V. SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

SUMMARY

INTRODUCTION

Measles virus is one of the most ubiquitous and persistent of human viruses causing a highly contagious disease with epidemics occurring frequently, leading to a high morbidity and mortality especially under conditions prevailing mainly in the developing world, e.g. unfavourable nutrition, high risk of concurrent infection and inadequate case management - particularly at home - which favour the development of complications and an adverse outcome.

WHO recognises measles as the most common communicable disease affecting virtually 100% of the unimmunised children, in the developing world between the age of 6 months and 3 years (326). Measles is the most common vaccine-preventable illness and vaccine-preventable cause of death in preschool children (308). In India, it is recognised as the third leading cause of death in 1-4 year old children and almost all children suffer from the disease by the age of 5 years (68). It is sobering to realise that with the availability of a highly effective and thermostable vaccine (184,307), these deaths could be prevented if measles protection were available to all children before they experience the natural disease.

However, measles appears to be a masked and neglected public health problem and very few studies are conducted up-till now to assess the incidence of mortality and morbidity related to the disease and to understand the epidemiology of measles in the free-living populations (68). Sufficient data is still not available to determine the optimum age for measles immunisation. Due to technical limitations in most of these studies, measles antibody titre had variable lower limits (19,68,106,138,157,158,282,294).

The present research was thus an attempt to study -

(i) the epidemiology of measles in the slums of Vadodara city (Epidemiological study),

(ii) the correlation between maternal and cord blood measles HAI antibody levels vis-a-vis birth weight, maturity and sex of the newborn (Maternal vs. cord blood study),

(iii) the waning of passive measles immunity (Waning of passive measles antibody study), and

(iv) the efficacy of measles vaccine at various ages, so as to suggest the optimum age for measles immunisation (Seroconversion study).

MATERIAL AND METHODS

The study was divided into two major groups -

I. Epidemiological study

   A. Baseline survey
   B. Follow up survey

II. Serological study

   A. Maternal vs. cord blood study
   B. Waning of passive antibody study
   C. Seroconversion study
   D. Methodology

I. EPIDEMIOLOGICAL STUDY

The city of Vadodara has 8 wards. All slums under each ward were listed. A total of 15 slums, each having a population of less than 1000, two from each ward, were randomly selected (except ward number 1, where the only slum was included in the study) (Fig.7).

A. Baseline Survey

A baseline survey was conducted in 15 slum areas of Vadodara city during the month of January 1983, a peak season for measles epidemic.

Demographic data

A total of 1754 families were surveyed and recorded by a house-to-house survey (Annexure:1). In the study area, there were 1581 children in the age group 0-6 years. The birth date, weight and vaccination status of each child were recorded. The age of the child and vaccination status were confirmed from the birth records given by the Corporation Health Authority or from the ICDS Anganwadi Card or from the parents. The children were weighed using a Salter spring balance which was checked frequently for accuracy. The nutritional grading was done as per IAP Classification (Annexure:2).

A history of measles disease during the preceding 10 days was elicited. The specific symptom complex of the disease and the nature and mode of the spread of the exanthematous lesion were inquired into to confirm the diagnosis of measles. A total of 200 cases were identified and recorded separately (Annexure:3). The beliefs regarding causation, rituals observed and treatment taken, if any, for measles disease were inquired into and recorded.

B. Follow up survey

Within 4-6 weeks of the first visit, all the recorded cases of measles were followed up. Of the 200 initial cases, 185 children could be contacted and recorded in the follow up study. During the second visit, the children were weighed and measles-related complications, if any, were inquired into and recorded. The diagnosis of the complications was made on the basis of detailed information about symptoms, signs and treatment taken, if any, for the same.

II. SEROLOGICAL STUDY

The study group consisted of newborns, their mothers and children attending the outdoor patient departments or admitted in the Pediatric Wards of S.S.G.Hospital and B.A.G.Hospital, Vadodara.

A. Maternal vs. Cord Blood Study

A total of 187 paired blood samples (2 ml each) from the mother and cord were collected at the time of delivery. The samples were designated to four subgroups, as per maturity and birth weight of the newborn, as follows -

(1) Full term adequate for gestational age (FTAGA)
(2) Full term small for gestational age (FTSGA)
(3) Preterm adequate for gestational age (PTAGA)
(4) Preterm small for gestational age (PTSGA)

The weights were taken on the Detecto horizontal bar infant weighing scale with minimum calibration of 25 gm. The maturity was determined after 24 hours of birth by the method described by Dubowitz (79). The observations were recorded in a proforma (Annexure:4).

