Review of Literature
REVIEW OF LITERATURE

GLOBAL SITUATION

MAGNITUDE OF THE PROBLEM:

In developing countries, one child under 5 years of age dies every 7 seconds due to acute respiratory infection (ARI)\(^3\). An average of 20-30 episodes of ARI occur in the first five years of life of a child. In 1000 surviving live born children ~ 20-25 deaths occur due to ARI in those < 5 years in the developing world as compared to less than one in developed countries\(^4\). Mortality due to ARI in developed and developing countries are difficult to compare due to striking differences in diagnosing technique and reporting in these countries. Global mortality reports came in first from pilot studies undertaken by 88 member countries of WHO\(^5\). This study found that overall mortality rate from ARI was 56.2 per 100,000 population and that Africa accounted for the highest incidence (103.2/100,000). Mean age specific mortality rate in infants was found to be around 762.2/100,000, to 101.3/100,000 in children aged 1-4 years. This decreased to 8.4/100,000 in children from 5 to 14 years. Yet in another estimate, rates as high as 1023/100,000 in infants and 300/100,000 in 1-4 years age group have been recorded\(^6\). These were found to be 20-50 times higher than those in the United States and Canada, where rates of 85/100,000 and 6/100,000 were found in 0-1 and 1-4 years, age group respectively. Incidence of pneumonia in India is around 94 per 1000 children with mortality rates
of 642 per 100,000 children under 5 years of age\textsuperscript{2}. A child in urban area suffers from 5-8 episodes of ARI in first 5 years of life, with a lower incidence in rural children\textsuperscript{2}. There are 300 million episodes of ARI in India every year, with 30-60 million moderate to severe in nature\textsuperscript{2}.

Incidence rates from BOSTID (Board on Science and Technology for International Development) project on ARI undertaken as a multicentric study in developing countries, ranged from 12.7 to 16.8 new episodes of ARI per 100 child weeks at risk. Rates of lower respiratory infection varied from 0.2 to 8.1 new episodes per 100 children, in studies involving Argentina, Philippines, Thailand, Pakistan and Uruguay\textsuperscript{7}.

**INDIAN SCENARIO:**

Problem of ARI in India had not been targetted until 1979, when the task force on acute respiratory diseases met under the Indian Council of Medical Research. Since then data have been collected and problems highlighted. At the national level involving many centres in India compiled data, projects of a rate of 15-20% mortality in infancy\textsuperscript{8} with ALRI accounting for 20-24% of these deaths\textsuperscript{9}. An estimation of 600,000 of deaths per year in the pre-school age period has been reported by Kumar\textsuperscript{10}. Estimations of ARI in urban and rural areas have been compared in very few studies. In a study by Datta-Banik et al\textsuperscript{11} and Gupta\textsuperscript{12}, 5-8 episodes of ARI per
year were recorded in urban children and 3-5 episodes in the rural areas respectively.

Various studies regarding the hospital admissions due to ARI have been undertaken. Data reveals ranges of 12-45% by Stansfield et al\textsuperscript{13}. Admission rates of 12-35\%\textsuperscript{14}, 25\%\textsuperscript{15} and 20\%\textsuperscript{16} have been reported from other studies. The burden thus borne by the hospitals in developing countries is considerable in the context of manpower, finances and infrastructure, not to mention overcrowding.

ARI infections of six episodes/child/year reported by Kamat et al\textsuperscript{17} in Southern India is higher than 3.9 episodes/child/year reported from Chandigarh\textsuperscript{18}.

\section*{HOST FACTORS IN ARI:}

\subsection*{AGE:}

Incidence of ARI in different age groups have shown a constant pattern in various studies. They are seen to be higher in younger than older children. Risk factor analysis enhances this factor, showing an increased incidence in children less than 18 months of age\textsuperscript{7}. Incidence of 81/1000 months in the first year is seen to decline to 68, 61, 56 and 31 per 1000 in the subsequent four years as shown by Gulati et al in a study in India\textsuperscript{19}. In contrast, another study in Haryana recorded an increasing incidence from 2.2 at infancy to 3.9 and 4.2 per year during 13-24 and 25-36 months of age\textsuperscript{18}. However, age specific incidence rates of ARI by year of age
have been shown to have a higher incidence in the lower than higher age groups in other developing countries. Six to 11 months was recorded as the peak age in Philippines, Guatemala, Papua New Guinea, Kenya and Argentia, with Nigeria and Uruguay recording 0-5 months as the peak age\textsuperscript{7}. Higher rates of ARI in infancy has also been reported in Pondicherry as compared to a lower incidence in the 1 to 2 years age group\textsuperscript{20}.

**SEX:**

Majority of studies conducted to determine the epidemiology of ARI have found a male preponderance in both community as well as hospital based studies. In India, an average ratio of male:female of 1.7:1 has been reported by Narain\textsuperscript{21}. Studies conducted in Pondicherry has reported a male:female ratio of 1:2 in the 0-5 years age group and 1.2:1 in the 5-13 years age group\textsuperscript{20,22}. Higher incidence of ARI in male child has been attributed to social character by most workers, where the tendency of parents to seek medical aid for a male child is noted in developing countries, there by resulting in a higher detection rate. A report by Glazen as early as 1973 from England has also recorded male preponderance upto six years of age beyond which it equalised\textsuperscript{25}. A study by Walia et al\textsuperscript{26} from Chandigarh however did not find any gender predisposition.

Studies from other developing countries have recorded a male predominance. 65.9% of ARI cases from Pakistan were seen in male children as compared to an
average of 55-60% in South American and other South-East Asian countries\(^7\). A study in Bangladesh\(^23\) reported almost equal proportion of boys and girls in higher age groups, the report however contained data on viral etiology only. In Papua New Guinea study on ALRI reported a slight increased incidence in girls\(^24\). Mortality has been reported to be higher among females than males\(^7\).

**RISK FACTORS INFLUENCING INCIDENCE OF MORBIDITY AND MORTALITY DUE TO ARI:**

Host and environmental socioeconomic factors affect incidence and severity of acute respiratory infections, and also influence case fatality rates. Among the common factors influencing the host are age, low birth weight, malnutrition including Vitamin A deficiency and chronic heart lung disease including asthma. Prior immunization status and underlying disease or infection are also important host factors\(^3\). Environmental factors include crowding, family size, birth order, child care practice, smoke pollution and sanitation\(^3\).

*Extreme young age* predisposes to severe form of ARI due to immature immune system, anatomical structure and weak respiratory muscles. Studies conducted in Indonesia and Nepal have recorded high mortality rates of 19% and 40% in infants below 3 months of age\(^3\). Selwyn in compilation of the data of BOSTID study on ARI done in developing countries, has noted highest case fatality rates in children less than one year of age\(^7\).
Low birth weight: Datta et al\textsuperscript{27} in a study conducted in Haryana have reported 8 times higher case fatality rates among low birth weight infants as compared to the normal, although the incidence was the same. ARI related mortality among low-birth weight babies in Papua New Guinea was reported to be four times as high\textsuperscript{28}.

