CHAPTER 3

METHODOLOGY

3.1. Research questions

3.1.1. Primary question

What are the risk factors associated with severe ARI in children under 5 years of age in an urban Bangladeshi community ?

3.1.2. Secondary question

What are the clinical outcomes of severe ARI patients even when admitted in hospital for treatment ?

3.2. Research objectives

3.2.1. General objective

To seek information on certain factors and to find out whether they are associated with the development of severe childhood ARI.

3.2.2. Specific objectives

A). To find out if there is any association between several risk factors and severe ARI in children under five years of age in an urban Bangladeshi community.

B). To assess maternal knowledge of and practice in case of ARI.

C). To register information on the clinical outcome from the severe ARI cases admitted in the hospital till their discharge or other sequelae.

3.3. Hypotheses

3.3.1. When compared with children having non severe ARI, children with severe ARI are more exposed to a list of factors which includes: malnutrition, low birth weight, lack of breast milk, crowded living place, indoor pollution, incomplete immunization and either having concurrent diarrhoea or history of recurrent ARI.

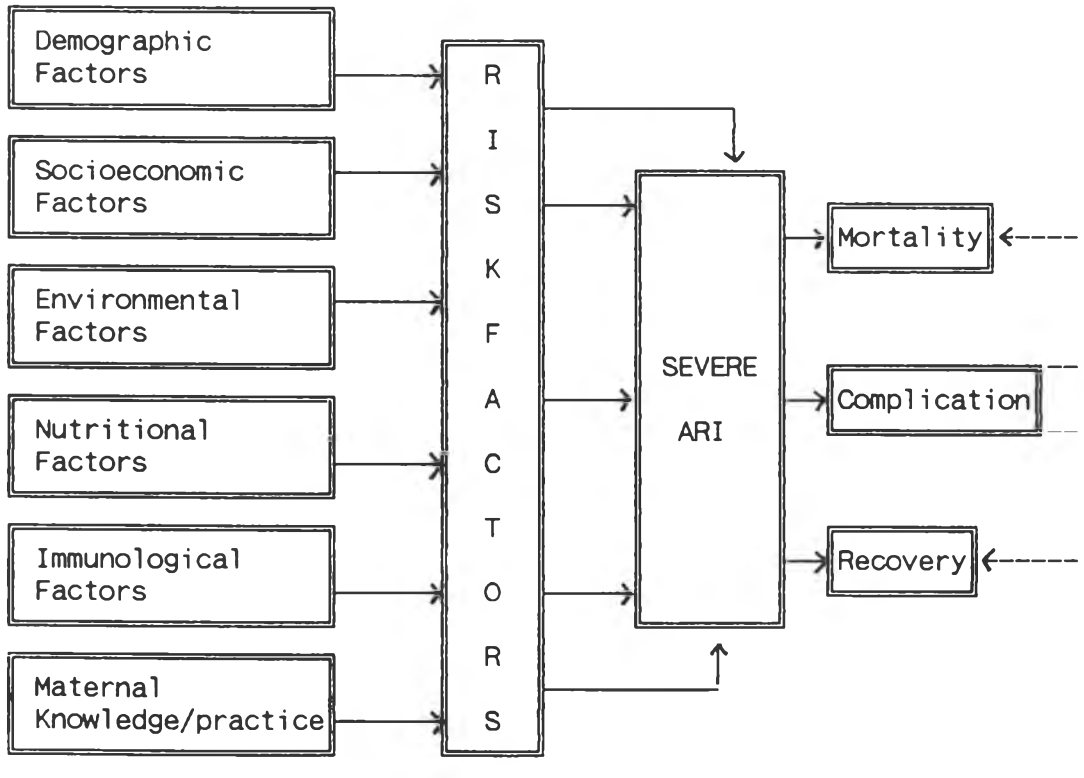
3.3.2. Lower maternal age, education and occupation, low family income, poor parental care and history of allergy as well as type of treatment offered and delay in initiating treatment increase the risk of severe ARI.

