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The current status of community-acquired pneumonia management and prevention in children under 5 years of age in India: a review

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Abstract: India has the highest number of global deaths of children under 5 years of age. In the year 2015, it was reported that there were 5.9 million deaths of children under 5 years of age globally, of which 1.2 million (20%) occurred in India alone. Currently, India has an under 5 mortality rate of 48 per 1000 live births. Community-acquired pneumonia contributes to about one sixth of this mortality. Fast breathing is the key symptom of community-acquired pneumonia. The World Health Organization recently categorized community-acquired pneumonia in children under 5 years of age into two, pneumonia, and severe pneumonia. Fast breathing with or without chest in-drawing is categorized as pneumonia and fast breathing with any of danger signs as severe pneumonia. Because effective vaccines against two of the common organisms causing community-acquired pneumonia, namely *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, are available, there should be urgent and phased introduction into the Indian Universal Immunization Programme. Several preventable risk factors of community-acquired pneumonia such as lack of exclusive breast feeding for first 6 months of life, inappropriate complimentary feeding, iron deficiency anemia, malnutrition, and indoor air pollution should be adequately addressed. The community should be aware about the signs and symptoms of community-acquired pneumonia and its danger signs so that delay in qualified care seeking can be avoided. To achieve the sustainable development goal of ⩽25 under five deaths per 1000 live births by 2030, a multipronged approach is the need of the hour.

Keywords: Community-acquired pneumonia, Children under 5 years of age, India

Introduction

In the year 2015, it was reported that there were 5.9 million deaths of children under 5 years of age globally, of which 1.2 million (20%) occurred in India alone [Lancet Report, 2015]. Currently, India has an under 5 mortality rate of 48 per 1000 live births [World Bank, 2015]. Community-acquired pneumonia (CAP) contributes to about one sixth of this mortality [United Nations Children's Emergency Fund (UNICEF) and World Health Organization (WHO), 2006].

CAP is an infective inflammation of lung parenchyma due to bacterial or viral pathogens. The key symptom of CAP is fast breathing. WHO [1994] has defined fast breathing as respiratory rate of >60 per minute for infants less than 2 months, >50 per minute for infants of 2–12 months, and >40 per minute for children more than 12–59 months. Previously, CAP was categorized into three groups by WHO namely pneumonia, severe pneumonia, and very severe disease. Fast breathing alone was categorized as pneumonia, fast breathing with chest in-drawing as severe pneumonia, and fast breathing with chest in-drawing along with any of the danger signs, namely inability to feed, drowsiness or altered consciousness, convulsion, cyanosis, as very severe disease. Recently, however, WHO [2014] categorized CAP in children under 5 years of age into two: pneumonia and severe pneumonia. Fast breathing with or without chest in-drawing is now

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categorized as pneumonia and fast breathing with any of the danger signs as severe pneumonia.

The rationale of the present review is to assess the current status of management and prevention of CAP with the aim to identify knowledge gaps and implementation inefficiencies. This can help to reduce mortality due to CAP and to achieve the Sustainable Development Goal (SDG) of ⩽25 deaths of children under 5 years of age per 1000 live births by the year 2030 [UNO, 2015].

Methodology

Study design

We adopted the standard methodology of conducting systematic reviews [Mathew *et al.* 2011]. Secondary data analysis (meta-analysis) was not done. The primary research question was 'what was the current status of pneumonia management and prevention in India' and secondary research questions were 'to assess the burden of pneumonia in children in India' and 'to describe the etiology of pneumonia in children in India'.

Inclusion criteria

Types of publications. In this review, articles published in the English language between April 1985 and March 2015 were screened. The lower cut-off year of 1985 was used because WHO launched its acute respiratory infection (ARI) program in this year. All type of study designs, including randomized controlled trials, case control, cohort, and other descriptive studies, were included. Two reviewers, K.K.Y. and S.A., did the search and critically appraised the papers independently for their suitability for inclusion. Disputes were resolved by consensus.

Types of participants. Publications were included where children aged 2–59 months were studied, either alone or as one of the groups.

Outcome variables. The outcome variables included CAP-associated mortality, incidence, etiology, risk factors, and its prevention.

Exclusion criteria

Studies were excluded if pneumonia in the specified age group was either ventilation associated, or hospital acquired or due to immune-compromised status of the host.

Literature search

Two primary databases, PubMed (http://www.pubmed.com) and Google Scholar (https://scholar.google.co.in/) were searched. Additional sites searched were WHO reports (http://www.who.int), documents of the UNICEF (http://www.unicef.org/india/), National Family Health Survey (http://www.nfhsindia.org/), and Ministry of Health and Family Welfare, Government of India (http://www.mohfw.nic.in).

For PubMed the search strings were (1) (epidemiology OR burden OR morbidity OR mortality OR incidence OR prevalence OR profile) AND (pneumonia OR community acquired pneumonia) AND (children OR children under 5 years) AND India (2) (management OR treatment) AND (pneumonia OR community acquired pneumonia) AND (children OR children under 5 years) AND India (3) (prevention OR control) AND (pneumonia OR community acquired pneumonia) AND (children OR children under 5 years) AND India were done (Table 1).