Malnutrition, which is the bane of many developing countries contributes a major risk factor in ARI of children. Alteration of immunity in the host, diminished energy stores and impairment of recovery of normal pulmonary tissue have been attributed to the cause of mortality in malnourished children\textsuperscript{3}. Reduction of antiproteinase activity of alpha-1 trypsin has been shown to predispose the lung tissue to chronic changes, thus leading to easy establishment of infection\textsuperscript{29}. Another direct evidence of malnutrition increasing mortality is due to the inability of the child to respond to hypoxia with tachypnoea, and therefore going into respiratory failure as has been reported by Wilson et al\textsuperscript{30}. In another study by James\textsuperscript{31}, an increased morbidity of respiratory infections was also associated with malnutrition in children. Increased incidence of bacteraemia and severity of ARI as evidenced by blood culture positivity in higher proportion of malnourished children was reported by Berman et al\textsuperscript{32} in Columbia. Filipino children were also seen to have an increased risk of ARI associated with malnutrition\textsuperscript{33}. In a study conducted in Pondicherry, Shabong reported 14.2\% of ALRI cases to have severe malnutrition with 27.6\% of all cases of ARI with malnutrition. However, there was no correlation with severity of the infection\textsuperscript{20}. Role of Vitamin A in reducing mortality has been demonstrated in a study
in Tanzania, where there was a reduction in total mortality of children due to measles following intervention\textsuperscript{34}. Breast feeding confers passive immunity to the infant. A lack of breast feeding therefore would predispose these children to infection. Chandra\textsuperscript{35} in a study comparing 35 breastfed infants with 35 infants fed on cows-milk over a period of 12 months, found 57 episodes of ARI in the first group as compared to 109 episodes in the second group. Similar results have been noted by Watkins et al\textsuperscript{36}.

**Smoking and pollution:** Other risk factors associated with increased morbidity and mortality include exposure to smoke and passive smoking. In India and Papua, New Guinea exposure to smoke pollution has been implicated in increased incidence of lung diseases in the population\textsuperscript{37,38}. This is due to the biomass fuels consisting of wood, manure, and other agricultural wastes, being used by 90% of rural population. This passive smoking alters the integrity of epithelial lining of respiratory tract making them vulnerable to infection\textsuperscript{39}.

Increased incidence of ARI due to passive smoking have also been reported from other developing countries\textsuperscript{40,41}.

**Overcrowding:** Crowding in families contributes to greater risk of acquiring ARI among siblings\textsuperscript{3,42}. An overall case fatality rates of ranging from 3% to 11% in all
pneumonia cases in infants have been reported by several Indian authors from Pune, Calcutta and Chandigarh\textsuperscript{43-45}.

**IMMUNIZATION AND ARI:**

Immunization status of the children in the developing countries is another factor contributing to ARI. Pertussis, diphtheria, measles and tuberculosis are four major respiratory illnesses which have been brought under the umbrella of immunization in a bid to control them. This effect has a dual role of controlling these infections and preventing or limiting secondary ARI thereby decreasing the morbidity and mortality. Pneumonia is a common complication of measles and pertussis\textsuperscript{21} accounting for 50% of all complications of measles\textsuperscript{46}. Measles is the major killer, being responsible for 2.3% deaths in children and 10% all childhood diseases seen below 5 years of age\textsuperscript{47}. One-third of all deaths due to acute respiratory infections in children are accounted for by measles\textsuperscript{48}. Measles related acute lower respiratory infections have been reported from Kenya, Columbia, Philippines and Nepal to the extent of 6%, 21%, 15% and 14% respectively\textsuperscript{42,49-51} based on studies conducted on hospitalised children in these countries. Measles vaccine has a potential to prevent a substantial proportion of cases of ALRI\textsuperscript{52}.

In developing countries, early acquisition of pertussis is due to limited preventive measures and mortality exceeds that seen 50-100 years ago in the industrialized world\textsuperscript{53}. No study has examined the full spectrum of pertussis in acute
respiratory tract infection and its role as a risk factor in morbidity and mortality of ARI. However, Morley et al have recognised that pertussis, like measles may be followed by a prolonged period of weight loss and recovery\textsuperscript{54}.

**Antecedent viral infections** as a risk factor has been emphasised in various studies undertaken in the developing world. Multiple or dual viral or concomitant viral and bacterial infections have been reported in patients with ALRI\textsuperscript{55}. Viral respiratory infection predisposes to bacterial superinfection by various mechanisms, such as neutrophil depression\textsuperscript{56} or damaged ciliary functions\textsuperscript{57,58}. Gwatney Jr et al\textsuperscript{69} have reported the spread of *Streptococcus pneumoniae* in families in a study to demonstrate the relation of transfer of *S.pneumoniae* to infections of cold and serum antibody. In various epidemiologic studies of ARI carried out under the BOSTID project, majority of the centres have documented concomitant viral and bacterial infections to the tune of two-third in Papua New Guinea\textsuperscript{24}, 26% in Pakistan\textsuperscript{60} and 24% in Gambia\textsuperscript{61}. Studies in India have also shown the co-existence of viral infections with bacterial lower respiratory tract infection, as evidenced by positive blood culture. Umapathy has reported Influenza-A infection with *Haemophilus influenzae*\textsuperscript{62} and John et al\textsuperscript{63} from Vellore have reported concomitant viral and bacterial infections in 8% out of 331 children studied. Respiratory syncytial virus was most common virus isolated in mixed infections followed by measles and para-influenza I, with *S.pneumoniae* and *Staphylococcus aureus* being the common bacterial isolates.
ETIOLOGY:

Bacterial Etiology of ARI:

Infections of the upper airway and lower respiratory tract are two different entities. Microbial agents involved are therefore two different groups, although there may be some overlap.

Upper respiratory infection (URI) includes pharyngitis or tonsillopharyngitis or tonsillitis. Organisms responsible for the infection are identified in 50-60% of cases. Viruses are involved in children younger than 5 years of age and bacterial etiology is more usual after this age. Twenty to thirty percent of children between 5-15 years of age are infected with Group A beta-haemolytic Streptococci (GABHS), which is the most common upper respiratory bacterial pathogen encountered in pediatric practice. In India, the prevalence of GABHS in upper respiratory tract infection ranges between 5 to 20% in the 5-15 years age group as seen in several studies in the country. Other haemolytic Streptococci reported to be responsible for pharyngitis are Group B beta-haemolytic Streptococci C, G and non-haemolytic Streptococci.

Although much less common than Streptococcal pharyngitis, C.diphtheriae continues to be a major cause of pharyngeal infection in the developing world. Other Corynaebacterium species (C.ulcerans, C.haemolyticum, C.pyogenes) can cause pharyngitis with or without the formation of membrane. ARI due to
C. diphtheriae still persists in India. Annually 25,000 cases of diphtheria are reported\textsuperscript{85}. However, it is believed that not only the incidence of diphtheria has come down, but fewer cases of severe diphtheria are seen in hospitals\textsuperscript{65}. Other rare causes of pharyngitis in children could be due to Mycoplasma pneumoniae\textsuperscript{74}. However, their prevalence and incidence in children in the developing world has not been documented.