3.4. Conceptual Framework

Almost all ARI deaths in young children are due to its severity, mainly pneumonia. Present evidences indicate that in developing countries bacteria play a major role in producing severity in contrast to developed countries where maximum cases are viral origin and comparatively non severe[22,59,60]. Both etiological studies and information on the prevalence of nasopharyngeal carrier of pathogenic bacteria support this fact[22,59]. The question very frequently faced by health personnel is why some of the patients follow and develop severity of the disease, when millions are getting say, cold (Non severe ARI) and getting cured every day ? It is now apparent that large number of pneumonia cases and deaths due to severe ARI in the early childhood has often

under estimated or misunderstood, which could be the sequelae of individual or interaction of several factors like inherently related with host, environment where he lives, the family and society where he belongs and grow, and the health system which provide him the care. This study has an intention to identify these factors and if possible to specify their role in producing severe ARI.

FIGURE 1
CONCEPTUAL FRAMEWORK



3.5. Research design

3.5.1. This study followed the unmatched case control design which was hospital based and the control subjects were selected along with the cases attending the same center.

A prospective cohort design could have been the ideal one to determine a causal relationship between one event and exposure, specially to characterize the temporal relation with effect. But to answer the present question it required considerable amount of finance, manpower, time and organizational backup to conduct the research. Besides several hospital based case control studies in different parts of the world were successful to identify risk factors of ARI[37,49,52]. The association and strength of them observed by these studies were consistent with the findings of other cohort and other type of studies. Recently these type of studies are encouraged by different world bodies like World Bank, WHO and UNICEF[7].

3.5.2. Justification of case control design

The chosen unmatched case control design had some methodological advantages over other designs in this present study. Apart from this, the uncertainty of financial assistance anticipated to be obtained favored to choose this design. For example the inherent properties of a case control study were applicable in this situation were;

A). Comparatively easier to conduct.

B). Less expensive.

C). Applicable when multiple factors were selected.

D). Allows small sample size.

E). Previous records of the subject can be used.

F). If the outcome event was not rare, could be finished within a considerably short period of time.

G). Concurrent control group to compare.

H). Can give good estimation of strength of association of factors under study.

The decision of unmatching was favorable for this study. Because the factors under study were multiple in number and as well as the nature of the confounders were not fully known.

Moreover, particularly in this study, the case control design allowed the advantage to define and admit the severe ARI cases in the hospital, which were usually alarming to general public concern. AT the same time it facilitated to follow them up closely for their outcome and to perform the investigations like complete blood count and chest X ray to answer the secondary question.

Considering all these, this design was well suited both from the methodological angle to answer the research questions and feasibility point to conduct the research possible. Along with these the main instrument of the research 'the questionnaire' was administered by interview and the mother respondents of the subjects were at hand for interview.

3.6. Definition of cases

Cases were patients under 5 years of age diagnosed to have severe ARI while attending the ARI cell of Dhaka children hospital fitted the eligibility criteria of this study.

Severe ARI was defined as the respiratory illness in under five children with cough and fever with or without wheeze and the presence of at least one of the following signs: Severe chest indrawing, rapid breathing (RR > 50/minute), stridor in calm child, unable to drink, drowsiness or convulsion.

3.7. Definition of controls

Controls were children under five years of age diagnosed to have non severe ARI while attending the ARI cell of Dhaka children hospital and fitted the eligibility criteria of the study.

Non severe ARI was defined as the respiratory illness in children under five years who had cough and fever with or without wheeze and had any one of the followings: running nose, blocked nose, earache with or without discharge, pharyngitis with or without cervical nodes and the absence of any signs of severe ARI[*]

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[*]Children under 2 months may sometime present without fever and with mild chest indrawing. This has been considered in the referred WHO manual. Please see appendix 2.

3.8. Research methodology

3.8.1. Setting

This study was conducted in the one of the largest paediatric hospital of Dhaka, the capital city of Bangladesh. Dhaka children hospital had the catchment area of the biggest urban slum and middle class dwelling of the city. Moreover this hospital offered the best tertiary treatment as well. So patients coming here represented all most all walks of Bangladeshi population. At the same time the routine practice of this hospital was convenient and feasible for the study, as this center provided an adequate pool of potential subjects required for this study.

3.8.2. Population and sample

Children under five years of age with varying degree of ARI who attended the Dhaka shishu (children) Hospital, were selected in this study by using the consecutive sampling technique. Given the practical constraints of this study, financial limitation and restriction of time this sampling procedure was deemed to be the most suitable and feasible for this study. Non probability sampling was sometimes the most convenient way of sampling procedure when the factors under study are multiple and widespread in the population and the anticipated working days were limited.