Burden of CAP

CAP is one of the major causes of morbidity and mortality in children under 5 years of age [UNICEF and WHO, 2006]. Incidence of CAP in children under 5 years of age was 0.27 [95% confidence interval (CI): 0.14–0.63] episodes per child-year in African region, followed by 0.26 (95% CI: 0.13–0.61) in South East Asian region, 0.23 (95% CI: 0.11–0.53) in Eastern Mediterranean region, 0.11 (95% CI: 0.05–0.24) in Western Pacific region, 0.08 (95% CI: 0.04–0.18) in American region, and 0.03 (95% CI: 0.02–0.04) in European region [Walker *et al.* 2013]. Annual deaths due to CAP in the same age group was 0.54 million in African region, 0.44 million in South East Asian region, 0.17 million in Eastern Mediterranean region, 0.024 million in American region and 0.018 million in European region [Walker *et al.* 2013].

In India, annually, 0.35–0.37 million deaths in children under 5 years of age have been reported due to CAP [Bassani *et al.* 2010; Farooqui *et al.* 2015], which accounted for 13–16% of total annual mortality in this age group [Smith, 2000; Selvaraj *et al.* 2014; Bassani *et al.* 2010]. Other Indian studies reported 3.6–4.0 million episodes of CAP in children under 5 years of age in the year 2010 [Farooqui *et al.* 2015] with 30.7–32.0 episodes per 1000 child-year of severe pneumonia [Rudan *et al.* 2013]. Among the Indian

Table 1. Search process.

Research question	Search string in PubMed	Titles no.	Abstracts no.	Full text	Included in study
1. What is prevalence pneumonia in children under 5 in India?	(epidemiology OR burden OR morbidity OR mortality OR incidence OR prevalence OR profile) AND (pneumonia OR community acquired pneumonia) AND (children OR children under 5 years) AND India	370	367	183	24
2. How pneumonia in children under 5 is treated in India?	(management OR treatment) AND (pneumonia OR community acquired pneumonia) AND (children OR children under 5 years) AND India	360	357	178	13
3. What measures are taken to prevent pneumonia in children under 5 in India?	(prevention OR control) AND (pneumonia OR community acquired pneumonia) AND (children OR children under 5 years) AND India	130	128	57	7

states, Uttar Pradesh has the maximum number of CAP cases and deaths (24% cases, 26% deaths) in children under 5 years of age followed by Bihar (16% cases, 22% deaths), Madhya Pradesh (9% cases, 12% deaths) and Rajasthan (8% cases, 11% deaths) [Farooqui *et al.* 2015]. The case fatality rate (CFR) due to CAP in children under 5 years of age ranged from 2.5% to 11.8% [Ramachandran *et al.* 2012; Sehgal *et al.* 1997; Tiewsoh *et al.* 2009; Agrawal *et al.* 1995; Rai *et al.* 2008]. Younger children had greater CFR. Correspondingly, the incidence of severe pneumonia requiring hospitalization gradually decreased with increasing age [Gupta *et al.* 2010; Ramachandran *et al.* 2012; Sehgal *et al.* 1997]. Also, CFR was higher in girls than boys [Bassani *et al.* 2010; Reddaiah and Kapoor, 1990]. With introduction of vaccines against *Haemophilus influenzae* and *Streptococcus pneumoniae* across India shortly, the incidence of CAP and CFR associated with it is likely to change. Hence, there is a need for establishment of a community- and hospital-based surveillance system to capture the change.

Clinical features

Children with pneumonia usually present with fever along with fast breathing with or without cough. They may also have chest retractions and any or more of WHO danger signs, including irritability or lethargy, inability to feed, cyanosis, convulsion, and respiratory failure.

Irrespective of the underlying etiology, signs of fast breathing and lower chest in-drawing are highly sensitive and reasonable specific for diagnosing CAP [Shann *et al.* 1984; Palafox *et al.* 2000; Singhi *et al.* 1994]. Fast breathing had reported sensitivity of 64–81%, specificity of 54–70%, while lower chest in-drawing had sensitivity of 17–35% and specificity of 82–84% [Mulholland *et al.*1992]. In several studies, fast breathing was reported as a better predictor of pneumonia compared with auscultatory findings [Campbell *et al.* 1988; Mulholland *et al.* 1992; Red *et al.* 1994].

Wheezing is more likely to be present when the probable etiology of CAP is viral rather than bacterial. However, in a study conducted in Pakistan in the year 1987 [Ghafoor *et al.* 1990], wheezing was reported in 36% and 44% children admitted with severe CAP with bacteremia due to *S. pneumoniae* and *H. influenzae*, respectively. Various other studies have reported that almost 1/3 to 2/3 of cases of nonsevere pneumonia had auscultatory wheeze [Gowraiah *et al.* 2014; Shah and Gupta, 2010; Hazir *et al.* 2004]. Likewise, wheezing was reported in approximately 26.8% cases of severe pneumonia from Pakistan [Hazir *et al.* 2004]. Classical findings of crepitations were reported only in 26–30% of WHO-defined pneumonia [Falade *et al.* 1995].