**Bacterial agents involved in childhood lower respiratory tract infections:**

Lack of simple and reliable methods for establishing an etiologic diagnosis limits the data on bacteria associated with ALRI. This is further confounded by the problem of many of these organisms colonizing the upper respiratory tract. However, following some of the recent studies on bacterial etiology of ALRI in developing countries, valuable data have been documented based on lung aspirates obtained from children hospitalized with pneumonia, and those who had not received prior antibiotics. The most common pathogens isolated were Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus, in that order\textsuperscript{3,75,76}. S. pneumoniae was isolated in more than 30% of cases in 60% of the studies, H. influenzae in 11-50% of the patients in all studies and S. aureus was isolated in less than 30% of cases. Overall isolation rate were 27% for S. pneumoniae and H. influenzae. These figures are similar to those in the developed countries before the antibiotics were widely available and control measures were taken\textsuperscript{77}. Serotypes of S. pneumoniae in LRI in three developing countries of
Papua New Guinea (PNG) the Gambia and Pakistan were seen to be variable. PNG study reported predominance of types 6, 14 and 19; Gambian study group reported types 1, 5 and 6 and Pakistan study group reported types 19, 31 and 16 in their isolates. Type b strains of *H. influenzae* are among the highest isolates in developing countries. Non-serotypeable strains and non-type b strains (type a) are also found to be a significant cause of invasive disease. In the Gambia, PNG and Pakistan non-typeable *H. influenzae* has been shown to be responsible for 31% to 56% of pneumoniae as evidenced by lung aspirates and blood culture studies. Children with non-typeable *H. influenzae* are not commonly bacteriæmic and therefore are not identified if cultures of blood are done alone. Increase in the incidence of non-typeable *H. influenzae* strains in the etiology of pneumonia in the developing world could reflect on the choice of treatment with appropriate antibiotics.

Indian studies conducted over the last decade reveal *S. pneumoniae* to be the commonest cause of ALRI in children, followed by *H. influenzae*. *Staphylococcus aureus* has also been found to be responsible for pneumonia, being the commonest organism isolated from empyema.

Group A beta-haemolytic *Streptococcal pneumonia* is uncommon in children. Viral infections such as measles, influenza, chicken pox may precede GABHS pneumonia, but it can also occur in healthy children. Disease is usually severe with
bacteraemia and pleural effusion. Increase in invasive disease like toxic shock syndrome and necrotising fasciitis may predict an increase in frequency of severe pneumonia due to GABHS.

Other causes of bacterial pneumonia include those caused by *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (TWAR). In children, over 5 years of age *M.pneumoniae* has been found to contribute to the etiology of pneumonia to a large extent. In recent years, *Chlamydia pneumoniae* (TWAR) has been recognised as an important cause of infection among 5-14 years of age with community acquired pneumonia in the developing world. Due to difficulty in cultivation of the organisms, in most of the laboratories in the developing world, including India, there are very few culture proven reports. Studies based on serological findings of *Mycoplasma pneumoniae* antibodies in children with pneumonia, have been reported by various authors from Delhi, Poona, Chandigarh and Calcutta, from data compiled by Mohapatra et al.

Pneumonia due to *Moraxella (Branhamella) catarrhalis*, in children is rare, but it is a common cause of otitis media, and is frequently isolated from the throat and nasopharynx of children. Reports of isolation of this organism from otitis media and less frequently from ARI cases have been documented. Studies have shown that *M.catarrhalis* is a significant cause of lower respiratory tract infection encountered in community practice, especially bronchitis and pneumonia seen in older children.
Underlying pulmonary and systemic conditions predisposing to infection of *M. catarrhalis* has been documented. Apparent increase in pathogenicity has probably coincided with increase in the beta-lactamase production, thereby making it a potential pathogen in drug resistant cases. Incidence of Moraxella infection in India is not known.

Pertussis still remains an etiologic agent of ARI in India and other developing countries. Around 300,000 cases of pertussis are reported annually in India, 10% of deaths due to pertussis are reported from other developing countries.

**Role of *Streptococcus pneumoniae* and *Haemophilus influenzae* in the pathogenesis of pneumonia:**

*Streptococcus pneumoniae*:

Based on the data available on isolates from lung aspirates, it is evident that *Streptococcus pneumoniae* and *H.influenzae* are the most frequent bacterial causes of pneumonia in children of developing countries, with pneumococcus taking a predominant role. Capsular serotypes responsible for infection in children around the world are confined to certain serotypes only. There are some differences in serotypes causing infection in children from different countries. *S.pneumoniae* is carried in the upper respiratory tract by many healthy children. Attachment of pneumococci to epithelial cells is mediated by disaccharide receptor of fibronectin.
Mechanisms by which pneumococci translocate, from nasopharynx to the lung thereby causing pneumonia, or migrate directly to blood, are poorly understood92,95. Most infections do not occur after prolonged carriage but recent acquisition of newer serotypes96. Failure of specific IgA and non-specific defences in the respiratory tract may lead to access of pneumococci to bronchi and lungs96. Epithelial damage caused by previous viral upper airway infection, mediated by neuraminidase is believed to be responsible for entry of pneumococci into the blood stream97,98. Unrestrained multiplication of pneumococci in the lungs results in pneumococcal lysis, lysozyme in secretion fluids augmenting by activating the autolysin99. Impairment of either phagocytic system or opsonin production augments pneumococcal infection as seen in hypogamma globulinaemia in children. There is an inability to produce anti-polysaccharide antibody against pneumococcal polysaccharide in IgA deficiency100. Virulence factors contributing to pneumococcal pathogenesis has been summed up in a review article by Alonsode Valasco et al101. It describes the factors present on the surface of intact pneumoccus such as cell wall polysaccharide (CWPS), capsular polysaccharide (PS) and phosphoryl choline (PC) pneumococcal surface protein A, which act in the beginning of the infection by inhibiting phagocytosis via complement inhibition. The second group consists of factors like autolysin, pneumolysin, that act at the stage of pneumococcal disintegration and lysis. At this stage complement activation enhances inflammation, whereby a “point of no return” appears in pneumococcal infection101.
Mechanism of death from pneumococcal pneumonia has not been clearly understood as many gaps still exist in the sequence of events leading to death\(^2\). Involvement of several toxins including haemolysins, purpura producing principle, virulin, leukocidin have been proposed, but none of the known pneumococcal substance during growth or autolysis have been incriminated\(^2\).

**Haemophilus influenzae:**

The only known reservoirs of *H. influenzae* in humans are the respiratory tract and conjunctiva to some extent. There is inadequate knowledge regarding the factors both microbial and host, that are responsible for establishment of *H. influenzae* in the respiratory tract\(^2\). Capsular polysaccharide may be an important determinant in facilitating the *H. influenzae* colonization as demonstrated by Moxon et al\(^3\), but other studies have found no difference between typeable and non-typeable (without capsular polysaccharide) strains\(^4\). Ciliary movement is an essential factor responsible for successful removal of inhaled particles including bacteria. Recent studies have shown that *H. influenzae* strains (both capsulated and non-encapsulated) elaborate one or more factors that act within minutes in vitro to inhibit ciliary activity\(^3\). Cilio inhibitory factors could impair clearance and facilitate bacterial multiplication as well as penetration of the mucociliary barrier and binding with receptors on epithelial cells\(^3\). Adhesions of *H. influenzae* that interact with receptors on human cells have been described and the role of fimbriae in enhancing adherence have been demonstrated by Sable et al\(^5\). IgAl protease, an enzyme
secreted by *H.influenzae* has been shown by several workers to have some role in the interaction of *H.influenzae* and epithelial cells\textsuperscript{106,107}. Histamine which contributes to the bronchoconstriction that accompanies bronchial infection has been shown to be synthesized by *H.influenzae*, like other gram negative bacteria in a recent study\textsuperscript{108}. *H.influenzae* lipo-oligosaccharide can damage respiratory epithelial cells as shown by Johnson et al\textsuperscript{109}. Thus a variety of circumstances, either alone or in combination allows *H.influenzae* to increase in number and to produce directly or indirectly localized damage to respiratory epithelial cells. Preceding viral infection due to RSV, Influenza A and adenovirus have been incriminated in the development of associated *H.influenzae* disease as they are responsible for loss of ciliated epithelia\textsuperscript{110}. Toxic effects of bacterial products such as glycopeptides or lipo-oligosaccharides, other enzymes and toxins could lead to the presence of adherent microcolonies of the bacteria on the epithelial cells and lead to invasion\textsuperscript{102}.

