatment failure rate was higher in those who did not receive antibiotics (risk difference of failure 4.2%, 95% CI 0.2%-8.2%). This suggests that a cohort of non-severe pneumonia with wheezing requires antibiotic treatment. The risk factors predictive of treatment failure were presence of vomiting (adjusted OR 1.50, 95% CI 1.14-1.98), history of previous bronchodilator use (adjusted OR 1.72, 95% CI 1.31-2.26) and respiratory rate >10/min over the age-specific cut-off (adjusted OR 8.24, 95% CI 4.46-15.20).

Conclusions and Comments

- Wheezing is fairly common among children with pneumonia diagnosed by the WHO criteria, but requires auscultation to be properly appreciated.
- Alternate diagnoses are more likely with history of recurrent wheezing and family history.
- Treating all children with antibiotics can result in overuse; on the other hand treating all children with bronchodilator results in overuse of the latter and potential delayed management of pneumonia.
- The solution lies in trying to achieve a reasonably accurate diagnosis for the cause of wheezing by auscultation and assessment of the background history. While this would be feasible in facility settings, feasibility and accuracy of detection of wheeze in the community settings requires more research

Knowledge gap

- Effectiveness of enlarging the scope of the current WHO definition to manage auscultable wheezing differently in the field setting is not known in the Indian context.

5. Family Practices in Management of Pneumonia

The latest NFHS [4] reported that 64.2% children with ARI or fever in the preceding two weeks, were taken to a health-care facility. The care-seeking was higher among urban residents (78.1%) compared to rural residents (59.9%). Care seeking for ARI was slightly higher in comparison to care seeking for diarrhea (total 58.0%, urban 65.3% and rural 55.6%). Children of mothers with low or no education, and those belonging to lower socio-economic status were much less likely to be taken to a health facility than those born to more educated mothers, and mothers of higher socio-economic status respectively [4] Only 13% of children with ARI symptoms received antibiotics.

A small-scale study in neonates in Lucknow [122] reported care seeking from unqualified providers (spiritual/traditional) as 23.5% for pneumonia and 33.3% for persistent diarrhea; use of traditional and/or home remedies delayed appropriate and timely care-seeking. In a study conducted in Kerala [123], among children with acute respiratory illness or diarrhea during a 2-week interval, 17% did not receive medical care. Among the 83% receiving medical care, 88% received allopathic medical care,

and 12% alternative medical care. In contrast, in rural Rajasthan [124], among 290 mothers interviewed 70% reported at least one medical neonatal condition requiring medical care with 37% reporting danger sign(s); however only 31% were taken to care providers; among which half were unqualified modern or traditional care providers. Decision to seek care outside the home almost always involved the fathers or another male member.

A very old prospective study [125] of 200 mothers reported that mothers' awareness of signs of pneumonia included a perception 'retractions' (*pasli chalna*); which correlated with actual retractions in over 90% cases. Honey and ginger were the most common home remedies used for relief of cough.

Reasons for prevailing client practices

A cross-sectional study in Wardha [120] noted that although two-thirds mothers knew newborn danger signs and nearly 90% agreed that the sick child should be immediately taken to a doctor, only 41.8% of such sick newborns actually received treatment either from government or private facilities. Over 45% sick babies received no treatment. The reasons for this included ignorance, financial constraint, faith in supernatural causes, non availability of transport, home remedy, non availability of doctor and absence of responsible person at home. An older Gujarat study [126] reported that women's education, income, family structure and kinship affiliation were significant predictors of use of service. Women seemed to be more sensitive to travel time to the health service and its associated costs (*purdah* restrictions, transportation and time costs) than to the direct costs of service.

An urban study in a RCH center and District hospital [127] reported mean out-of-pocket expenditure on neonatal illness as Rs 547.5 and for hospitalization (for IMNCI illnesses) Rs 4993. Another prospective study [128] found that prices and income were significant determinants of the choice of healthcare provider in rural areas. Distance to healthcare facilities negatively affected demand for outpatient care, an effect that was mitigated as access to transportation improved. Age, sex, educational status of the household members and the number of children and adults living in the household also affected the choice of healthcare provider in rural India. Major reasons for non-utilization of health-care facilities include: (*i*) absence of nearby facility; (*ii*) facility timing being inconvenient, (*iii*) absence of health personnel, (*iv*) unacceptably long waiting time; and (*v*) poor quality of care [129].

Potential solutions

Behavior change communication (BCC) interventions appear to improve care-seeking practices as demonstrated by a study in two urban public hospitals at Lucknow [130]. A study to assess the satisfaction of parents with the immunization services [131] reported that although over 90% people were satisfied with immunization services, dissatisfaction with accessibility and information provided by health workers were responsible for lower acceptance; this could be important for all community strategies.