B. Waning of Passive Antibody Study

A total of 623 blood samples (2 ml each) were collected randomly from children (0-6 years) to determine the passive measles haemagglutination inhibition (HAI) antibody seropositivity at different ages. Children with any acute illness or fever at the time of observation, a prior history of measles or measles vaccination, or a contact with a patient suffering from measles in the preceding two weeks, were excluded from the study. The age, sex and address of each were recorded. The age was recorded in number of completed months. Each child was weighed and the nutritional status was assessed according to the IAP Classification (249) (Annexure:2)

The children were designated to 9 subgroups according to their age (months).

(1) 0
(2) 3-5
(3) 6-8
(4) 9-11
(5) 12-14
(6) 15-17
(7) 18-20
(8) 21-23
(9) 24-72

C. Seroconversion Study

A total of 327 children in the age group of 6-72 months, who were eligible for measles vaccination were included in the study. The weight, sex, address, nutritional status, time of vaccination and dates of blood collection (pre- and postvaccination) were recorded (Annexure:5). They were divided into seven subgroups according to their age (months) at the time of vaccination.

(1) 6-8
(2) 9-11
(3) 12-14
(4) 15-17
(5) 18-20
(6) 21-23
(7) 24-72

The blood samples (2 ml each) were collected from each child twice - once on the day of vaccination and a repeat $\geq$ 4 weeks after vaccination. The Schwarz strain of further attenuated, lyophilised freeze-dried vaccine (Rouvax-Merieux, France or Rimevax-Smith Kline RIT, Belgium) was used in the study. The cold chain was maintained scrupulously. A dose of 0.5 ml of reconstituted vaccine was administered subcutaneously on the anterolateral aspect of the left thigh. The potency of the vaccine used was tested randomly at the Central Research Institute (CRI), Kasauli, Himachal Pradesh and was reported to be in the range of 2000 to 3000 $TCID_{50}$ per dose.

D. Methodology

The haemagglutination-inhibition (HAI) test, as described by Saha SM, CRI, Kasauli (281) was used. The author underwent a training at the CRI, Kasauli, for the same.

1. Collection of Blood Samples

About 2 ml of cord or venous blood was collected in autoclaved plain bulbs. The cord blood was collected directly under sterile conditions while venous blood was drawn by venepuncture using sterile disposable needle

and syringe. The samples were allowed to clot at room temperature, centrifuged and the sera thus separated were transferred to sterile bulbs which were then stored in a deep freeze until tested.

2. Haemagglutination Inhibition Test

Measles virus has been shown to possess the capacity of adsorbing to Rhesus monkey red blood cells and causing their agglutination. This haemagglutination is readily inhibited by the specific antibody to measles. The HAI test furnishes a sensitive method for detecting measles HAI antibodies (25,34,171,311,338). This method can detect the antibody titre as low as 1:2 (356).

3. Computerisation

The data and results obtained were entered into IBM-PC-XT compatible computer system using d-base 3+ and analysed with the help of a Statistical Package for Social Scientist (SPSS) Programme.

4. Statistical Analysis of Data

1. Mean, Standard Deviation (S.D.) and Standard Error (S.E.) were calculated for all quantitative parameters.

2. Geometric Mean Titre (GMT) was considered at log base 2.

3. Percent prevalence was calculated for all qualitative parameters.

4. Chi-square test was employed to determine the significant differences amongst various age groups for the qualitative parameters.

5. For quantitative analysis :
   - Oneway anowa test was applied to analyse multiple variables.
   - Paired 't' test was used to compare differences between maternal and cord blood measles HAI antibody titres in various subgroups.
   - Independent 't' test was used to compare quantitative parameters between subgroups.

6. Levels of significance selected were -

   * = Significant at $P \leq 0.05$
   ** = Significant at $P \leq 0.01$
   *** = Significant at $P \leq 0.001$

RESULTS, OBSERVATIONS AND DISCUSSION

I. EPIDEMIOLOGICAL STUDY

The point prevalence of measles was 12.65% with the highest incidence (67%) in the 1-4 years age group. The majority (85.50%) of children suffered from measles under the age of 4 years. Of the total infants suffering from measles, 10.81% were below the age of 6 months. The measles vaccination coverage was only 2.85% compared to BCG vaccination coverage of 74.45%.