**Viral Causes of ARI:**

Viral causes of ARI form a major aetiological factor in children. They are responsible for primary infection among children to a large extent, causing around 30-40% of all ARI infections\textsuperscript{64}. The damage that these viruses cause to the respiratory tract inturn leads to secondary bacterial infection. Most common viral agents responsible are the respiratory syncitial virus Influenza A, Para influenza and adenovirus\textsuperscript{57}. A large number of literature regarding viral association with acute respiratory infections have been published. However, since the purview of this
thesis is limited to bacterial etiology only, these works have not been reviewed in
detail, unless in association with bacterial causes, as risk factors.

ETIOLOGIC DIAGNOSIS OF ACUTE LOWER RESPIRATORY INFECTION:

Non-invasive Techniques:

Much of the etiologic diagnosis of pneumonia depends on the non-invasive
techniques to isolate the causative agent, although, there is no simple and reliable
method for establishing the etiological diagnosis. Expectorated sputum, throat swab
and nasopharyngeal swab constitute the non-invasive techniques for diagnosis.

Sputum examination and culture: Although microbiological examination of
carefully obtained sputum can yield valuable diagnostic information in adult patients
with pneumonia, sputum is rarely used as a diagnostic specimen in children, as the
very young do not produce it\textsuperscript{111}. In older children and adolescent, the diagnosis is
complicated by indigenous flora of the mouth and pharynx\textsuperscript{112}. There is poor
correlation between the results of sputum culture and smear and blood culture in
pneumococcal pneumonia\textsuperscript{113,114}.

Throat swabs and nasopharyngeal swabs have limited use as diagnostic
procedure for ALRI, as both sample the normal flora of the upper respiratory tract.
There are however a few studies which show significant statistical differences
between children with ARI and healthy controls\textsuperscript{111}. Throat swab is the ideal
specimen for diagnosing upper respiratory tract infections. Most cases of pharyngitis due to GABHS and other pathogens are diagnosed by throat swab cultures, either directly on to culture plates or on filter paper strips for transport\textsuperscript{68}. Results from throat swab cultures are not found very useful in interpreting bacterial pathogens of LRI\textsuperscript{111}.

*Direct examination of sputum and upper respiratory specimens:* Rapid presumptive diagnosis of ALRI however can be made by gram stain of respiratory specimens. A sensitivity of 49\% and specificity of 99\% has been made of Whitby et al\textsuperscript{121}.

*Quellung reaction:* Pneumoniae due to *S.pneumoniae* and or *H.influenzae* can be diagnosed by quellung reaction, using the specific antiserum\textsuperscript{74}. Diagnostic reliability of quelling reaction (QR) has been found to be better than counter immunoelectrophoresis\textsuperscript{122}. This technique however does not differentiate the colonization of these bacteria in the upper airway from that of the offending organism of the lower tract. Rates of colonization are found to be very high in many developing countries, to the tune of 10-70\% in different age groups\textsuperscript{123}, hence limiting the use of QR as diagnostic aid in these areas.

*Fluorescent antibody staining* has been used with advantage in the diagnosis of ALRI due to viral agents. Their use in pneumococcal or *H.influenzae* pneumonia\textsuperscript{3}
have been limited. Direct fluorescent antibody testing for detecting Group A Streptococcal infection of the upper respiratory tract however has been widely used\textsuperscript{74}. A sensitivity of 88\% and specificity of 98\% has been observed by Anhalt et al\textsuperscript{124}.

**Blood culture:** In patients with severe pneumonia in developing countries blood cultures are found to be positive for bacteria in as many as 36-50\% of those patients whose blood is cultured\textsuperscript{3,24,45}. In ambulatory patients with pneumonia the range is between 3-10\%\textsuperscript{113,115}. Twenty-five percent of Pneumococcal pneumonia give a positive blood culture. *Haemophilus influenzae* isolation from blood tend to be higher than those obtained for pneumococci, as evidenced by the isolation rates quoted by Ann Funkhouser et al\textsuperscript{123}. Blood cultures are performed more commonly in children who are hospitalized, and therefore are likely to have bacterial disease\textsuperscript{123}. One-third of children with Staphylococcal pneumonia and 89\% of those with disseminated disease give a positive blood culture\textsuperscript{116}. In patients with pleural effusion proportions of positive blood cultures is found to be high as reported by Hertal et al\textsuperscript{125}. Prior antibiotic therapy, even a few doses can affect the results dramatically, and it is often difficult in these settings to determine by history or body-fluid analysis if antibiotics have been administered previously\textsuperscript{123}. Effect of prior antibiotic therapy on outcome of blood culture has been demonstrated by several authors\textsuperscript{128,127}. Correlation of antibiotic in the body fluid and blood culture negativity has been reported by these authors.
**Invasive diagnostic technique:** These techniques are generally reserved for patients in whom non-invasive methods fail to provide a diagnosis or in those with progressive clinical deterioration. 

**Lung aspirates / Lung punctures:** Etiologic studies of pneumonia that use isolation of bacteria from lung punctures give valuable and accurate information if positive. In developing countries 50-70% of lung aspirates from those who have not received prior antibiotics are positive for bacteria. Other workers have reported ranges from 46 to 50%. However, the results are dependent on the technical skill to target involved areas of lung in lobar pneumonia. This procedure if not undertaken with due care is often associated with complications of pneumothorax. Despite the underlying difficulties, in doing a lung puncture or needle aspiration, the results obtained probably give the best existing evidence regarding bacterial etiology of pneumonia. Lung biopsy is considered an important adjunct in the diagnosis of pneumonia. It has been found to have high diagnostic yield.

**Pleural tap:** In patients with significant pleural effusion examination of pleural fluid has been found to be an useful diagnostic procedure. Diagnostic yield has been found to be around 60-80% in the presence of empyema. Isolation of organisms from Staphylococcal empyema has been reported to be around 36%, 68% and 70% from several studies in India.
Bronchoalveolar lavage (BAL) and flexible bronchoscopy (FB) are relatively safe and effective in parenchymal lung disease. Its overall diagnostic yield has ranged from 27 to 75% in pediatric patients with different underlying diseases\textsuperscript{120}. However, bronchoscopic protected catheter brushing during flexible bronchoscopy has very low yield for cultures in children\textsuperscript{120}.

**RAPID TESTS FOR DIAGNOSING ARI IN CHILDREN:**

Over the years, many rapid diagnostic methods have been evolved, based mainly on antigen detection from specimens or body fluids. Review of immunodiagnostic technique in URI reveals numerous antigen detection tests for Group A streptococci which have been developed over the last decade. Compared to cultural techniques, most are highly specific but not as sensitive. The tests are based on antigen extraction by various rapid extraction techniques by nitrous acid, hydrochloric acid or enzymes. The detection methods are counterimmuno-electrophoresis, latex agglutination test, staphylococcal co-agglutination test, enzyme immuno assays (EIA)\textsuperscript{129}. Of these enzyme immuno assays have been widely used. Sensitivities of EIA have been shown to be more than the agglutination techniques. Results as high as 90% to as low as 62% have been recorded by EIA, direct Strep. A EIA sensitivity - 79\%\textsuperscript{130}, microwell enzyme immuno assay - 88\%\textsuperscript{131}. Specificities of most of the enzyme immuno assays have been reported to be high, in the range of 80 to 95\% by most of the workers\textsuperscript{130-132}. Usefulness of antigen detection
following antibiotic treatment has been shown by Beach et al\textsuperscript{133} 29\% of children, 18-24 hours following antibiotic were still positive.

