CHAPTER 2

REVIEW OF RELATED LITERATURES

2.1. General consideration of risk factor studies

Acute respiratory infections(ARI) are widely recognized to be the most important cause of childhood morbidity and mortality, especially in developing countries. As a result the World Health Organization has urged its member states to accord high priority to research directed to the development of simple and effective methods for their treatment and prevention. There is however no agreed protocol of methods for research into ARI although plans exist for projects in various parts of the world. It is clearly highly desirable that the methods used allow international comparisons to be made. An important gap at present is the lack of a questionnaire and clinical classification of ARI which satisfactorily meets the needs of both epidemiologist and clinician[18]. A child's health status influences the degree to which he or she is susceptible to infection. Again not all children are at equal risk of infection or to develop severity. Children live in a condition which they do not control. Most of the time they can not take care of themselves. Thus they are vulnerable in a number of ways. To seek and specify the different host related, environmental, immunological and behavioral factors are extreme difficult task. These diversified nature of risk factors, their methods of study and heterogeneity in the presentation of respiratory infections are also reflected in published literatures. It has been already pointed out that no simple classification of acute respiratory infections for international use has yet been agreed, though several have been proposed[18]. Most risk factor studies reported the risk for ARI as a whole, only a few differentiated ARI into further categories. Again when differentiated, the classification of ARI was debatable and different among studies.

One may consider that community based studies are the better ones to probe the risk factors for severe ARI. Because most of the risk factors are distributed in the community. But when comparing community studies with hospital based studies, both types yielded similar results. Moreover hospital based studies have the facility to conduct etiological studies side by side. Hospital based were more reliable in determining the cases and their management. In hospital severe cases are easily diagnosed by radiology and bacteriology and other available procedures which are always not possible in the community. Whereas hospital studies have the inherent drawback of missing some cases occurring in the community.

Another important sector of severe ARI, which so far rarely investigated in developing countries must be mentioned here. Each year a significant number of nosocomial pneumonia occur in the developing countries' hospitals. Although no data is available from developing countries, data from one developed country showed that severe ARI is responsible for 35% of all nosocomial infections in the National Children Hospital, San Jose, Costa Rica in 1982[3]. In developing countries this figure could be more higher for their mismanaged hospitals, low profile hospital efficiency and shortage of finance.

It is important to investigate risk factors along with some behavioral factors affecting the sequelae of cases. Both the WHO and national ARI programme has given importance in research in this point. Several ethnographic studies were conducted in different parts of the world according to the research protocol developed by WHO. The perceived importance to different ARI illness and mothers recognition of important signs of ARI varies widely in these studies[2]. Social health seeking behavior is also an important aspect of this type of study.

2.2. Comparison of ARI case control studies

Keeping in mind the nature of present study, a comparison was made of several published case control ARI risk factor studies which probably would demonstrate the controversies discussed, more clearly (Appendix 3). Another table given in the appendix will show a comparison among different types of studies on the risk factors of ARI and severe ARI(Appendix4). Of the five studies compared, the lack of homogeneity among them was marked and made them difficult to compare. The study site, population and subjects were different, so were the detected risk factors. Moreover ARI was classified in different ways. Severity of illness and their sequelae thus varyingly associated with different factors; host, socioeconomical, nutritional, immunological and cultural factors. The degree of association also differed with type of study, place, population and study site. Therefore it could be useful to consider them individually;