Pneumonia due to *Mycoplasma* or *Chlamydia* generally present subacute onset of headache, malaise, nonproductive cough, low grade fever, and rhonchi. CAP can also present with local complications like parapneumonic or synpneumonic effusion; empyema; lung abscess or remote complications like meningitis, pyopericardium, septicemia, septic ileus or diarrhea; and osteomyelitis.

Table 2. Burden of CAP children under 5 years of age in India.

Serial no.	Author/year of publication	City/district, state	Study design	Results
1.	Acharya *et al.* (2003)	Udupi, Karnataka	Longitudinal study	1. Incidence of ARI = 6.12 episodes per child-year 2. Pneumonia 8.2% and severe pneumonia 0.5% of all ARI
2.	Deb (1998)	West Tripura, Tripura	Longitudinal study	1. Incidence of pneumonia: 16/1000 children in urban and 5/1000 children in rural areas
3.	Awasthi and Pande (1997)	Lucknow, Uttar Pradesh	Community-based prospective cohort	1. Incidence of CAP: 9.6 per 100 child-year
4.	Reddaiah and Kapoor (1990)	New Delhi, NCR	Prospective cohort study	1. Incidence rate of pneumonia = 0.29 per child-year 2. Severe pneumonia = 0.5% of all cases

ARI, acute respiratory infection; CFR, case fatality rate; CAP, community-acquired pneumonia; NCR, National Capital Region.

Diagnosis

Diagnosis of CAP is largely clinical. Peripheral blood smear usually showed leucocytosis with neutrophilic predominance. Among the commonly studied biomarkers, levels of acute phase reactants, C-reactive protein (CRP) and procalcitonin (PCT) were found to be increased [Don *et al.* 2005; Yadav *et al.* 2015]. PCT was found to be a better predictor of severity of CAP in children than CRP [Yadav *et al.* 2015]. X-ray of the chest is not routinely required for diagnosing CAP but needed when there is a doubt in the diagnosis, persisting symptoms, suspicion of complications like pleural effusion, pneumothorax, and so on [Harris *et al.* 2011]. To decrease intra- and interobserver variation, WHO [2001] classified X-ray chest findings found in CAP into non-end point infiltrates, end point consolidation, and pleural effusion. In various studies [Harris *et al.* 2011; Kabra *et al.* 2004; Swinger and Zwarenstein, 2000], X-ray chest performed poorly in differentiating viral from bacterial pneumonia. However, according to the WHO [2001] radiological findings of end point consolidation and pleural effusion were likely to be bacterial etiology, mainly *S. pneumoniae*.

Identification of possible etiological organism of CAP can be done by blood culture. Reported yield of blood culture ranged between 2% and 27% in Indian studies (Table 3) [Mathew *et al.* 2015; Bahl *et al.* 1995; Tiewsoh *et al.* 2009; Kabra *et al.* 2003; Capoor *et al.* 2006]. Lung puncture aspirate (LPA) gives a greater yield and can be specific. But LPA is an invasive procedure and associated with serious side effects, including pneumothorax and pulmonary hemorrhage. Hence, it is rarely performed in CAP.

A relatively newer method of blood culture namely Bact T/ALERT 3D system gave nearly four times higher yield than conventional blood culture [Capoor *et al.* 2006]. Because of low yield and long reporting time, traditional blood culture is not very useful as a diagnostic tool. Therefore, researchers have used nasopharyngeal aspirate (NPA) to assess possible etiology. However, the NPA reflects the organism present in nasopharynx and does not necessarily reflect the causative organism of CAP [Chaudhary *et al.* 1998; Pandey *et al.* 2000; Maitreyi *et al.* 2000]. Immune assays of serum for presence of specific antibodies have also been used, mainly for diagnosing *Mycoplasma* and *Chlamydia* infections, as these organisms require live tissue culture media. However, the antibodies against these organisms appeared 2–3 weeks after primary infection and persisted for up to 2–6 months, complicating the interpretation of seropositivity [Kuo *et al.* 1995]. Urine assays for antigens of specific bacteria like *S. pneumoniae* and *H. influenzae* have been also used but have not gained wide acceptability as there was kit-to-kit variation on detection rates.

Polymerase chain reaction (PCR) is a rapid and sensitive method for detection of bacteria, including atypical ones and viruses causing CAP, but it requires high start-up cost of equipment as well as trained personnel. Multiplex PCR platforms have been developed that can identify viral and bacterial

Table 3. Isolation of bacteria in children under 5 years of age with CAP in India.