3.8.3. Method of selection

Dhaka children hospital outpatient service used to work through 8 AM to 2 PM in the day from saturday to thursday of the week. All patients with any respiratory illness were usually guided to ARI cell situated here. The normal routine was to single out the severe cases for admission and non severe subjects for advice or home management. Non severe cases were also advised to revisit after two days. In case of failure, a health assistant used to follow them up in the community. The method proposed in this study was exactly suitable to this routine. So the selection of cases and controls was quite straight forward. The details of selection of cases and controls has been described in the data collection portion of this paper (please see section 3.17).

3.9. Possible sources of bias

3.9.1. Sampling bias

The probable source of bias in this case control study could be the sampling bias, if the cases and controls were not selected properly as the true representation of the target population. To overcome this several measures were taken:

A). Cases and controls were selected in the same way to minimize the selection variation.

B). Explicit definition of the cases and controls were given and suitable eligibility criteria had been set up

to get the true representative as well as adequate sample size.

C). Since both the cases and controls were selected from the same population, hopefully it would minimize the sampling bias.

3.9.2. Measurement bias

To avoid and keep the measurement bias as minimum as possible following steps were taken:

A). This study utilized the clinical classification of ARI developed by WHO, which was now the national program for ARI control and which had been registered as having high sensitivity and specificity after extensive trial and field study[60].

B). The personnel involved in this study had an intensive training and a mock study had carried out with their participation before the study began.

C). The main instrument in this study, the questionnaire was standardized by several testing and subsequent modification along with multiple expert opinion.

D). Throughout the study one trained physician performed all necessary measurement and interview. There was one pathologist and one radiologist who reported the blood count results and the X ray results respectively.

E). The research team was ever vigilant and there was arrangement of regular supervision.

3.10. Eligibility criteria

Inclusion criteria

1). Children under 5 years of age with any degree of ARI.

2). Children who lived with the family and whose mothers were alive.

Exclusion criteria

1). Isolated child.

2). Congenital heart disease.

3). Heart failure.

4). Chronic lung diseases.

5). Any conditions require antíbiotic therapy except ARI.

6). All the preventable diseases for which the current immunization program was going on were excluded.

3.11. Sample size calculation

The number of subjects included in this study of disease exposure relationship was a fundamental consideration in planning the research. The number should be large enough to detect an association if it existed (Power) and the allowance for chance was less than 5% (significance).

A sample of 180 cases and 180 control were selected for this unmatched case control study. The sample size calculation was done with the perception that the sample should be suitable and appropriate to answer the research question and the objectives of the study. Usually as routine epidemiological practice the proportions from two independent

population in an unmatched case control study, drawn samples of cases and controls are described in 2x2 tables and tested by chi-square test. So when comparing two independent proportion the following formula was found suitable to calculate sample size[61].

If p_0 denoted the estimated exposure rate among the control subjects and R denoted the estimated odds ratio (approximated relative risk) of interest, and when the level of significance(α) and Power (β) of the study was set, the formula used was:

$$n = \frac{[Z_\alpha \cdot \sqrt{2pq} + Z_\beta \cdot \sqrt{p_1 q_1 + p_0 q_0}]^2}{[p_1 - p_0]^2}$$

[In 1990 Lemeshow et al suggested using p_2 (the average exposure rate in cases and controls) instead of p_0 (the proportion exposed in the control group) in the above formula. The reason they gave for this was that the population was usually made up of many more people like the controls than it was of people with the condition or disease of interest(cases). In addition the exposure rate in controls was often known with a high degree of precision and under H_0 this was the same as the exposure rate for the cases[62]]. Putting the values of p_2, the values for p_1 and q_1 and q_2 could be calculated by using the following formula: So where

$$p_1 = \frac{p_2 R}{[1+p_2(R-1)]}, q_1 = 1-p_1, q_2 = 1-p_2$$

The estimation of p_2 came from literature. Malnutrition was considered to be the most important risk factor, as this factor was recognized to have high degree of association with wide confidence in almost all previous studies. In Bangladesh the prevalence of malnutrition in general population is more than 50%, a range of 30% to 80% [6]. Also for other important factors the prevalence in controls varied from 35% to 85% in different studies[21,37,48,52]. Moreover Victora et al estimated p_2 as 30% in their study[21]. In this study p_2 was estimated as .30, the lowest of the range to allow the maximum sample, which might intern render the study valid. Alpha was set at 5% and beta was chosen at 10%.

