Summary
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Problem of ARI is enormous in terms of lives lost in the most vulnerable group of the population, the children. Besides mortality the extent of morbidity, it is responsible for, constitutes a tremendous burden on the fragile health care system of most of the developing world and their society at large.

Mortality due to ARI in India constitute 15-34% of all childhood deaths. 20-40% of children seeking medical attention in the outpatient department and 12-35% of all children admitted to the hospitals on an average in India are due to ARI. There is a lack of information regarding pathogens involved, their prevalence in sick and healthy children and other epidemiological features.

Information on prevalence of antibiotic resistance among common bacterial pathogens of the respiratory tract, to the routinely used antibiotics in respiratory infections is also inadequate or absent. Certain laboratory diagnostic methods to confirm the etiological diagnosis of ARI and their feasibility studies are also needed to be evaluated to help a clinician in the specific management of ARI.

Knowledge regarding the extent of recovery of potential respiratory pathogens in disease and carriers, and distribution of various serotypes of these organisms in
the healthy and sick children is essential to design and implement preventive strategies, both in terms of chemoprophylaxis and immunoprophylaxis.

This study was undertaken to get an insight into some of the lacunae that exist in our knowledge of acute respiratory infections in children in the Union Territory of Pondicherry.

The study was divided into three phases carried out over three different periods. It involved school survey in the first phase to study certain parameters of Group A beta-hemolytic Streptococcal pharyngitis. The second phase involved children with ARI seeking medical attention in the primary health care setups. The final phase of the study involved children with ALRI requiring hospitalization in JIPMER, a tertiary medical care centre.

1.1 Group A Streptococcal pharyngitis was diagnosed in 9.4% of ambulatory children attending selected urban and rural schools in Pondicherry. Incidence was significantly higher in the male children than the females, and among the younger children between 5-9 years of age than the older group of 10-15 years. Infection was further confirmed in the younger age group with 47% of them showing antistreptolysin O titres ≥ 300 IU and 39% of older children had raised antibody titres.
1.2 Feasibility of a rapid antigen detection assay in the rural school children was carried out using an enzyme immuno assay kit. The test had a sensitivity of 92.5% and specificity of 89.4%, with a low positive predictive value of 65.8% and high negative predictive value of 98%. However, the cost effectiveness of this assay method was limited, due to its high cost, short shelf life of the reagents and nonavailability with the local suppliers. Antigen detection kits for field use in the developing countries therefore does not seem a feasible alternative to the culture method in spite of the problems inherent with it. Filter paper strips for transportation of the samples was found useful by us in the field survey.

1.3 Antibiotic susceptibility of GABHS was carried out to determine its sensitivity to alternate drugs which are commonly used in penicillin treatment failures. This was found necessary in the light of emergence of penicillin tolerant strains of GABHS and increasing reports of treatment failures with penicillin. 4.3% of the strains were found to be resistant to erythromycin, and 10.8% resistant to tetracycline. A high resistance rate of 34% was found against cotrimoxazole. This finding is disturbing, as the drug has been chosen by WHO and National ARI Control Programme of India as the first line drug in the management of ARI in India and other developing countries. This could lead to treatment failures and increasing emergence of resistant strains. All the isolates were found to be sensitive to clindamycin. Susceptibility pattern did not vary between isolates from urban and rural children.
GABHS therefore still continues to be a problem in Pondicherry with varying degrees of resistance to some of the commonly used antibiotics. ASLO determination is a useful adjunct to culture in differentiating cases from carriers, and predicting the exposure level and consequent complications which might arise, therefore warranting chemoprophylaxis and cardiovascular monitoring to prevent rheumatic fever and rheumatic heart disease. Rapid antigen detection from throat swabs to establish diagnosis have a limited role to play in school surveys.