Serial no.	Author/year of publication	City/district, state	Study design	Inclusions	Specimen	Lab method	Results
1.	Nisarga *et al.* (2015)	Bangalore, Karnataka	Hospital-based surveillance	Suspected invasive pneumococcal disease or pneumonia	Blood, CSF, and pleural fluid	1. Bac T Culture 2. PCR	1. Incidence of IPD: 17.8/100,000 2. Highest incidence: aged 6 months to <12 months (49.9/100,000) 3. The most frequent diagnosis: pneumonia syndrome (12.5/100,000)
2.	Tiewsoh *et al.* (2009)	New Delhi, NCR	Hospital-based prospective study	WHO-defined severe and very severe pneumonia	Blood	Blood culture	1. Blood culture positivity: 15 % 2. The most common organism- *Streptococcus pneumoniae* (40%)
3.	Capoor *et al.** (2006)	New Delhi, NCR	Hospital-based prospective study	Radiological CAP	Blood	Bac T and conventional blood culture	1. Blood culture positivity: 27.4% (by combine method of Bac T and conventional methods) 2. *S. pneumoniae* (35.3%), *Staphylococcus aureus* (23.5%), *Klebsiella pneumoniae* (20.5%) and *Haemophilus influenzae* (8.8%).
4.	Kabra *et al.* (2003)	New Delhi, NCR	Hospital-based prospective study	ALRTI	Blood	Blood culture	1. Blood culture positivity: 16%
5.	Pandey *et al.* (2000)	New Delhi, NCR	Hospital-based prospective Study	ALRTI	Blood	Blood culture	1. *S. pneumoniae* isolated in 12.8% of all ALRTI 2. *S. aureus* isolated in 7.1% of all ALTRTI
6.	Patwari *et al.** (1996)	New Delhi, NCR	Hospital-based prospective study	Clinical and radiological CAP	Throat swab, NPA, lung aspirate, and blood	Culture of blood, lung aspirates and urine	1. In infants <3 months (i) *Escherichia coli* (50%), *Klebsiella* (25%), and *S. pneumoniae* (18%). 2. Between 7 and 24 months (i) *H. influenzae* (31%). 3. In all age group (i) *S. pneumonia* and *S. aureus*: common

ALRTI, acute lower respiratory tract infection; CAP, community-acquired pneumonia; CSF, cerebrospinal fluid; IPD, invasive pneumococcal disease; NCR, National Capital Region; NPA, nasopharyngeal aspirates; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.
*Not restricted to children under five.

etiology using whole blood or NPA samples [Picot *et al.* 2014; Levine *et al.* 2012]. Also, serotyping of certain bacteria has been attempted by PCR method [Picot *et al.* 2014].

Etiology

From cases of WHO defined CAP in children bacteria, viruses, and atypical bacteria have been isolated in different studies (Tables 3–5). The rate of isolation of organism was different in various studies and age groups. Unlike the developed countries where viruses were responsible for most cases of pneumonia in children between 2 months and 5 years, bacterial infections contributed maximum number of cases in developing countries [Berman, 1991].

Several studies showed that *S. pneumoniae* was most common organism (30–50%) [Capoor *et al.* 2006; Farooqui *et al.* 2015; Rudan *et al.* 2013; Mathew *et al.* 2015; Tiewsoh *et al.* 2009; Awasthi and Pande, 1997; Pandey *et al.* 2000; Bahl *et al.* 1995] followed by *H. influenzae* type b in 8.8% [Capoor *et al.* 2006] and *Staphylococcus aureus* 7–23% [Capoor *et al.* 2006; Tiewsoh *et al.* 2009; Pandey *et al.* 2000]. In Indian children, different serotypes of *S. pneumoniae* were isolated with serotypes 1 and 5 being most prevalent followed by 4, 6A and 6B, 7, 12, 14, 15, 19F, 23, and 45 [Nisarga *et al.* 2015; Balaji *et al.* 2015; John *et al.* 1996; Kurien *et al.* 1999; Kanungo and Rajalakshmi, 2001].

Other organisms had also been isolated like *Acinetobacter* in 20% [Capoor *et al.* 2006] and *Klebsiella pneumoniae* in 3.3–20.5% [Capoor *et al.* 2006; Tiewsoh *et al.* 2009; Mathew *et al.* 2015]. In the Severe Pneumonia Evaluation Antimicrobial Research (SPEAR) study [Rai *et al.* 2008] and the CAPES study [Nisarga *et al.* 2015], *S. aureus* was the commonest organism isolated from severe cases of pneumonia in children under 5 years of age.

There is a relative dearth of studies on viral etiology of CAP. This may be because viral isolation is difficult as compared with bacterial isolation,

Table 4. Isolation of virus in children under 5 years of age with CAP in India.

Serial no.	Author/ year of publication	City/district, state	Study design	Specimen	Lab method	Detection rate
1.	Maitreyi *et al.* (2000)	New Delhi, NCR	Hospital-based prospective study	NPA	Cell line culture, and IIF	1. RSV: 17% of all ALRTI 2. Influenza viruses: 14.5% of all ALRTI 3. Parainfluenza: 11.5% of all ALRTI 4. Adenovirus (1.5%) of all ALRTI
2.	Patwari *et al.* (1996)	New Delhi, NCR	Hospital-based prospective study	NPA	IF and EIA	1. Infants <3 months (i) RSV (44%) 2. Between 7 and 24 months: RSV (47%) 3. In children: RSV (14%)
3.	John *et al.** (1991)	Vellore, Tamil Nadu	Hospital-based prospective study	NPA and throat swab	Cell line culture, IIF	1. Virus detection rates: 37% of pneumonia 2. RSV-commonest (32%) followed by Parainfluenza (10.8%), adenovirus (3.6%) and Influenza (1.5%).