A recent IMNCI evaluation survey reported that in clusters where it was implemented, the proportions of the population failing to (*i*) seek care, (*ii*) seek care within 24 hours of illness, (*iii*) seek appropriate care, and (*iv*) seek care from an appropriate care provider within 24 hours; were significantly lower among the IMNCI clusters for severe illness and moderate illness. Based on analysis of District Level Household Surveys 2 and 3, it was estimated that proportion of children seeking treatment for ARI increased by 6.7% in IMNCI districts; whereas it declined by 11.1% in the control areas (Mohan P, personal communication). In an earlier study [132] conducted in Rajasthan, PHC physicians of the intervention sites were trained on counseling families on care-seeking. While the interventions resulted in significant improvements in knowledge of caretakers on when to seek care, it did not result in significant improvements in actual care-seeking.

Conclusions and Comments

- Care-seeking for ARI among children is poor: even when families do seek care, they often do so from the private informal providers.
- Cost of care, distance from the health facilities, and poor quality of care (including factors such as absence of staff at health facilities and long waiting times) are the major supply side reasons

why families do not seek care from public health facilities.

- In addition, faith in supernatural causes and in efficacy of home remedies are other demand side factors that affect care-seeking.
- Education and counseling by health workers appear to improve care seeking, though the benefit is not clear.

Knowledge gap

- The effectiveness of community empowerment on improving care-seeking for sick children, including those with ARI has not been tested.

6. Providers' Behavior and Practices

This section is not restricted to prescribing practices, but also includes physician and provider behaviour and practices. The WHO-UNICEF document [7] states that although it is critical, globally, only 1 of every 5 caregivers knows that fast breathing and difficult breathing are indicators of pneumonia.

A study [133] comparing physicians' diagnosis with IMCI algorithm diagnosis in hospitalized children (2-59 months) reported low concordance. A UNICEF study [134] to record procedures for ARI reported that of 228 episodes where respiratory rate counting was required, it was done in only 76% and correctly in only 57%. A study on physician practices showed that majority of private practitioners prescribed antibiotics (77%), antihistaminics (47%), allopathic cough syrups (43%) for ARI. For pneumonia, 96% prescribed antibiotics and 28% prescribed steroids. X-ray to diagnose pneumonia was suggested by over 90% practitioners.

A study of antibiotic prescribing practices in Uttar Pradesh [135] observed an overall prescription rate of 82%; especially in the presence of fever, lower age of patients and higher socioeconomic status. Government health-facilities had a lower prescribing rate. In Sikkim [136], among 562 URTI prescriptions for children, aged 0-12 years the average number of medications prescribed was 2.37; 59.2% were fixed-dose combination products and two-thirds of FDCs were respiratory medicines. Others included antimicrobials (30.7%) and analgesic-antipyretics (18.8%). Respiratory medicines included cough and cold preparations, nasal drops and bronchodilators. In another study [137], among interns' prescriptions, the average number of drugs per prescription was 2.47. The commonest drugs prescribed were antibiotics (33.9%), analgesics and anti-inflammatory (17.0%), vitamins (13.0%), cough syrups (10.5%) and antihistamines (8.6%). The authors estimated that only 57.9% of the antibiotics used were appropriate. Interns often omitted to write the diagnosis (43%), signs and symptoms (50.2%), dosages and frequency of treatment. A study based in a village health center [138] also reported high level of antibiotic over-prescription for common respiratory illnesses including upper and lower respiratory tract infection. The existing guidelines were totally ignored and cephalosporins were the most commonly prescribed antibiotics across all age groups (cefadroxil in <1 yr old infants and cefixime beyond 1 year of age). Azithromycin was prescribed in only one fourth of older children.

A recent IMNCI review noted that performance of IMNCI trained community health workers was affected by poor supervision and inadequate essential supplies. In Nepal [139], an integrated program for community-based ARI and diarrhea control includes trained to diagnose, assess disease severity and danger signs, treat children and refer them to health facilities. This program also provides nutritional and immunization services. Training curricula and modules based on WHO's Integrated Management of Childhood Illness (IMCI) strategy were simplified and adapted to make them interactive and suited to participation by these groups. In districts without the program, facility-based care and immunization programmes continued. The rate of reported ARI cases was higher in intervention districts, showing that community-based interventions enable early detection and classification of children with ARI.

Conclusions and Comments

- About one-third families do not seek care for their children suffering from ARI. Even when they seek care, they often consult informal providers, especially in northern states. Education and counseling by health workers appear to improve care seeking, though the benefit is not clear.

- On one hand, a small proportion of those who do seek care receive antibiotics, on the other, many modern providers prescribe antibiotics indiscriminately.
- Performance of community health workers in management of childhood illnesses is affected by quality and intensity of supervision and by availability of drugs and logistics

Knowledge gaps

- There is limited understanding and/or application of interventions that promote care-seeking for sick children including those for ARI.
- Interventions to improve and maintain providers practices in appropriate management of ARI/ pneumonia need to be identified and evaluated.

7. Existing Strategies/Policies/Initiatives/ Programs that can Impact ARI Control/ARI Outcomes in India

The various National programs/strategies that include/involve ARI management are not listed/ described here. Only the current programs are mentioned.