2.3. Review of the important risk factors

2.3.1. Mortality as a proxy of severity of ARI:

As mentioned earlier most of the ARI deaths are due to its severity or it's complications. So mortality studies were carried out as a proxy of severity of the disease and to find out the risk factors involved. In the community studies reviewed, the lack of consistency in the inclusion of the diseases causing death from ARI was striking. In 10 studies, deaths due to ARI were not further differentiated even anatomically. ALRI, when where specified, mostly referred to deaths from pneumonia[19]. One study classified ARI under the heading "symptoms, signs and ill defined diseases". The validity of the causes of death surely depends on the validity of the diagnosis. Most of the studies measured factors by verbal autopsy. Sensitivity and specificity of the criteria used in verbal autopsies depend not only on their own characteristics but also on the capacity of the family to notice and report the symptoms. Variation in clinical case definition and their poor validation may sometimes give the idea of the nature of the severity of ARI, but did not confirm the cause of death. A number of risk factors for death were identified but this did not differ between children whose death was ascribed to ALRI and those whose death was attributed to other causes. It is possible that, in the study community, none of the variables that were investigated are true risk factors for death from ALRI. It is also possible that the proxy markers derived from the risk factor questionnaire were non specific for the risk factors they were purported to measure[20].

In a Brazilian study the authors concluded that the case control approach of mortality study may miss factor like VIT A deficiency, stage of malnutrition and feeding practice totally or fail to measure accurately, which might have been affected by the illness itself[21].

2.3.2. Demographic factors

A). AGE

Severe ARI as a part of ARI is more marked in infancy. In a meta analysis arranged by Board on science and technology for international development (BOSTID) of National Academy of sciences National Research Council, Washington D.C., concluded that LRI are higher in younger than in older children in all studies. Risk factor analysis enhances these findings; in all studies the incidence of ARI were higher in children < 18 months of age no matter what the other characteristics were[22]. In another comprehensive study published by the World Bank, the authors stated that age was inversely related with the incidence and severity of ARI[11]. However the specific age group particularly vulnerable to severe ARI varied in different studies. While a good number of studies reported the highest incidence of ALRI and pneumonia in < 5 months age group, some studies identified age 6 - 11 months as the most vulnerable[23,24]. Studies in several developing countries have demonstrated that pneumonia occurred 1.5 to 1.8 times as frequently among infants as among children 2 to 4 years of age[25]. Conversely in Guatemala, the investigators identified age 6-23 months as the risky group[26]. The differences in these studies were probably for the variation in their study design and objectives. Sometimes children were grouped in such a way that the groups were either very broad or too small to compare among studies. Whether these finding were true differences or difference due to study design or statistical flaws remained to be speculative.

B). SEX

There is slightly increased incidence of both overall ARI and severe ARI among males[1,22,27], although female children have been noted to have higher case fatality ratio in some countries, probably due to poorer access and quality of care during illness episodes[23]. In BOSTID analysis this difference was marginal although this figure could be very high in Bangladeshi context. In a hospital based study in Bangladesh, the researchers reported the male preponderance upto 64% of all cases[22,28]. This fact is also supported by a rural community study conducted by International Center for Diarrhoeal Disease and Research (ICDDR,B) in Matlab area in Bangladesh. They concluded that among children 1-11 months, more female died than males due to ARI[17]. This again supports the hypothesis; the sociocultural believes and health care seeking practice play an important role in modifying the disease process and its sequelae.

2.3.3. Nutritional factors

A). Nutrition: Birth weight, Weight for age

Poor nutrition lowers both systemic and local defenses against ARI, including the reduction of the effectiveness of epithelial barriers, systemic immune responses and cough reflexes. Nutritional status is inversely related to both the incidence and the case fatality ratio for pneumonia. In Costa Rica, in a longitudinal study the investigators followed two groups of malnourished and normal weight infants for 54 consecutive weeks. The incidence of total ARI episodes was similar in two groups: However in malnourished children, respiratory infections were of significantly longer duration and the likelihood of pneumonia was 12 times higher than in normal weight children[29]. The frequency of pneumonia and hospitalization in malnourished infants were 71% and 32% respectively, compared to a frequency of pneumonia of 65 in normal infants who had no hospitalization. A hospital based study in Philippines compared the frequency of ARI complication and case fatality rates in malnourished and normal children with the use of weight for age classification[30]. The case fatality rate among the children with severe malnutrition was 27 times higher (14.5%) than that among normal children (0.6%). Similarly a seven fold increase in mortality was noted in children hospitalized with pneumonia in Cali, Colombia[31]. The cited studies did not use comparable anthropometric methods, thus limiting the comparability of the available data and our understanding of the effects of mild and moderate malnutrition as a risk factor for ARI and severe ARI. The combined analysis of BOSTID revealed a stronger association between lower percentile for age measures and higher rates of ARI and LRI in older children than in children < 18 months of age[22]. Smith et al in their longitudinal study marked a higher incident rate with low weight for age and ALRI with no evidence of cutoffs above which nutritional status had no effects. Marginal or no relation was found with height for age and weight for height[32]. Heywood reported a tendency for wasted children to suffer more severe disease[33]. A very clear relationship between severity of ARI and weight for age was reported by Lehman et al in patients admitted to hospital. Children who died from severe ARI were considerably lighter than those who recovered, however weight for height was not assessed[34].