ALRTI, acute lower respiratory tract infection; CAP, community-acquired pneumonia; EIA, enzyme immunoassay; IIF, indirect immunofluorescence; NCR, national capital region; NPA, nasopharyngeal aspirate; RSV, respiratory syncytial virus.
*Included children less than 6 years.

resulting in an underestimation of viral contribution to CAP [Weber *et al.* 1998]. Table 4 shows that studies have reported variable proportions (37–44.5%) of viruses isolated from cases of CAP [Maitreyi *et al.* 2000; John *et al.* 1996]. The most common virus isolated was respiratory syncytial virus (RSV) (17–32%) followed by influenza virus (1.5–14.5%), parainfluenza virus (10.8–11.5%), and adenovirus (1.5–3.6%) [Maitreyi *et al.* 2000; John *et al.* 1996].

Atypical bacteria were reported as an important cause of CAP in children under 5 years of age against previous conception that they were mainly responsible for the disease in older children. *Chlamydia pneumoniae* contributed to 1–20% [Jain *et al.* 2007; Mathew *et al.* 2015; Kabra *et al.* 2003; Chaudhary *et al.* 1998; Pandey *et al.* 2000, 2005] and *Mycoplasma pneumoniae* to 4–30% [Mathew *et al.* 2015; Kabra *et al.* 2003; Chaudhary *et al.* 1998; Pandey *et al.* 2000] cases of CAP in children under 5 years of age (Table 5).

It has to be noted that most of the studies were hospital based and therefore included severe cases only. There are limited studies that have done concomitant investigation for bacterial and viral etiology of CAP and their clinical correlates; hence, more work is needed.

Antimicrobial resistance pattern in India

Cotrimoxazole and amoxicillin are the two antibiotics that are commonly recommended in the case management of CAP. Variable levels of resistance against these antibiotics have been reported in *S. pneumoniae* and *H. influenzae* type b (Table 6).

In the Invasive Bacterial Infection Surveillance (IBIS) study [Kurien *et al.* 1999], only 5.4% of isolated *S. pneumoniae* were resistant to cotrimoxazole in age group <1 year that increased to 16% in age group <2 years and 64% in age group 2–5 years. Similar findings of increasing resistance to cotrimoxazole with increasing age among isolated *S. pneumoniae* were also reported by other Indian studies [Jebaraj *et al.* 1999; Coles *et al.* 2002]. Similarly, 66.3% of isolated *S. pneumoniae* from NPA of children under 5 years of age visiting ambulatory health care with WHO-defined nonsevere pneumonia were resistant to cotrimoxazole [Intensive Statin Therapy for Chinese Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention (ISCAP) study, Awasthi *et al.* 2004]. Not only India but also Bangladesh has reported a high prevalence (64.1%) of resistance in isolated *S. pneumoniae* to cotrimoxazole [Saha *et al.* 1999]. Resistance against penicillin was reportedly low

Table 5. Detection of atypical bacteria in children under 5 years of age with CAP in India.

Serial no.	Author/ year of publication	City/district, state	Study design	Sample	Lab method	Results
1.	Jain *et al.*(2007)	Lucknow, Uttar Pradesh	Hospital-based prospective study	Serum	MIF	1. 5.5% CAP in children under 5 contributed by *Chlamydia* sp.
2.	Pandey *et al.* (2005)	New Delhi, NCR	Hospital-based prospective study	Throat swab	Direct IF, solid-phase EIA	1. Incidence of *Chlamydia* sp. was 20% of ALRTI.
3.	Kabra *et al.* (2003)	New Delhi, NCR	Hospital-based prospective study	Serum	IF	1. ALRTI caused by (i) *Mycoplasma*-in 24% (ii) *Chlamydia*-in 11%
4.	Pandey *et al.* (2000)	New Delhi, NCR	Hospital-based prospective study	Serum, throat swab	IIF, MAT	1. *Mycoplasma pneumoniae*: 30% of total ALRTI 2. *Chlamydia pneumoniae*: 2.8% of total ALRTI
5.	Chaudhary *et al.* (1998)	New Delhi, NCR	Hospital-based prospective study	Serum	MAT, indirect solid-phase EIA	1. Prevalence was 27.4% *M. pneumoniae* and 6.4% *C. pneumoniae.*

ALRTI, acute lower respiratory tract infection; EIA, enzyme immune assay; IF, mmunofluorescence; IIF, indirect immunofluorescence; MAT, microparticle agglutination test; MIF, microimmunofluorescence.

in all age groups and none of the isolates were resistant to injectable third-generation cephalosporin [Kanungo and Rajalakshmi, 2001; Jebaraj *et al.* 1999; Kurien *et al.* 1999]. Therefore, WHO [2014] has recommended the use of amoxicillin for management of CAP in children under 5 years of age.