II. Primary health centres form the first line in health care delivery system, and this is the first meeting ground of a sick child with a qualified doctor in the major part of our country. Data on incidence of ARI in these health care delivery centres is lacking. We studied a total number of 1059 children presenting with acute respiratory infection in some of the PHCs and Government General Hospital in Pondicherry. Incidence of ARI was recorded to be higher in the younger age as compared to the older children. Male preponderance was noticed more among the urban children, than rural. A male to female ratio of 1.2:1 was noticed among the urban and 1.09:1 in the rural children.

II.1 GABHS colonization was seen in children above 5 years of age with an overall carriage rate of 2.2%, this finding was lower than the findings in the first phase of our study, among asymptomatic carriers, in school children who were
suffering from pharyngitis unlike the children attending PHCs, who had complaints of lower respiratory infection.

II.2  *S. pneumoniae* colonization was seen in 9.2% of children. Youngest child colonized was a 2 month old male. Colonization rate declined slightly upto 3 years of age. There was a sudden rise in the rate of upto 16.6% in the 3-4 years of age group, following which the decline continued upto 15 years of age. There was no sex difference in the urban and rural children with regards to colonization by *S. pneumoniae*. Urban children were found to have higher colonization rate than rural children.

II.3  Colonization of the nasopharynx of urban and rural children with *H. influenzae* did not show any significant difference as regards sex or urban and rural predisposition. Overall carriage rate was 7.5%. There was no significant age group difference in the carriage of *H. influenzae* although the same trend of decline of carriage rate was observed with increasing age similar to that seen for *S. pneumoniae*. Youngest age at which colonization started was found to be 3 months.

II.4  Serotype distribution among the *H. influenzae* colonizers was seen to be the highest (51%) for type b. Non-typeable strains was found to be 32.9% and type a was 13.9%. Type b *H. influenzae* was found to colonize from 3 months onwards.
Nontypeable strains were seen in infants 7 months onwards. There was no difference in the serotype distribution among urban and rural children.

11.5 *Moraxella catarrhalis* was seen to colonize the nasopharynx of 9% of all children. Colonization was detected in the neonates who were brought to the health centres. 3.1% of all the isolates were found in infants below 6 months of age.

**ANTIBIOTIC SUSCEPTIBILITY OF THE ISOLATES:**

11.6 GABHS isolated from children attending the health centres showed variable resistance to erythromycin (12.5%) with highest MIC$_{90}$ of $\geq 8 \mu g/ml$, tetracycline (25%) $\geq 8 \mu g/ml$ being the highest MIC$_{90}$ level. Contrimoxazole resistance was seen in 37.5% of strains with MIC$_{90}$ of 32/128 (trimethoprim/sulphamethoxazole). Percentage of resistant strains were seen to be similar to that seen in the school survey.

Penicillin resistance was seen among 18.3% of *S.pneumoniae* isolates. MIC$_{90}$ at 8 $\mu g/ml$ was seen in two strains. Erythromycin and chloramphenicol resistance was detected in 4.8% of the isolates with MIC$_{90}$ at 4 $\mu g/ml$ and 8 $\mu g/ml$ respectively. Highest level of resistance was seen against cotrimoxazole (59.8%) MIC$_{90}$ at 16/128 $\mu g/ml$. 
Slight variation was seen among the rural and urban distribution of resistant strains with regards to penicillin and cotrimoxazole. Urban strains showing minimally higher rates. *H. influenzae* showed higher rates of resistance than *S. pneumoniae*. 35% of the colonizers were found to be resistant to ampicillin with 90.5% of the strains producing beta-lactamase. Alteration of penicillin binding protein could be a mode of drug resistant among some of the non-betalamase producing *H. influenzae* resistant strains. Highest MIC was seen at 16 μg/ml for ampicillin. Chloramphenicol resistance (27%) with highest MIC at ≥ 8 μg/ml was observed. A high degree of erythromycin resistance was also seen among the *H. influenzae* isolates (59%) with highest MIC at 16 μg/ml. Cotrimoxazole resistance was observed in 50% of the isolates, with MIC<sub>90</sub> at ≥ 32 μg/ml. 39% of type b were found to be resistant to ampicillin, 31% to chloramphenicol and 51% to cotrimoxazole. Nontypeable strains were less resistant to ampicillin and chloramphenicol at 23% each and 46% to cotrimoxazole. Higher rates of cotrimoxazole resistance was seen in the older age groups as compared to the other antibiotics. Resistant strains of *S. pneumoniae* and *H. influenzae* were found to colonize as early as 3 months of age.