Studies elsewhere have generally found malnutrition as a risk factor for LRI, but little or no relationship was found with URI. Tomkins et al in the Gambia found no relation between prevalence of any respiratory illness and anthropometric indices although diarrhoea and fever were both associated with low weight for age[35]. Tupasi et al in Philippines could not demonstrate an effect of weight for age on incidence of all respiratory infections but found an effect on ALRI fatality[30]. Neither Tomkins et al nor Tupasi et al reported the effect of malnutrition on infection in lower respiratory tract particularly[30,35].

Low birth weight (LBW), is seen in 20-50% of infants in many developing countries, also increases the risk and case fatality ratio of ARI. In Haryana, India Datta et al in a prospective case management intervention study compared the incidence of severity of ARI and case fatality ratio (CFR) for lower respiratory infection (LRI) in LBW (<2500 gms) and normal weighted infants. LBW infants experienced the same respiratory illness attack rate as normal weighted infants in the first year of life (4.65 vs 4.5 episodes) but had a much higher CFR (24.6 vs 3.2 per 100 episodes)[36]. Also in Brazil, Victora et al in their case control study found that a birth weight of < 2500 gms was associated with increased mortality from respiratory infections, and this relation persisted after adjustment for parental income, education and employment status[37]. These data suggest that low birth weight children do not experience higher rate of respiratory illness, but do experience more severe infections. Confounding from other factors affecting the LBW are quality of maternal care, gestational factors, crowding etc were not adjusted in these studies and recognized as difficult to assess their effect on low birth weight.

B). **Breastfeeding**

In developed countries breastfeeding exclusively in early infancy appears to be clearly protective against the risk of acute otitis media but perhaps not against other types of respiratory illness, specially severe ARI[38,39]. But in Gambia Francisco found, no relation between breastfeeding and the risk of ARI mortality[40]. In developing countries gathered evidence support the protective effect of breastfeeding. In Brazil Victora et al documented that completely weaned infants ran the risk of 3.6 times of ARI mortality than continued breastfed infants[41]. Similar results were also reported from

Rwanda[42]. But whether the protective effect of breast milk is from its conferred anti infective properties, improved hygiene or from nutritional factors and better parental care per se is not entirely clear. Nonetheless improved hygiene is more likely to protect against diarrheal disease than the respiratory infections. And literature suffered from wide variation in definitions of feeding practice and types of ARI. A summarized review by Jason in this regard failed to document any protective effect of breastfeeding[43].

C). Vitamin A deficiency

The importance of vitamin A in maintaining the integrity of mucosal surfaces as well as in ensuring compliment cell mediated immune responses has led to a critical evaluation of its protective effect against ARI. Sommer et al demonstrated that in the clinically vitamin A deficient group mortality rate was 8.6 times higher than non xerophthalmic group[44]. Although causes of death were not documented. In two placebo controlled vitamin A intervention study showed reduction of respiratory illness in one, but failed in another[45,46]. In Thailand the investigators found that supplementation of vitamin A offered some protection against ARI, but this varied with age and length of follow up, probably due to small sample size[47].

In most of the cases the impact of Vitamin A deficiency on severe ARI was not assessed.