When α = 0.05 and two tailed then Z_α = 1.96
β = 0.10 (90% power) then Z_β = 1.28
p_2= 30% = 0.3 and R = 2, the smallest odds ratio to be detected then n was calculated as 180 subjects per group when using 1:1 cases and controls.

3.12. Measurement

This study attempted to identify the risk factors for severe ARI from a wide list of variables. The investigator was meticulously cautious to perform an unbiased measurement. The primary aim was to detect any association between these

factors and the outcome under question. So all the observational criteria for causation could not be employed, namely biological plausibility, dose and time relationship. Instead this study emphasized on the strength of association, consistency, specificity, collateral evidence if any and whenever possible to demonstrate temporal sequence.

3.12.1. Variables measured with operational definitions

A). Severe ARI which was considered as the dependent variable of ARI in this study, was diagnosed according to the clinical classification of WHO. Radiological examination was done for every selected cases as well as their simple blood count.

B). Variables which were considered as possible risk factors and independent variables in this study, can be assigned into several groups. Which might provide easier reference and understandings are as follows;

Demographic variables

1. Age of the child: This was measured in months. Months when reported after decimal had been rounded up to the next integer, with the assumption that they were already within that months' period.

2. Sex of the child: Male or female was recorded.

Socioeconomic variables

1. Age of the mother: Maternal age was measured in years.

2. Marital status of mother: Recorded as whether mother was married, separated or divorced. The idea behind was, to assess care taking pattern of the child, whether by single parent or by both.

3. Education of mother: This was measured as number of years mother studied in general education system.

4. Occupation of mother: This measured the quality of care given to the baby in terms of time spent by mother in taking care of the child. This variable enquired whether mother was house wife or working outside and the distance of the work place from dwelling as well as working hours.

5. Income: Total family income per month, an average of last 12 months preceding the interview was recorded.

Environmental variables

1. Ventilation: Ventilation of the bedroom of the child: Three scale response of good, average and poor was recorded.

2. Cooking place: This was measured as its location in the house, viz distance from child's bedroom.

3. Smoke outlet and window were enquired as merely their presence or absence in the cooking place.

4. Smoker: Number of smoker in the family was recorded.

2 5. Kind of fuel used for cooking purpose was recorded.

6. Number of under 5 years children in the family was recorded.

7. A variable noted as number of persons sleeping in the child's bedroom.

8. A variable recording the sleeping habit of the family, specially the child. Kind of bed used for sleeping was noticed.

9. Mother's report on concurrent ARI in the family in last fortnight was recorded in a variable.

Nutritional variables

1. Present weight of the child was measured in grams by a standard scale.

2. Present nutritional state of the child was estimated according to Gomez classification, which measure the weight for age[63]. This classification compare the measured weight with the standard NCHS chart of particular sex.

3. Birth weight of the child mainly obtained from maternity card of mother or immunization card of the child, and when these were unavailable by recall (Some researchers showed that mothers can accurately recall birth weights of their children)[64].

4. Breast feeding, This variable recorded the type of milk consumed by the child after birth.

5. Another variable took into account, type of breast milk given when mothers had responded to breastfed their children after birth.

6. Duration of exclusive breast feeding period was noted.

7. A variable enquired the usual feeding practice (food given to the baby) by mother during this illness.

8. Solidfood/Fluid, measured the quality and nature of food given to the child.

9. Mothers were asked whether they had stopped breastfeeding during this illness and if so, the reason for it. Mother's response was noted.

Immunological variables

1.Vaccine: Routine vaccine given to the child or not. Recorded from immunization card or recall.

2. If vaccine were given, completed for that age or not.

3. A variable measured if vaccination was incomplete, whether it was incomplete DPt or Measles.

4. Maternal report of previous ARI episodes of the child in last year was recored.

5. One variable included the type of ARI illness suffered by the child during last year.

6. diarrhoea: Maternal report of concurrent diarrhoea of the child in last fortnight.

7. Atopisity: Maternal report on any history of allergy in the family. If yes, who suffered, type of allergy and its duration.

8. Vit A Deficiency: Clinical examination report of the child for any signs of vitamin A deficiency Also it was double checked by maternal response of any symptoms like night blindness etc if presented by the child.