A high degree of *M. catarrhalis* resistant strains were encountered in our study. They could be responsible for transmission of drug resistance to other resident potentially pathogenic flora of the nasopharynx. Beta-lactamase production was also seen in 48.9% of these strains.
Drug resistant strains of *S.pneumoniae* (10% of them being multidrug resistant) have been shown to colonize the nasopharynx of children with ARI in Pondicherry. Emergence of drug resistance does not bode well, for management of invasive pneumococcal diseases including pneumonia. This calls for constant monitoring and judicious use of antibiotics. A high degree of resistant *H.influenzae* were also encountered. Although type b was the predominant serotype, nontypeable strains were seen in a large number of cases. This will have a bearing on the efficacy of Hi b conjugation vaccines among our child population.

III. A child with acute respiratory infection is frequently admitted to the hospital with severe illness, often with complications. The third phase of our study involved 329 such children age and sex matched with healthy controls below 5 years.

III.1 Nasopharyngeal carriage among cases and controls with regards to *S.pneumoniae* and *H.influenzae* did not vary statistically. Antibiotic resistance among the strains isolated from cases and controls did not show any difference. Serotype distribution was found to be uniform among the two groups. *H.influenzae* type b was the major group followed by nontypeable strains. Type a and type d were the other serotypes isolated from the nasopharynx of hospitalized children. Most of the resistant strains were found to belong to serotype b.
III.2 Blood culture proven ALRI was seen in 8.5% of cases. Gram negative enteric bacteria were seen to be the major isolates (37%). One isolate of *S.typhi* was also encountered which was found to be sensitive to ampicillin, chloramphenicol and ciprofloxacin. The next major isolate was *Staphylococcus aureus* (22.9%). *Haemophilus influenzae* was isolated from 18% with *S.pneumoniae* and GABHS from 11% of cases. All *H.influenzae* isolates were type b excepting one strain which was nontypeable. Only one isolate of *H.influenzae* type b was resistant to ampicillin and chloramphenicol and was a beta-lactamase producer.

III.3 Previous history of antibiotic therapy and serum bactericidal activity of the hospitalized children had a significant correlation, reflecting on the low rate of culture positivity among these children. Blood culture outcome and serum bactericidal activity also had a significant correlation. Although such a relationship was established, negative parental reporting regarding prior therapy and blood culture outcome did not correlate significantly.

III.4 Antigen detection in the serum from children hospitalized with acute lower respiratory tract infection gave variable results with regard to various assay methods applied. Commercial kit based on latex agglutination gave a low sensitivity of 15%, but a high specificity of 99%. It had a low positive predictive value (60%) but a high negative predictive value (94%). *H.influenzae* coagglutination assay revealed a sensitivity of 8.5% with a specificity of 99.6%. It also had a low positive predictive
value of 80% and negative predictive value of 86%. Antigen detection using
*S. pneumoniae* coagglutination assay method gave a very low sensitivity of 4.4% and
high specificity of 99.6% was achieved. Positive predictive value was found to be
low like the other two assays and the negative predictive value was 86.8%. These
results do not favour the use of antigen detection assays to confirm the diagnosis of
acute bacterial lower respiratory tract infections. A test done to rule out bacterial
pneumonia based on the high negative predictive value does not seem attractive
considering the cost effectiveness of such tests in the developing world. However,
with a positive predictive value between 60 to 80%, these assays can be improved
with regards to their sensitivity if it is to be used as a diagnostic aid in ALRI.