Like *S. pneumoniae*, there is increasing resistance in *H. influenzae* against commonly used antibiotics in India. In the IBIS study [Steinhoff *et al.* 2002], 50% of isolated *H. influenzae* were resistant to chloramphenicol, 38% to ampicillin, and 45.5% to cotrimoxazole, while none were resistant to third-generation injectable cephalosporin. The ISCAP study [Awasthi *et al.* 2004] reported that 57.6% of NPA isolates of *H. influenzae* were resistant to cotrimoxazole and 24.7% to chloramphenicol.

Management

Early diagnosis and appropriate use of antibiotics are the best strategies to reduce CAP-related mortality in children. Non-severe pneumonia can be managed at home with oral antibiotics, but monitoring, timely and appropriate referral and follow-up are crucial. Both oral cotrimoxazole and amoxicillin were used extensively in home-based treatment of CAP. There is growing evidence of development of *in vitro* resistance in *S. pneumoniae* and *H. influenzae* against cotrimoxazole in Indian children [Kurien *et al.* 1999; Awasthi *et al.* 2004; Steinhoff *et al.* 2002; Saha *et al.* 1999]. Therefore, oral amoxicillin is the next alternative choice of antibiotic for treatment of CAP. A randomized trial study [Rajesh and Singhal, 2013] on children under 5 years of age reported higher treatment failure in oral cotrimoxazole group (39.1%) than oral amoxicillin group (8.1%). A systematic review done earlier [Kabra *et al.* 2006] also reported better efficacy of amoxicillin over cotrimoxazole in management of CAP. The British Thoracic Society [Harris *et al.* 2011] and Indian Academy of Pediatrics [Agarwal *et al.* 2007] recommended oral amoxicillin as the antibiotic of first choice for nonsevere pneumonia. Now, the WHO [2014] also recommends domiciliary treatment with oral amoxicillin (40 mg/kg/dose) two times in a day for 3 days for pneumonia without chest in-drawing and 5 days for pneumonia with chest in-drawing. A study [Awasthi *et al.* 2004] clearly showed that 3 days of oral amoxicillin was equally effective as 5 days treatment in cases of nonsevere pneumonia. If there is no improvement in 48 h, amoxicillin should be replaced with co-amoxiclav [Dekate *et al.* 2011].

In hospitalized children with severe CAP, injectable chloramphenicol was found to be inferior to

Table 6. Antimicrobial resistance pattern in *Streptococcus pneumoniae* and *Haemophilus influenzae* in India.

Serial no.	Author/year of publications	City/district, state	Study population	Study design	Specimen for culture and sensitivity	Results
1.	Awasthi *et al.* (2004; ISCAP)	Multicenter (seven) in India	Children aged 2–59 months visiting OPD because of nonsevere pneumonia	Double blind, placebo-controlled, randomized trial	NPA and nasopharyngeal swab	1. 66.3% of isolated *S. pneumoniae* were resistant to cotrimoxazole, 4.1% to chloramphenicol, 15.9% to oxacillin and 2.9% to erythromycin. 2. 57.7% of isolated *H. influenzae* were resistant against cotrimoxazole, 24.7% against chloramphenicol, 29% against erythromycin and 18.2% against ampicillin.
2.	Steinhoff *et al.* (2002; IBIS)	Multicenter (six) in India	Patient aged 1 month to 50 years (75% under 5 years of age) who had disease likely to be bacterial in etiology	Hospital-based prospective surveillance	Blood and CSF	1. 38% isolated *Haemophilus influenzae* were resistant to ampicillin 2. 50% of isolated *H. influenzae* were resistant to chloramphenicol 3. 45.5% isolated *H. influenzae* were resistant against cotrimoxazole 4. None was resistant against injectable third-generation cephalosporin
3.	Kanungo and Rajalakshmi (2001)	Pondicherry, UT	Hospitalized children and adults with suspect of invasive pneumococcal infections	Hospital-based prospective cohort	Blood	1. 7.3% of isolated *S. pneumoniae* were resistant to penicillin.
4.	Naq *et al.* (2001)	Lucknow, Uttar Pradesh	All age groups visiting either OPD or IPD because of pneumonia	Hospital-based prospective study	Sputum, nasopharyngeal and oropharyngeal swabs	1. 33.3% of isolated *H. influenzae* were resistant against cotrimoxazole 2. 21.1% of isolated *H. influenzae* were resistant against ampicillin and 7.8% against cefalexin and chloramphenicol, separately.
5.	Kurien *et al.* (1999; IBIS)	Multicenter (six) in India	Children and adults with clinical syndromes of bacterial infection	Hospital-based prospective surveillance	Blood, CSF, pus and other body fluids	1. Among isolated *S. pneumoniae*, 1.3% were intermediate resistant to penicillin while 56% and 17% were resistant to cotrimoxazole and chloramphenicol, respectively. 2. 5.4% of isolated *S. pneumoniae* showed resistance in age $<$1 year, 16% in age $<$2 years, and 64% in age 2–5 years to cotrimoxazole 3. None of isolates were resistant to injectable third-generation cephalosporin

CSF, cerebrospinal fluid; IBIS, Invasive Bacterial Infections Surveillance group of INCLEN network; IPD, indoor patient department; NPA, nasopharyngeal aspirate; OPD, outdoor department; RCT, randomized controlled trial; UT, union territory.

injectable ampicillin plus gentamicin [Rai *et al.* 2008; Kabra *et al.* 2006]. Injectable ampicillin plus gentamicin is now first choice for hospital-based treatment of severe CAP [WHO, 2014]. In absence of satisfactory improvement in next 48 h, antibiotics should be changed to ceftriaxone [WHO, 2014]. Addition of cloxacillin is recommended, if features of *S. aureus* infection like boils in skin or abscesses anywhere in the body, rapidly progressive or deteriorating pneumonia, post measles pneumonia, and complications like empyema, pneumatoceles, and pneumothorax are present [Dekate *et al.* 2011].