ARI knowledge and practice of mothers

1. Illness: The name of present illness as reported by mother.

2. A variable measured the maternal response as to any treatment had been given to the child before coming to hospital.

3. Another variable recorded If there was any treatment, maternal report on type of treatment given.

4. Total duration in days of treatment given as reported by mother was recorded.

5. Reason put forwarded by mother for coming to hospital for treatment was also recorded.

6. Clinical signs and symptoms presented by the child at interview date as reported by mother and the exact verbatim used for them by mother were also noted in one question.

7. Maternal report of signs and symptoms had present in the child on the first day of illness, and on subsequent days, were noted down in two variables.

8. Two variables measured the maternal response of any delay on initiating treatment for the child and if there was any delay, the reason for it.

9. Total duration of illness in days before coming to hospital was noted by one question.

Others

1. Investigation reports: CBC (Complete blood count) and CXR (Result of X ray chest) as reported by the pathologist and the radiologist of the study.

2. Final sequelae in cases and controls after 2nd day and after 7th day were recorded in each subject.

3.12.2. Instrument design

1. Clinical examination: It had been mentioned already that the only ARI physician of the research team performed all the clinical examination through the study. Weight was taken by the same weight machine and respiratory rates were counted by the WHO/UNICEF supplied ARI stop watch. The criteria were prefixed and pre selected. So chances of variation in clinical examination could be very less.

2. Health records: Birth weight and immunization status of the subjects were recorded from health records of the child. In case of non availability of health records data was collected by recall of mothers. In case of birth weight recall could be less precise, but in case of vaccination at

least mothers were able to tell how many times they had brought their child for vaccination.

3. Standardized questionnaire administered by interview: The questionnaire used in this study had been prepared in the proposal phase and pretested several times.

The investigator followed tediously all textbook procedure to standardize the questionnaire. A published standardized acute respiratory illness questionnaire was scarce in the literature. So a new questionnaire was prepared with the guidance of content experts in this field. An useful guideline came from the paper of prof D.H Miller of London school of preventive medicine[18]. Guidelines were also obtained from an acute respiratory questionnaire administered in Thailand[65].

Validity and reliability of the questionnaire: Items used in the questionnaire were selected from published literature. Factors which showed consistent association through studies were entered into the questionnaire as well as some exploratory variable which were thought to be worthy investigating in Bangladeshi context. Language and forms were checked and discussed over and over. Reading scale and interpretation level was tested in a small sample of mothers and subsequently improvements were made. Complex and multiple meaning questions were avoided and response scale was kept to 'yes' 'no' or simple scoring of 1 and 2. Moreover system of administration by interview was chosen intentionally to avoid

embarrassment of illiterate mothers and to avoid any ambiguity in this regard.

The knowledge and practice portion of the questionnaire were taken with little modification from the WHO FES(Focus ethnographic study) manual. To asses the reliability of this portion a consistency test(Kuder Richardson-20) was done at the preparatory phase which had a score of 7.2. The questionnaire appeared to have no problem regarding its items, source, form and language and the content was approved by the experts. Subsequently several pretesting were done and improvement after each. A mock test was carried out along with research team before being set out for data collection.

4. Laboratory tests: Throughout the study one radiologist, one pathologist performed all the blood count and reporting of chest films. Although these results were related with the secondary outcome of the study, yet there seemed to be had little variability if any.

3.13. Ethical consideration

Written consent was obtained from the hospital authority (Dhaka children hospital) to conduct the research in their facilities. The hospital ethical committee also reviewed the proposal and approved it. Verbal consent was taken from the mother respondents before interview. Treatment was not withheld in any cases. So there was no ethical problem throughout this study as had been anticipated.

3.14. Limitation

1). The primary limitation of this study was the inherent limitation of the case control design. In same variables data was collected as recalled by mothers. The lack of fund and time did not allow to recheck these information.

2). The study missed some cases coming from higher socioeconomic status and some cases get admitted in the hospital through emergency room during holidays.

3). Measurement of some factors like vitamin A deficiency, birth weight of the child could not be done very precisely.

3.15. Obstacles and strategies to solve them

1). Since no particular fund was available to conduct this research, the investigator had to compromise by allowing time to collect some personal fund to start. So there was delay in starting to collect data.

2). Severe constraint of fund also did not allow this investigator to engage enough personnel to continue enrollment everyday except for the six workdays of the week.

3.16. Administration and time schedule

1). After initial consent and other formalities were met, the director of the institute of child health was approached to be the local advisor of this investigator. This ensured cooperation, quality and solved many problems.