Direct agglutination test using latex particles has shown sensitivities of 76.1\% and specificities of 98\% by Manasse\textsuperscript{134}. These results are almost similar to those obtained by Pharmacia Phadirect Strep.A test in a comparative analysis done by Kaufhold et al\textsuperscript{135}. However, in another study by Wegner et al\textsuperscript{136}, a comparison of blood culture using two plates and 5 antigen detection kits, a low sensitivity of the kits was found around 41\% with individual kit sensitivities ranging from 31\% to 50\%, with false positive rates varying from 0 to 28\%, concluding that direct antigen tests were insensitive.

Liposome immuno assay is a solid phase immuno assay for rapid diagnosis of GABHS pharyngitis giving a sensitivity of 91\% and specificity of 83\% with 88\% and 87\% positive and negative predictive values\textsuperscript{136}. The other immuno assay claiming superiority is Optical Immuno Assay, which has a sensitivity of 78\% and specificity of 90\%. This has been found to be less sensitive than culture in seeded experiments and missed 22\% of positives in clinical practice, hence cannot be used as the sole assay for GABHS pharyngitis\textsuperscript{137}.  

Molecular based techniques provides rapid detection of infectious diseases\textsuperscript{138,139}. Gen-probe Group A Streptococcus direct test is an assay which utilises a non-isotopic chemiluminiscent, single stranded DNA probe that is complementary to the ribosomal RNA of the target organism\textsuperscript{140}. Results are available in little over one hour. The sensitivity and specificity are 91\% and 97\%. Authors claim that this technique could replace culture and rapidly identify GABHS\textsuperscript{139}, where as all other negative streptococcal antigen test results have to be confirmed by culture methods\textsuperscript{140}.

**ANTIGEN DETECTION IN SPUTUM AND NASOPHARYNGEAL ASPIRATES:**

Methods for rapid processing of large numbers of specimen of sputum and nasopharyngeal aspirates for detection of pneumococcal polysaccharide include co-agglutination (CoA), Latex particle agglutination, counter immunoelectrophoresis\textsuperscript{141} and ELISA\textsuperscript{142,143}. Rates of antigen detection varies in different studies. Forty-six percent of sputa revealed the presence of antigen latex agglutination\textsuperscript{144}. Co-agglutination has been found to be almost equal to ELISA and latex agglutination in sensitivity for detecting capsular antigen of pneumococci\textsuperscript{141}. Whitby et al\textsuperscript{142} reported 74\% sensitivity and 98\% specificity with CoA, 71\% and 99\% by LA and 67\% and 98\% by CIE in pneumococcal antigen detection. Quantitation of pneumococcal C polysaccharide by Parkinson et al\textsuperscript{143} showed that less than 5 \( \mu \)g/ml of the antigen could be detected, with a specificity of 90.1\%. Use of antigen detection in upper respiratory tract secretions gives rise to false positives due to
cross reaction with normal flora consisting of alpha-haemolytic streptococci. In a study comparing the various specimens from the upper respiratory tract\textsuperscript{145}, Boersma et al. have found pneumococcal antigen in 29% from oropharynx, 8% from nasopharynx and 16% from saliva of pneumococcal carriers. False positive antigen results in saliva are due to cross-reactions with alpha-haemolytic streptococci. Washing of sputum samples are found to decrease the antigen detection as evidenced by a study by Holloway et al.\textsuperscript{144}. There have not been many studies on the detection of \textit{H.influenzae} antigen from sputum or nasopharyngeal aspirate.

**ANTIGEN DETECTION IN BODY FLUIDS:**

Several antigen detection tests have been evaluated for detection of pneumococcal and \textit{Haemophilus} antigens in the serum, urine and pleural fluid of patients with pneumonia. These tests are mainly based on use of polyvalent antisera in CIEP, CoA, LA and EIA\textsuperscript{146} or type specific antisera. Sensitivity and specificity of the tests depend on the potency and specificity of the antisera in use\textsuperscript{121,142}. Capsular polysaccharide antigen in serum is closely associated with bacteraemia in pneumococcal pneumonia. Concentration of antigen is found to progressively decline following treatment\textsuperscript{147}. Presence of antigen has been used as a prognostic indicator. Martin et al.\textsuperscript{148} have shown that there is an absence of antigenemia in non-bacterimic children. Comparison of bacteremia and antigenuria by Co-A and LA have been shown to give higher positive by antigen detection methods (2% as compared to 24%)\textsuperscript{149}. Commercial latex agglutination kits for
detection of \textit{S.pneumoniae} and \textit{H.influenzae} type b antigen in serum and urine have shown sensitivity of more than 90\% for \textit{H.influenzae} antigen and to a much lesser extent for \textit{S.pneumoniae} antigen\textsuperscript{150}. Various agglutination kits give results varying from 27\% to 38\% for pneumococcal antigen thereby having limited use in pneumococcal pneumonia\textsuperscript{150}. Comparison of LA and CIEP by Cerosaletti et al showed 46\% detection by LA and 15\% by CIEP, with bacteraemic patients showing proportionately higher positivity by LA\textsuperscript{151}. Comparison of CIEP, Co-A, ELISA and LA in their ability to detect antigen has shown ELISA to be most sensitive (76\%) followed by Co-A and LA (both 47\%) and the least with 24\% sensitivity by CIEP\textsuperscript{152}. Antigen detection in urine however showed less sensitivity.

Cross reaction between pneumococcal polysaccharide and \textit{H.influenzae} type b has been noted by Requezo et al\textsuperscript{153}. They also noted that treatment with EDTA reduces the cross reactivity. Cross reaction between Pneumococcus type B and \textit{H.influenzae type} b has also been noted by Witt et al in a study in Gambia\textsuperscript{154}. Latex agglutination tests using latex beads coated with antibodies to all pneumococcal serotypes have been found to be insensitive on both urine and serum of patients with pneumococcal disease\textsuperscript{150}. A series of 10 latex reagents, each coated with commercial antiserum to a single pneumococcal serogroup and used to test the concentrated urine of patients with pneumococcal disease had a reported sensitivity of 76\% and specificity of 87\% and 96\% among children with pneumonia due to other organisms and healthy carriers\textsuperscript{155}. In a study by Harrison et al using monovalent latex
agglutination test on specimens of urine from several developing countries, average sensitivity of 46% (ranging from 44% to 50%) and specificity of 88% was achieved, showing it to be more useful than multivalent latex agglutination tests\textsuperscript{158}.

Concentration methods for antigen detection have been tried by various workers to improve the sensitivity of the test systems for detecting antigen in urine and serum. Boiling with EDTA for concentration of serum samples have been used\textsuperscript{155,157}. Urine has been concentrated by boiling\textsuperscript{155}, filtration\textsuperscript{158} and ethanol precipitation\textsuperscript{157}. Increased sensitivity and specificity have been noted by Requejo et al\textsuperscript{153}. Although increased sensitivity was seen on concentrated serum samples by Premanand et al, there was no difference between concentrated and unconcentrated urine samples\textsuperscript{159}.