Apart from antibiotic therapy, children need supportive care, including oxygen therapy. Because clinical signs and symptoms have poor diagnostic accuracy for predicting hypoxemia [Lodha *et al.* 2004; Basnet *et al.* 2006], as far as possible, pulse oximetry should be use for early detection. Pulse oximetry has shown promising results in reduction of mortality due to CAP by early detection and therefore treatment of hypoxemia [Duke *et al.* 2009]. WHO [2005] recommends oxygen therapy where pulse oximetry is not feasible in very severe or severe pneumonia and SpO_2 less than 90% at room air.

Risk factors and prevention

Preventable risk factors for CAP can be classified into nutritional, environmental and social and behavioral. Nutritional risk factors for CAP were lack of exclusive breast feeding for first 6 months of life [Tiewsoh *et al.* 2009; UNICEF and WHO, 2006], inappropriate timing and content of complimentary feeding [Bhat and Manjunath 2013; Shah *et al.* 1994], iron deficiency anemia [Hussain *et al.* 2014; Bhat and Manjunath 2013; Ramakrishnan and Harish, 2006] and malnutrition [Bhat and Manjunath 2013; Broor *et al.* 2001; Deb, 1998] (Table 7). The most important nutritional risk factor for CAP was lack of exclusive breast feeding for first 6 months of life. This can increase the risk of CAP up to 1.5–2.6 times [Acharya *et al.* 2003; Shah *et al.* 1994; Mihrshahi *et al.* 2008]. This can also translate into 30–42% increased incidence of respiratory infections in children in underdeveloped countries [Ladomenou *et al.* 2010]. Therefore, the WHO and UNICEF advocate exclusive breast feeding in first 6 months of life in their global action plan to prevent pneumonia (GAPP). Despite these, in India, only 46.4% children were exclusively breast fed for their first 6 months [NFHS III 2007].

Various studies [Hussain *et al.* 2014; Bhat and Manjunath 2013; Ramakrishnan and Harish, 2006] reported 5–7 times increased risk of CAP in children with anemia. Because in India, 69.5% of children are anemic [NFHS III 2007], the CAP-related mortality is high. Undernutrition is an independent risk factor for mortality in children under 5 years of age. In India, 42.5% of children are undernourished [NFHS III 2007]. Hence, effective strategies for prevention of anemia and malnutrition in children have to be implemented.

Among the environmental risk factors of CAP, indoor air pollution due to use of biomass fuel for cooking has been extensively studied. Ambient air pollution resulted in two- to fourfold increased risk of CAP [Bhat and Manjunath 2013 Broor *et al.* 2001; Mahalanabis *et al.* 2002]. Still in rural India, 61.7–65.4% of households use coal and wood as source of fuel for cooking [NFHS III 2007; DLHS III 2010]. Other important environmental risk factors are overcrowding [Tiewsoh *et al.* 2009; Shah *et al.* 1994], upper or lower respiratory infection in a family member [Broor *et al.* 2001 Bhat and Manjunath 2013], poor housing and indoor or parental smoking [Acharya *et al.* 2003] (Table 7). Despite statutory warning against tobacco, smoking by parents is prevalent in India.

Among the social and behavioral risk factors of CAP, hand washing is the most important, because this is simple and can reduce the incidence of CAP by 24% [Wiley Online Library, 2006]. At community level, there is delay in recognition of CAP as fast breathing is not commonly recognized by community and grass root health-care workers [Awasthi *et al.* 2015]. There is delay in qualified care seeking for CAP as the preferred health-care provider is the village-based unqualified doctor [Awasthi *et al.* 2015; May *et al.* 2014]. Home remedies and self-medication further delay care seeking [Awasthi *et al.* 2015; Kumar *et al.* 2008; Mohan *et al.* 2008]. There is a distrust in the public health system, and in most cases, children reach a government tertiary care center when they have been ill for a week or so and have been treated by two to three health-care providers [Awasthi *et al.* 2015; Srivastva *et al.* 2009; Deshmukh *et al.* 2009].

Prevention of CAP by immunization

Immunization is a major step to prevent CAP in children. In 1978, India introduced six childhood vaccines (BCG, TT, DPT, DT, Polio, and

Table 7. Risk factors for mortality and morbidity of CAP in children under 5 years of age in India.