Malnutrition was higher in females as compared to males in all the age groups, it being significantly higher in the 1-4 years age group. A majority of parents (83.5%) attributed measles to a divine visit of 'Mata' or goddess while none thought it to be a viral disease. Thus, the rituals observed and treatment taken for the cure of measles were visit to the temple by the majority (87.57%) and offering prayers (18.92%). Medical treatment taken by 36.92% of the cases was always given after a visit to the temple.

Bronchopneumonia and diarrhoea were the commonest complications observed due to measles, accounting for 78.38% and 55·13% respectively of the total complications. Detrimental effect of measles on the nutritional status was observed and significant weight loss was seen in the 1-4 years age group.

II. SEROLOGICAL STUDY

A. Maternal vs. Cord Blood Study

No measurable measles HAI antibody was observed in 6.42% of cord blood samples which corroborated well with 5.30% of maternal blood samples. A highly significant correlation was observed between maternal and cord blood measles antibody titres ($r=0.49$; $P \leq 0.001$).

Prematurity and IUGR had no impact on cord blood measles antibody titre suggesting the probable passive transplacental transfer of measles antibody before 28 weeks of gestation.

B. Waning of Passive Measles HAI Antibody Study

Passive measles HAI antibody seronegativity showed a significant increase in children upto 8 months of age (from 5.59% at birth to 78.95% in the age group 6-8 months).

Similarly, a significant fall in measles HAI antibody levels (GMT) from birth to 8 months of age (from 3.14 to 0.38) was observed.

However, measles seropositivity and titre (GMT) showed a rising trend after 8 months of age suggestive of subclinical infection.

Nutritional status and sex were found to have no effect on the waning of measles HAI antibody seropositivity and titre (GMT).

C. Seroconversion Study

Seroconversion rates were significantly lower in children vaccinated at <9 months of age as compared to those in children vaccinated at ≥ 9 months of age. Seroconversion rate of 78.22% was observed in the age group of 9-72 months against only 25% in the 6-8 months age group.

An inverse relationship was observed between prevaccination titre and seroconversion rate. With a prevaccination titre $\leq$ 1:2, the seroconversion rate was maximum (82.06%). None with prevaccination titre $\geq$1:16 demonstrated seroconversion.

Nutritional status and sex of the children had no impact on the seroconversion rates.

An inverse relationship between prevaccination titre and postvaccination rise in antibody level(GMT) was observed with maximum rise being observed in the group with prevaccination titre $<$ 1:2. (4.24 ± 0.09).

Age at vaccination, nutritional status and sex of children had no influence on postvaccination rise in antibody titres.

CONCLUSIONS

1. Measles disease and its related complications constitute a major health problem, especially in the under one year age group; and the vaccination coverage is poor.
2. Irrespective of their sex, preterm and IUGR infants are as well protected against measles as their FTAGA counterparts and have similar levels of transplacental passive measles HAI antibody.
3. Irrespective of nutritional status and sex, there is a rapid increase in the proportion of measles seronegative infants and a significant decline in passive maternal measles HAI antibody titre from birth to eight months of age, thereby rendering them susceptible to measles disease.
4. A rising trend is observed, both in the number of seropositive children and their measles HAI antibody titres, after eight months of age, due to subclinical infection.
5. Satisfactory seroconversion is observed after the age of eight months, the seroconversion rates and the postvaccination rise in measles HAI antibody titres being similar in all the age groups.
6. The maximum seroconversion rate is seen with a prevaccination titre of $\leq$ 1:2.
7. The maximum postvaccination rise in measles HAI antibody titre is observed with a prevaccination titre of $<$ 1:2.
8. Irrespective of sex, both seroconversion rates and postvaccination rise in measles HAI antibody titres, are similar in undernourished and well nourished children.

RECOMMENDATIONS

1. Further research is needed to identify factors other than transplacental HAI antibodies interfering with successful seroconversion when using currently available vaccines and techniques.

2. Long term prospective studies are required in India to determine the duration of protection conferred by measles vaccine and the need, if any, for the booster dose.

3. More studies, especially in the developing countries like India, are required to evaluate alternative techniques of measles vaccine administration using different strains (e.g. Edmonston-Zagreb strain by aerosol), at various ages, so as to achieve 100% seroconversion.

4. Long term follow up studies are necessary to determine the measles immune status of the newborns of the next generation, born to the female infants vaccinated today, so as to re-evaluate vaccination strategy against measles for the future generation.