2.3.4. Immunological factors

A). Immunization

By routine immunization four major highly communicable diseases which are associated with severe ARI can easily be prevented. Two other conditions associated with measles viz bronchopneumonia and laryngotracheobronchitis can also be prevented. Non compliance with childhood immunization has been demonstrated as an risk factor for severe ARI. Apart from preventing target diseases it is postulated that routine immunization may confer some nonspecific immunity against common respiratory pathogens. On the other hand failure to vaccinate the child could be an important index of quality of parental care for the child[48]. Both failure to vaccinate and incomplete vaccination appeared in the literature as risk factor for severe ARI. Recently Naunchan et al in Thailand in her case control study noted that incomplete immunization for age was associated with development of URI (OR 3.39, 95% C.I. 1.5-7.31) and LRI(OR 2.93, 95% C.I. 1.21-6.80), but incomplete immunization was not further classified in this study[48]. Investigators in Argentina differentiated this into incomplete DPT and incomplete measles. They noted that risk increased with incomplete DPT 4 times than completed group, while incomplete measles had only marginal effects[49]. Conversely in Uruguay lower immunization rate(28%) did not increase the rate of ARI[50]. However the prevalence of these preventable diseases in the cited areas might have role on the results.

B). **Recurrent and concurrent infections**

Previous infections and recurrent exposure to respiratory pathogens may increase susceptibility to ARI. Other diseases also increase the risk. Infection with HIV can lead to opportunistic respiratory infections including episodes of bacterial pneumonia[4]. History of concurrent ARI in the family and recurrent ARI in the index subject were investigated in many studies. Also a relation of ARI and diarrhoea had been established in Dhaka, Bangladesh. In a case control study in Adelide Australia, it was shown that children who had frequent respiratory illness were 11 times more likely to experience bronchitis, bronchiolitis or pneumonia in the first year of life than children who experienced low level of morbidity[51]. After adjusting for other factors the relation remained strong (OR 9.5, CI 5.5-16.6). Bronchopneumonia is one of the important complication of measles. Upto 15% of ARI deaths were found to be associated with measles in studies in Papua New Guinea and Bangladesh. Children who had recovered from measles might also be at increased risk of infections during subsequent months[4]. Similar data was reported from different retrospective and prospective studies suggest that chest infection in early infancy may predict subsequent levels of respiratory infection morbidity at least in childhood[51]. In a matched case control study in Argentina, the investigators reported significant relationship of bronchial hyperactivity, presence of persistent ARI symptoms and concurrent ARI in the family with ALRI[52]. Similarly Rahman et al found a relation between concurrent diarrhoea and LRI but not with URI[53]. However all these analyses did not entirely disentangle acute from chronic morbidity, nor did they address the etiology of symptomatology, i,e, whether it was infective or non infective. Whether childhood respiratory infections act as a marker for genetically programmed subsequent respiratory morbidity or whether act as a true risk factor remained to be investigated. Of course allowance for poor socio economic condition, nutrition, low birth weight, state of immunization, crowding and air pollution should always be considered.

2.3.5 Environmental factors

Environmental conditions that may increase a child's susceptibility to severe ARI include exposure to smoke, crowding and dampness or chilling. Many of the studies in this field suffered the flaw of small sample size or failed to clear that the effect was due to that particular factor under investigation. As yet there have been no studies which have explored the impact of specific environmental modification on respiratory illness, in under five age group.

A). Indoor air pollution

It has been estimated that about 30% of urban household and 90% in rural areas use biomas material for the source of domestic energy in developing countries[4,54]. Usually in Asian countries people use traditional stoves that burn wood, agricultural wastes, manure, kerosene and other carbon based fuels in their domestic living areas. In these homes indoor air pollution level are almost 20 times than in homes in developed countries[4]. Studies from Nepal, Zimbabwe, South Africa and Argentina have reported high incidence of respiratory illness among young children living in such condition[4,54]. A semi quantitative epidemiological study in Nepal by Pandey et al reported a direct relation between the incidence of ARI and the number of hours an infant spent near a stove[55]. Two follow up study in the same area confirmed the findings subsequently. With coal burning it was estimated in a case control study that the children exposed to coal smoke decrease their SIgA in saliva by 32.5% and activity of lysoenzyme by 17.3%[54,56].