Serial no.	Author/year of publication	City/district, state	Study design	Results for risk factors for CAP
1.	Patel *et al.* (2015)	Multicenter in India	Multicentric, open label RCT	(i) Age (3–11 months) and (ii) Use of biomass for cooking
2.	Hussain *et al.* (2014)	New Delhi, NCR	Case-control study	(i) Anemia
3.	Jain *et al.* (2013)	Nagpur, Maharashtra	Case control study	(i) Infancy), (ii) severe malnutrition, (iii) very fast breathing at baseline, (iv) lack of measles immunization, (v) hypoxemia at baseline, and (vi) bacteremia
4.	Bhat and Manjunath (2013)	Manipal, Karnataka	Case control study	(i) Low SES, (ii) URTI in family members, (iii) inappropriate weaning period, (iv) malnutrition, (v) pallor, and (vi) cooking fuel other than LPG
5.	Ramachandran *et al.* (2012)	Chennai, Tamil Nadu	Retrospective cohort study	(i) Infancy, (ii) weight for age <-2 Z score, (iii) altered level of consciousness, and (iv) congenital heart disease
6.	Tiewsoh *et al.* (2009)	New Delhi, NCR	Hospital-based prospective study	1. Less likely to respond on first line antibiotics (i) Lack of breast feeding in first 6 months exclusively, (ii) Overcrowding, (iii) Abnormal chest radiograph 2. Greater risk of mortality (i) Presence of cyanosis, (ii) head nodding, (iii) altered sensorium, (iv) pallor, and (v) high leukocyte count
7.	Mahalanabis *et al.* (2002)	Kolkata, West Bengal	Case control study	(i) Use of biomass for cooking, (ii) history of asthma in the child, (iii) use of biomass for cooking, and (iv) co-habitation of with farm animals
8.	Broor *et al.* (2001)	New Delhi, NCR	Case study	(i) Lack of breast-feeding, (ii) URTI/LRTI in mother, siblings or other family member(s), (iii) severe malnutrition, (iv) cooking fuel other than LPG, and (v) inappropriate immunization for age
9.	Deb (1998)	West Tripura, Tripura	Longitudinal Study	(i) Malnutrition and (ii) unimmunized or partially immunized
10.	Agrawal *et al.* (1995)	Baroda, Gujarat	Prospective cohort	(i) Malnutrition
11.	Shah *et al.* (1994)	Trivandrum, Kerala	Case-Control Study	(i) Infancy, (ii) lack of immunization, (iii) delayed weaning, (iv) overcrowding, (v) low parental education, (vi) environmental pollution, (vii) Lack of exclusive breast feeding in first 6 months, (viii) malnutrition, (ix) hypovitaminosis A, (x) low birth weight, (xi) previous history of severe ARI, (xii) unresponsiveness to earlier treatment, and (xiii) use of non-modern medicine

ALRTI, acute lower respiratory tract infection; ARI, acute respiratory infection; CAP, community-acquired pneumonia; LPG- liquid petroleum gas; RCT, randomized controlled trial; SES, socioeconomic status; URTI, upper respiratory tract infection.

Typhoid) in its extended program of immunization (EPI). Measles vaccine was added much later, in 1985, when the Indian government launched the Universal Immunization Programme (UIP). A WHO review reports that a 31–46% relative reduction in childhood mortality can be brought about by more than 80% coverage of measles vaccine. In India, District Level Household and Facility Survey III (DLHS III) reported 69.1% coverage of measles vaccine in first 2 years of life. Vaccine against *H. influenzae* type b was not included in UIP; however, recently,

a pentavalent vaccine (Pentavac by M/s Serum Institute of India) was introduced in Kerala and Tamil Nadu in year 2011 and later in the states of Goa, Pondicherry, Karnataka, Haryana, Jammu and Kashmir, Gujarat and Delhi. At present, this vaccine has been introduced in rest of the Indian states also.

Because the magnitude of invasive pneumococcal diseases in children in India is high, prevention through vaccination is desirable. In India, two types of pneumococcal vaccines are available. One is unconjugated pneumococcal polysaccharide vaccine 23 valent (PPSV23), which cannot be used before 2 years of age. For use in children less than 2 years, pneumococcal conjugate vaccines (PCV 10 and PCV 13) are available. PCV 10 covers 64% and PCV13 covers 73.3% of invasive pneumococcal strains [Manoharan *et al.* 2013]. Efforts are being made to include PCV into UIP. An Indian company with active support of Department of Biotechnology, Government of India, is developing 15-valent vaccine containing two additional serotypes, 2 and 12F to existing PCV 13.

Conclusion

CAP in children is a major contributor to mortality in children under 5 years of age. There is sufficient data to show that *S. pneumoniae* and *H. influenzae* contribute to >50% cases of CAP. Because effective vaccines against both of them are available, there should be urgent and phased introduction into the UIP. Several preventable risk factors of CAP like lack of exclusive breast feeding for the first 6 months of life, inappropriate complimentary feeding, iron deficiency anemia, malnutrition, and indoor air pollution should be adequately addressed. The community should be aware of the signs and symptoms of CAP and its danger signs so that delay in qualified care seeking can be avoided. To achieve the SDG, a multipronged approach is need of the hour.

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