With molecular methods gaining importance and replacing the conventional antigen detection kits, their utility and applicability need to be reviewed. In vitro DNA amplification by the polymerase chain reaction (PCR) has gained considerable implication for the diagnostic microbiology for its exquisite sensitivity and specificity\textsuperscript{160}. It can detect low number of pathogens in clinical samples. Whole blood and its buffy coat fractions have been used as samples for amplification by PCR as a diagnostic method for pneumococcal pneumonia\textsuperscript{161}. The sensitivity of the assay was 37.5% for the whole blood and 75% for the buffy coat. Clinical potential of the PCR method in the diagnosis of pneumococcal pneumonia is limited by the
complexity of the sample preparation\textsuperscript{161}, and causative organisms not being bacteremic. Paula Salo et al have targeted the gene coding for pneumococcal pneumolysin for the PCR assay\textsuperscript{162}. Pneumolysin, which is secreted by all clinical isolates of pneumococci\textsuperscript{163} is a toxin with virulent properties\textsuperscript{164}. Sensitivity of PCR of 20 clinical samples of acute phase sera was found to be 100%. These PCR positive samples were also positive by hybridization with specific probe. The specificity was seen to be 94%. Pneumolysin PCR according to Paula Salo et al could be a promising method for diagnosis of pneumococcal pneumonia. However, blood culture negative pneumococcal pneumonia need to be evaluated for pneumolysin detection by PCR. Specificities of primer sets for different types of \textit{H.influenzae} and sensitivities of the assay on isolated DNA and bacterial cells have been described\textsuperscript{165}. PCR assay as diagnostic tool for \textit{H.influenzae} meningitis have been evaluated by Vanketel et al\textsuperscript{166}.

Interpretation of antigen in body fluids and other specimens needs to be done with care. Presence of antigen in body fluids which are normally sterile is clinically significant. Whether it suggests active infection depends on the organism that the antigen is indicative of and the level of antigen in the body fluid\textsuperscript{167}. Presence of \textit{H.influenzae} type b antigen may persist beyond the stage of active infection. Studies have documented its persistence 4-5 weeks beyond the need for treatment\textsuperscript{168}.
Detection of antigens that pass through contaminated areas such as the oropharynx may indicate colonization rather than active infection. Negative results have been difficult to interpret in the presence of clinical disease, as the quantity of antigen may have been below the sensitivity of the reagent used.

SEROLOGICAL DIAGNOSIS OF ARI:

Serological Diagnosis of Streptococcal Pharyngitis:

Serology has a limited role in diagnosing acute respiratory tract infections. However, their role in determining exposure to the infection and response to vaccines remains valuable. Serological test for Streptococcal pharyngitis is important for diagnosing non-suppurative sequelae. Various tests are in use to detect antibodies against different Streptococcus Group A antigens based on latex agglutination and enzyme immunoassays. The conventional neutralisation test for determining antistreptolysin O is the most sensitive. Latex agglutination tests such as ASO latex test, Rapitex ASO kit, Rheumagen ASO are simple to perform but their sensitivity and specificities by various workers have given different results. Streptozyme test, has shown to give less false positive results, than other tests due to the presence of lipoproteins, or oxidised Streptolysin O. However, Gerber et al have shown this test to be no better than ASO or anti-DNase B test. With resurgence of rheumatic fever, and absence of sore throat or pharyngitis in many patients a serodiagnosis of Streptococcal infection is based on elevated serum
antibody titres to Streptolysin O or Dnase B. In a comparison of ASO and anti-DNase B tests, the latter has been found to show a higher positive detection rate for Streptococcal pharyngitis than the former in a study by Wang in children with Streptococcal pharyngitis. M-associated protein antibodies of the IgG class have been demonstrated by various workers following Streptococcal infection. Anti cell membrane antibodies have been shown to be high following Streptococcal infection in an EIA test by Yoshimoto et al, which was found to be higher than ASO in children with Streptococcal pharyngitis. ELISA and RIA have been used by Wahi et al to demonstrated high anticarbohydrate antibody tests to Group A Streptococcal infection in children with pharyngitis.

**Serological Diagnosis of Pneumococcal and Haemophilus Infections:**

With the development of vaccines to Pneumococci and *H. influenzae*, estimation of antibodies in the vaccinees to determine the level of protection has become essential. Role of antibody detection as a diagnostic tool in pneumonia is limited. Protective antibody, against various types of antigens have been estimated in experimental animals as well as children.

Detectable levels of IgM against pneumococcal capsular antigen are observed in infants after infection. Carriage also sometimes results in IgM detection. Antibodies are also present in older children. Antibodies to cell wall polysaccharide have been detected by various immunoassays. Antibodies to
pneumolysin\textsuperscript{184,185} and pneumococcal proteins\textsuperscript{186} are also sensitive indicators of hosts immune response. Enzyme immuno assays for the determination of antibodies to capsular polysaccharide (various serotypes) and C-polysaccharide has been evaluated by Padiukov et al, in various body fluids for evaluation of dynamics of pneumococcal infection in children\textsuperscript{187}. IgG, IgA and IgM antibody response to polysaccharides were noted in three quarters of the vaccines by Sarvas et al\textsuperscript{188}. In children, IgG1/IgG2 ratio induced by pneumococcal PS is inversed compared to adults, children were noted to produce large amounts of IgG1 and small amounts of IgG2\textsuperscript{189}. \textit{Haemophilus influenzae} vaccines available since 1985, have been evaluated by the detection of antibodies to various types of vaccines\textsuperscript{180}. IgG1 and IgG2 have been detected against Hib capsular polysaccharide polyribosylribitol phosphate antigen\textsuperscript{190,191}. Secretory antibodies to \textit{H.influenza, Branhamella catarrhalis} and Pneumococcal type specific capsular polysaccharide have been measured by ELISA to give variable results\textsuperscript{192}.

PREVALENCE AND RESISTANCE MECHANISMS OF COMMON BACTERIAL RESPIRATORY PATHOGENS:

Antimicrobial resistance is being increasingly reported among respiratory bacterial pathogens\textsuperscript{193}.
Group A Beta hemolytic Streptococci:

Penicillin tolerant GABHS has been reported from cases of pharyngitis who have failed to respond to penicillin G therapy, in various parts of the world, as reported by several workers\textsuperscript{194,195}. Relatively penicillin resistant GABHS with altered penicillin binding protein (PBP) have been selected in the laboratory, but have not been recovered from cases so far\textsuperscript{196}. Production of beta-lactamase by other pharyngeal or tonsillar flora has been suggested to contribute to treatment failures\textsuperscript{197}. Levels of erythromycin resistance of GABHS has reached to the extent of 20\% to 44\% in some parts of the world\textsuperscript{195,197,198}. Prakash et al\textsuperscript{199} from India have reported a steady increase in erythromycin resistant from 1980 to 1985 with an increase of MIC from 11.5 \(\mu\)g/ml in 2.7\% of isolates to MIC of more than 100 \(\mu\)g/ml in 5.1\% of isolates.

The same authors have reported resistance to lincomycin in 3.3\% of their isolates of GABHS from cases of pharyngitis in 1985. Resistance to erythromycin being plasmid mediated has a great likelihood of spreading fast\textsuperscript{197}. Chloramphenicol resistance has been reported to a level of 5\%\textsuperscript{200}. Resistance to trimethoprim-sulphamethoxazole has shown a wide range from 8\% of isolates to 76\%\textsuperscript{200}. Tetracycline resistance has been detected in approximately 20\% strains\textsuperscript{193,200}. Tetracycline resistance has been shown to be due to ribosomal protection by Tetracycline-M or other uncharacterized determinants, thereby resulting in the efflux of the drug\textsuperscript{201}. 