B). Smoking

A substantial body of data exists for risk of ARI with exposure to passive smoking[44,49,50]. The association is stronger for infants and for children whose mothers' smoke[57]. Data on 4000 Brazilian children followed through the first year of life, showed a 50% increase in pneumonia episodes referred to hospital among children with parents who smoked, as oppose to children with parents who did not smoke[4]. Negative reports have also been reported, but have been found to be criticized by factors such as small sample size or did not report effect on below 2 years children[58].

C). Crowding

Because most of the severe respiratory infections are contagious disease, general condition of crowding favor their propagation. In Brazil, household with three or more children were associated with more than twice as many deaths from pneumonia[21]. Similar association was reported for the density in the sleeping quarter of the child[21]. But no relation was found between these factors and ARI in a Gambian study[20]. It is to be noted, in either cases ARI were not classified into further categories.

D). Chilling and dampness

It is a popular belief that chilling and dampness increase the risk of respiratory illness. Some studies showed winter peaks for ARI, but this was perhaps due to increased crowding than the climate[22]. Despite increase exposure to cold and dampness in rural areas in developing countries, the incidence of ARI and its severity is much less than in the urban areas.

2.3.6 Socioeconomic factors

Socioeconomic status(SES) has been measured in a number of different ways, including level of income, parental education status and with an emphasis to maternal factors such as mother's age,marital status, occupation and the time she spent in caring the child. Nonetheless it has been clear from many studies that, no matter how it is measured SES is associated with high incidence of ARI. In Columbia and Papua New Guinea it was found that young mother with young child are 3-4 times at risk of developing LRI, but not URI than the older mothers[22]. An inverse relation was found with maternal education and LRI in Uruguay, but this finding was not consistent among other studies[22]. Tupasi et al confirmed that SES within developing countries predict risk of ARI, but were unable to separate out the effects of factors such as malnutrition, immunization status and crowding.

2.3.7 Knowledge and practice

Another important area that needed further researching was the role of cultural and behavioral patterns in these risk factors. Understanding the social and cultural context is essential if interventions are to be successfully introduced. Many people do not believe that ARI is transmitted through germs; rather it is thought to be caused for example by spiritual condition. Education about changing behavior must make sense within local belief system[4,16].

Two factors have been detected so far important in the development of severe ARI. Failure of mothers to recognize the important signs of severe ARI and the failure to bring their child to physician, and delay in seeking care due to other reasons like financial, initial traditional home care etc cause every year a high toll on the mortality of children under five years. In a focus ethnographic study carried out in Bangladesh by Mitra and associates reported that one forth of the children with pneumonia and 17% of the severe pneumonia had not received any treatment for more than two days and 18% of the pneumonia and 12% of the severe ARI cases had not received any treatment during last month[16]. Fast breathing and chest indrawing were recognized by 25% and 30% of the urban slum dwelling mothers respectively. Only 12% out of them thought that a child with first breathing should be treated first at a hospital. About 55-75% of mothers would treat their child at home initially. Home made remedies was the first choice of drugs in 60-73% of cases[16]. Similar or varying results were reported from through out the world. Although FES studies are semi quantitative and can not prove an association statistically, yet they are very efficient to give an inside view of the society within a short span of time.

It is true that advances have been made since the initiation of ARI studies, and during last two decades in different parts of the world, but in Bangladesh the progress is very slow. A handful of researches which were published in this regard were not properly structured and the information obtained from them were questionable. Therefore it is urgently needed to identify and prioritized the important risk factors of severe ARI amenable by intervention, before many lives are lost, much is spent. Virtually in all areas reviewed above further data are required; also is required to explore a few other factors which could emerge as strong risk for severe ARI and which are particular in Bangladeshi context.