National ARI Control Program

The National ARI control program was launched in 14 districts in 1990; initially as a pilot project. Another 10 districts were included during 1991. Thereafter the ARI strategy became integral to the Child Survival and Safe Motherhood (CSSM) program in 1992; and was continued into the RCH Phase I project in 1997. Under this program, cotrimoxazole tablets are made available at health facilities above the level of subcenters.

Integrated Management of Neonatal and Childhood Illness (IMNCI)

The Government of India adapted the WHO-UNICEF Integrated Management of Childhood Illness [140] strategy to the Integrated Management of Neonatal and Childhood Illness (IMNCI) [101]. The generic IMCI strategy targets 5 important childhood healthcare issues *viz* pneumonia, diarrhea, measles, malaria and malnutrition. The main components of the IMCI strategy are improved case management, health system strengthening and improved household practices. One of the limitations of IMCI was that it excluded the vulnerable early neonatal period (<7 days); this lacuna was taken care of in India's IMNCI strategy along with other innovations such as a Basic health worker module, Home visit module by provider for care of newborn and young infant, and Home based training. The training duration was shortened from 11 to 8 days; with 50% of the training time devoted to newborn and young infants. The current focus is to scale up further with 'IMNCI Plus' that includes a comprehensive range of interlinked interventions which is the backbone of the newborn and child health component of the RCH Phase II program. IMNCI is currently being implemented in 323 districts. The National Rural Health Mission (NRHM) [141] has incorporated the Facility Based Integrated Management of Neonatal and Childhood Illness (F-IMNCI) package to empower the health personnel with skills to manage new born and childhood illness at the community as well as facility level. F-IMNCI focuses on appropriate inpatient management of birth asphyxia, sepsis and low birth weight among neonates and pneumonia, diarrhea, malaria, meningitis, and severe malnutrition in children.

No data were available on state level actions to manage the burden of childhood ARI/pneumonia in India.

International experiences relevant in Indian context

UNICEF Accelerated Child Survival and Development (ACSD) program [142] in 11 West African countries showed decline in mortality in children in ACSD areas by 13% in Benin, 20% in Ghana and 24% in Mali. ACSD districts showed significantly greater increases in coverage for preventive interventions delivered through outreach and campaign strategies in Ghana and Mali, but not Benin. Although the project did not accelerate child survival in Benin and Mali focus districts relative to comparison areas, this could be due to coverage for effective treatment interventions for malaria and pneumonia not being accelerated, and causes of neonatal deaths and undernutrition not being addressed.

An evaluation of IMCI in Peru and Honduras [143] documented increase in mothers' knowledge of exclusive breastfeeding, vaccination coverage, recognition of danger signs for pneumonia and diarrhea and antenatal check-ups. There was associated reduction in malaria. In Pakistan [144], community-based Lady Health Worker (LHW) Program and IMCI are used for improving nutrition, reducing indoor pollution, improving mass vaccination, and introducing newer vaccines effective against important respiratory pathogens. An old report from three counties in China and Fiji [145] noted that factors important in the success of a community program included improved recognition of the signs of childhood pneumonia by parents, earlier presentation to health-care facilities, availability of antimicrobials at the primary health-care level, and rational usage decisions by health-care workers. An even older report showed that in Nepal, pneumonia case management by female community-based workers decreased under-five mortality by 28% [139].

DISCUSSION

To the best of our knowledge, this is the first systematic review that has meticulously collected and collated evidence from a variety of sources (including but not restricted to peer reviewed publications), to guide the initiating and/or scaling up of advocacy and actions for tackling the burden of childhood pneumonia in India. This is a critical first-step in today's era of evidence-informed decision-making. Previous reviews tended to have methodological limitations such as incorporation of outdated data; or selective inclusion (or omission) of evidence supporting a particular viewpoint. Another strength of this review is that we could access current data relevant to India from multiple sources including Health Ministry documents, NFHS series etc. Therefore, this systematic review can be regarded as current, comprehensive and oriented to facilitating informed decision making, especially at a programmatic level.

Nevertheless, some limitations of this review must also be recognized. We did not undertake critical appraisal of the included publications, except for Methodology. Therefore we have not presented insights into the applicability, transferability or appropriateness of cited evidence; with specific reference to the Indian context. Owing to constraints of resources (manpower and finances), we could not undertake secondary analysis of the data presented in the included publications. Therefore, we are unable to present a weighted average for numerical data or other meta-analyses. We have reported data as presented in the original publications, without filtering or treating them to fit a common reporting format. This can make it slightly difficult to compare (for example) odds ratios for one outcome in a systematic review with risk ratios for another outcome. Although we have accorded highest priority to recent systematic reviews, some conclusions presented in systematic reviews could stem from a limited number of trials (in some cases, even one RCT) and participants. It must also be noted that we have not undertaken literature search for some relevant issues like need (or otherwise) of chest radiographs in childhood CAP, potential role of vitamin C in preventing ARI, subgroup analysis in malnourished children, the effect of HIV on childhood pneumonia etc; since these were not identified *a priori*.

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