STREPTOCOCCUS PNEUMONIAE:

First case of Streptococcus pneumoniae resistant to penicillin was reported from Australia as early as 1967\textsuperscript{202}. Since then gradual increase in resistance has been detected in this organism world wide\textsuperscript{203}. Pneumococcal resistance to penicillin has reached alarmingly high levels in Spain, Chile, South Africa and Alaska\textsuperscript{204}. Some European countries have also reported high levels of penicillin resistance among their isolates\textsuperscript{204} with 20\% of all strains exhibiting an MIC of > 1 µg/ml. In a study by Morton A from Hungary 58.5\% of the strains had MIC > 0.15 µg/ml and 14\% had MIC > 5 µg/ml\textsuperscript{205}. Various serotypes have been associated with penicillin resistance in different geographical area. South African isolates predominantly belonged to serotype 6A and 6B, 19A, 14 and 23F\textsuperscript{206}. In a study from Korea Hoan-Jonglee et al have reported very high levels of resistance to penicillin to the tune of 70\% belonging to serotypes 6, 14, 19F and 23F\textsuperscript{207}. Altered penicillin binding proteins with low penicillin affinities and abnormal molecular sizes have been noted in these strains which is thought to originate via horizontal transfer of genetic material, probably from another bacteria\textsuperscript{208}. Nasopharyngeal colonizers were seen to be resistant to a level of 12\% in a study in Durban, South Africa\textsuperscript{209}.

Erythromycin resistant strain in cases of pneumonia have been reported by Santiago Moreno et al\textsuperscript{210} from Spain. A study in Korea also reported around 19\% of strains resistant to erythromycin\textsuperscript{16}. This resistance has been attributed to RNA methylases that modify adenine in 23S ribosomal RNA so as to reduce binding to
Cephalosporin resistant strains are also being increasingly reported with failure of treatment with second and third generation cephalosporin’s like cefotaxime, ceftriaxone and cefuroxime. However, these have been reported from meningitis cases, who have failed to respond. Among the penicillin resistant strains reported from Korea, many were seen to be concomitantly resistant to cephalosporins also. Many of these strains were from respiratory tract. Changes in several PBPs are said to be responsible for the phenotypic changes seen in cephalosporin resistant strains. Resistance to chloramphenicol from Korea (24%), Hungary (25.5%) and US (1.2%) has been documented. Tetracycline resistance of 6.5% from Hungary has also been reported. A high degree of resistance to Sulphamethoxazole - trimethoprin has been noted in pneumococcus from the Hungarian study to the tune of 39.7% of all their isolates. Mechanism of resistance to this drug is not known, although mutation has been hypothesised.

**Haemophilus influenzae:**

Ampicillin resistant strains of *H.influenzae* first emerged in 1970 and now accounts for almost 15%-20% of all strains isolated. *H.influenzae* type b shows a slightly higher incidence of resistance at 30%. Most resistant strains carry plasmids encoding for Beta-lactamase. Mortensen in 1990, has reported 34.4% of type b and 22.1% of non type b isolates to be producing Beta-lactamase. Respiratory isolates of *H.influenzae* have also been recorded to show Beta-lactamase production to an extent of 34%. Some ampicillin resistant strains owe their resistance to
altered penicillin binding protein mechanism and not to the production of Beta-lactamase\textsuperscript{216}. Such strains are found to be less susceptible to amoxycillin/clavulanate and cephalosporins, like cefotaxime, cefuroxime and cefaclor\textsuperscript{217}.

Resistance to chloramphenicol, tetracycline and trimethoprim sulpha-methoxazole have been reported increasingly from Spain and other European countries\textsuperscript{218}. Chloramphenicol resistance is due to the production of chloramphenicol acetyl transferase\textsuperscript{218}, or due to the loss of production of chloramphenicol acetyl transferase\textsuperscript{218} or due to the loss of protein on the outer membrane, thereby causing a permeability barrier\textsuperscript{201}. Tetracycline resistance by H.influenzae is due to the production of Tetracycline B gene which is plasmid mediated. Trimethoprim resistance is due to the over production of dihydrofolate\textsuperscript{219}.

**Moraxella catarrhalis:**

Beta-lactamase strains of *Moraxella catarrhalis* were first detected in 1970\textsuperscript{193}. At present around 80 to 90% of strains are shown to have become resistant to ampicillin in the recent years\textsuperscript{215,220}. Beta-lactamase produced *M.catarrhalis* are BRO-1, BRO-2, BRO-3, which are closely related but are different from TEM or other beta-lactamases seen in *H.influenzae*\textsuperscript{221}. Erythromycin, chloramphenicol and TMP-SMZ resistance have been reported, but their mechanisms still remains unknown\textsuperscript{222}. Tetracycline resistance has been reported with the gene located in the
chromosome\textsuperscript{223}. With the significance of \textit{M. catarrhalis} increasing as a pathogen in respiratory tract infections and being a common colonizing agent of the upper respiratory tract in children, the sensitivity pattern of this organism and mechanisms of resistance is gaining importance\textsuperscript{222}.

**IMMUNOPROPHYLAXIS OF ARI:**

**Pneumococcal and Haemophilus vaccines in the prevention of respiratory tract infections:**

**Pneumococcal vaccines:**

Pneumococcal vaccines using killed pneumococci have been attempted since the beginning of the century\textsuperscript{224}, however they were not found to be very successful. Development of new serotypes around 1930's saw the purified pneumococcal polysaccharide vaccines which gave better results, and it culminated in the licensing of hexavalent pneumococcal polysaccharide vaccine. With the therapeutic efficacy of antibiotics, the pneumococcal vaccine was withdrawn from the market\textsuperscript{224}.

Despite the use of antibiotics, mortality rate of systemic pneumococcal disease remains very high\textsuperscript{225}. Because of emergence of antibiotic resistant pneumococci, efforts have been geared upto develop better and more efficient vaccines in the 1970\textsuperscript{225}. In 1978, a 14 valent vaccine was licensed in the US and in
1983 a 23 valent became available which included new serotypes based on the current serotype distributions and cross reactivity between various serotypes. Vaccine trials among adults in the US army and South African gold mines had been carried out in the early part of the century and as late as 1970 in Africa. Although not very successful earlier, there was 80% reduction of pneumococcal pneumonia diagnosed by culture of blood or sputum in cases due to the serotypes specific to vaccines. Field trials of adult immunization has also been carried out in Papua New Guinea where mortality was reduced by 44% and incidence came down significantly. Successful adult immunization led to the inclusion of children in vaccine trials because the morbidity and mortality was found to be even higher. A 14 valent vaccine was studied by a double blind trial in children between 6 months to 4 years. This vaccine was later substituted by a 23 valent vaccine. Efficacy of the vaccine in children less than 5 years was 59% when ALRI was the sole cause of death and 19% for children whose deaths were due to all causes. Anti PS antibody produced by children is lower than that produced by adults, substantial antibodies produced against the pediatric serotypes 6A, 14, 19F and 23F are observed after 4 to 5 years. Antibody response to different serotype pneumococcal vaccines have been measured by radioimmunoassay by Schiffman et al and that nitrogen level of 300 mg (AbN/ml) is proposed as satisfactory immune response. Conflicting results have been obtained regarding the protection by the vaccine in children less than 2 years from death. Determining the preimmunization and postimmunization antibody levels in a group of Australian infants 6-17 months of age, it was shown that
levels of AbN/ml of more than 300 ng to serotypes 1, 3, 12F, 14, 23F preimmunization, and to types 2, 4, 71, 9N, 25 postimmunization were achieved. These data suggested that certain pre-immunization antibodies could interfere with response to certain serotypes. ELISA has been used to measure antibody IgG in a small case control study in Goroka, Papua New Guinea to evaluate immunization. The study showed large and significant differences in patients and controls less than 6 months and no difference between 6-14 months, where levels were extremely low. Poor response below 5 years of life have been reported by Sell et al. Reports of field trials of pneumococcal vaccines are limited in the developing world due to inadequate epidemiologic data regarding prevalent serotypes pes and their distribution. Development of new generation of pneumococcal vaccines is underway as evidenced by recent literature.