2). A research team was created comprising the local advisor, this investigator and the ARI physician responsible for all measurement and interview, a nurse and a field assistant. (Details of their respective duties was described in the section 3.17 in data collection portion) Monthly meetings were arranged to review the progress of the study. Regular supervision was maintained by this investigator. An intensive training was arranged for the physician before the study began.

3). The pretesting and standardization of the questionnaire started in the month of June 1995. Printing and other preparation ended by July 1995. Enrollment started from July 16th' 95 and completed by December 20th' 95.

4). For the sake of non availability of computer facilities the data entry and analysis were done in Bangkok from the month of January 1996.

3.17. Data collection

1). This study tried to follow the procedures described in the thesis proposal. In every step the investigator tried to control the quality of collection of data as good as possible.

2). After initial preparation, permission, printing and recruitment was finished an intensive training (5 Days) was arranged for the medical officer, nurse and the field assistant. They were oriented about their own tasks in this

regard. Practice with questionnaire was carried out and all the steps of data collection was revised.

3). The medical officer was in charge of examination of the child, review the health record of the child, interview the mother, filling up the questionnaire and getting the investigation and follow up report from the nurse and the field assistant.

4). The nurse was assigned to follow up the severe ARI cases admitted in the hospital, ensuring their investigations and keeping their records.

5). The field assistant was responsible for following up the non severe patients(controls) in the community when they failed to report back on the 2nd day, the usual routine day to follow up as was set earlier.

6). The whole data collection procedure including the performance of the medical officer, nurse and the field assistant was periodically supervised by the investigator as well as the advisor.

Patients with ARI used to attend the children hospital everyday and were treated under the ARI control program of the hospital. Data was collected everyday of the week except the holidays. Pathological investigations were done in the inpatient area.

7). The severe ARI patients who were eligible as cases according to criteria mentioned in the protocol were admitted in the hospital. Their mother respondents were

interviewed by the project medical officer after verbal consent and then collected data was recorded. Those who were taken up in the study as control subject were examined clinically, weighed and other information from health card were noted. These patients and their mother respondents were requested to report back after two days for follow up. Sometimes vitamins were given as incentives to ensure their return. The mothers whose children were found to be cured on follow up day, were interviewed and data was recorded. Those who failed to report on second day, were subsequently followed up in the community by the health assistant and their condition were recorded. During follow up visit in the community the health assistant asked the family to revisit the hospital on next day. The mother respondents of cured controls were interviewed on that day. In only a few number of occasions when the mother refused to come to hospital, the medical officer had gone to their home for interview.

8). Treatment was not withheld in neither cases and controls. Mostly control subjects received home remedies and case patients were treated in the hospital mainly with co-trimoxazole tablets. Some case subjects were given amoxycillin and parental penicillin.

9). The questionnaire was updated and standardized before use (pl.see section 3.12.2). A precoded record file was created using the EPI INFO5 program. All data collected was entered in this file. When data entry was finished, validity

and the quality of data entry was checked by variable wise data checking, comparing with original questionnaire data collection sheet. Several re-checking was done.

3.18. Data analysis

1). The initial analysis of data was done by computer, by using a software program "EPI INFO (Version 5)" developed by the Global Program on AIDS/World Health Organization, Geneva, Switzerland meant for general use. Subsequent analysis and multiple logistic regression was done by using the software Spss/PC+.

2). A frequency distribution of variables was done to see the general distribution of them. Subsequently distribution of variables among case and control group was observed. Several 2x2 and 2xk tables were made.

3). To mark the crude exposure of the factors under investigation odds ratios were calculated for each variable from 2x2 tables. Ninety five(95%) confidence interval of the observed odds ratios were calculated.

4). Chi square analysis was done to see whether the obtained results were significant or not. This result was expressed all through the study at a level of 5% ($p < .05$) as significant. A continuity correction (Yates correction) was done for each chi square value.

In some instances Fisher's exact test was done, if the expected value in any cell was less than 5. All values had a two tailed probability.

5). This study also took the facility of finding consistency of the odds ratio after adjustment. So stratification was done during analysis, whenever felt necessary and ultimately a multiple logistic regression model was used to determine whether the crude odds ratio alter its magnitude after adjustment or not. In order several important variables which were found to be significant in univariate analysis and thought to be probable confounder were fit in this regression model. Odds ratio and (95% C.I. of OR) significance level of them were reported.