Coupling of pneumococcal PS or OS to protein have been shown to increase immunogenicity. Possible application of peptides as carriers for conjugate vaccines has been explored successfully by Lett et al. and Alonso De Velaso et al. They opine that peptides offer the advantage of being able to be selected on the basis of the B and T-helper cell immunogenicities, thereby minimizing the risk of anticarrier Ab mediated suppression while still providing sufficient Th cell activation.

Antibodies against SpA and pneumolysin are partially protective against pneumococcal infection in mice. Pneumolysin mutant which is nontoxic but has
retained is immunogenicity has been successfully conjugated to pneumococcal capsular PS of serotype 19F. This conjugate was shown to induce higher antibody titres than did the PS alone, thus suggesting that Th-cells are activated by the carrier protein\textsuperscript{237}. One epitope for Th-cell has been demonstrated in pneumolysin\textsuperscript{234}.

\textit{H.influenzae vaccines}

Immunization of children less than 4 years of age with \textit{H.influenzae} type b (Hib) has become part of the routine immunization schedule in United Kingdom and the Republic of Ireland\textsuperscript{236}. Following this 85\% of reduction in Hib disease in children aged less than 5 years has been reported in 1993. Adams et al\textsuperscript{239} and Peltola et al\textsuperscript{240} from the US have reported decline in Hib infection in children, following immunization. Carriage rate of \textit{H.influenzae} in the oropharynx has also been reported to have decreased in American Indian children, following Hib-meningococcal conjugate vaccination\textsuperscript{241}.

In a review of current status of \textit{H.influenzae} type b vaccines, Santhosham\textsuperscript{242} has compared the efficacy of different Hib vaccines including the pure polysaccharide vaccine which showed to be efficaceous in children below 18 months of age. Use of bacterial polysaccharide immunoglobulin (BPIG) which was a passive immunization strategy had 86\% efficacy for 4 months period after administration. Conjugate vaccines of Hib with diphtheria toxoid, have shown limited efficacy (35\%) in Alaskan native children\textsuperscript{243} as compared to other studies in the US where efficacy
of 96% was estimated\textsuperscript{244}. Haemophilus type b oligosaccharide conjugated with a nontoxic mutant diphtheria toxin (CRM197) carrier has been licensed and recommended for use in the US recently\textsuperscript{123} following trials in various places which showed efficacy of 89% to 100% depending on the dose of immunization\textsuperscript{123}. Hib \textit{Neisseria meningitides} outer membrane protein complex has been used by Santhosham et al\textsuperscript{242} in a trial to evaluate the efficacy and safety of the vaccine among Navajo infants. Point efficacy of 95% was noted in children below 18 months of age. Based on their data the Hib OMPC has been licensed for use in infants beginning at 2 months of age in the US\textsuperscript{242}. This vaccine has a dramatic antibody response even in young infants to the initial dose unlike other vaccines\textsuperscript{245} as shown in Gambian children.

\textit{H.influenzae-PRP-tetanus} toxoid conjugate vaccine has been used successfully in US, Finland and France and has shown antibody levels of 6-10 $\mu$g/ml in infants immunized with three doses during the first six months of life.

In developing countries, in the absence of Hib vaccination, serotypes other than type b and nontypeable strains are responsible for respiratory infections. Hib vaccination does not offer protection against this, therefore there is potential need for the development of a nontype b or nonserotypeable \textit{H.influenzae} vaccine.
Control of acute respiratory infections in India has been taken up as a national ARI control strategy under a three pronged approach of i) Standard case management, ii) Vaccines against preventable disease and iii) Health education. Under this programme development of pneumococcal and H.influenzae vaccines and trials are part of the second objective. However, prevalent serotypes of Streptococcus pneumoniae and H.influenzae have to be determined before a vaccine trial can be undertaken. There is no available data on pneumococcal and H.influenzae vaccines in the Indian subcontinent.

TREATMENT OF ARI DUE TO BACTERIAL CAUSES

Pharyngitis:

A number of pharmacologic options are available for treatment of patients with GABHS pharyngitis. These include penicillin V, a number of cephalosporins and erythromycin. Newer macrolides like clarithromycin and azithromycin are also finding increasing usage.

Penicillin V has the advantage of still being the drug of choice but multiple doses, long duration gives rise to less compliance. Recent reports of bacteriologic failures after penicillin therapy to an extent of 30% has raised questions of its usefulness as first line of treatment. Cephalosporins have demonstrated higher bacteriologic eradication. Erythromycin still continues to be the drug of choice following penicillin. But resistance to this drug has been reported therefore limiting
its use. Studies with azithromycin by various workers in recent years shows greater promise.

ALRI

_Pneumococcal pneumonia_ being the most commonest cause of bacterial pneumoniae in children, penicillin continues to be the drug of choice. However, with increasing relative resistance to this drug being reported from different parts of the world, an increased dose of penicillin have to be administered to bring about an effective cure. Choice of antibiotic is based on the frequency of the pathogens in various age groups, local antibiotic resistance pattern, clinical presentation, host factors and epidemiological data.

Treatment of neonatal pneumonia is similar to the treatment of severe neonatal septicemia, and initial therapy includes coverage of both Gram positive and Gram negative organisms particularly Group B Streptococcus, and Gram negative enteric bacilli. Penicillin and ampicillin with aminoglycosides such as gentamicin, amikacin and tobramycin have been recommended by Jo-Ann Harris. In case of Gram negative organisms and _Staphylococcus aureus_, the choice is usually dependent on antibiotic susceptibility pattern of the isolates. In children between three months to 5 years, majority of the pneumonias are caused by respiratory viruses. However, with secondary bacterial infections including β-lactamase producing _H.influenzae_ third generation cephalosporins have been reported by
various workers\textsuperscript{249,250}. Empyema due to \textit{Staphylococcus aureus} needs to be treated by a penicillinase resistant penicillin. Pneumonias in children above five years of age are mainly due to \textit{C.pneumoniae} and mycoplasma\textsuperscript{81}. However, \textit{S.pneumoniae} also plays a major role. Macrolides erythromycin, clarithromycin and azithromycin have shown good efficacy against both mycoplasma and pneumococcus. Tetracycline also has been found to control the infection (in children above 8 years of age). Studies have shown higher concentration of clarithromycin and azithromycin in lung parenchyma than erythromycin\textsuperscript{251}. Ampicillin, amoxycillin, chloramphenicol and gentamicin are found to be useful by various groups in India\textsuperscript{126}. 