5 MATERNAL AND CHILD HEALTH

Malnutrition and infections among the reproductive age group women, particularly during pregnancy and lactation can have irrevocable effects on the infant's health. Particularly infections and ill health duration pregnancy and lactation may necessitate long-term therapy of the mother with drugs that subsequently get transferred to the infant. Exposure of the nurslings to these drugs can be potentially harmful as it occurs during their rapid growth and development phase. The extent to which these therapeutic drugs are likely to be transferred to breast milk and the nursing infant are being studied. In another study which is a part of a larger study with ICMR, the probable causes of death of both male and female in a specified population in Maharashtra are being assessed.

5.1 Model to Predict Milk/Plasma Ratios of Maternal Therapeutic (Anti-Tuberculosis) Drugs and Study of Genetic Polymorphisms in the Drug Metabolizing Enzymes (*Partly Funded by Indian Council of Medical Research under the Functional Genomics and Molecular Medicine Programme*)

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Duration: 2002-2005

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It is now well recognized that a number of drugs ingested chronically by lactating mothers are transferred to breast–milk in significant amounts and from there into the nursling. Our earlier studies have demonstrated that some of these drugs suppress activity of the infant's drug metabolizing enzymes. This is an important issue particularly in Indian context as, chronic maternal drug therapy and breast-feeding is common in the Indian scenario. Among such drugs administered chronically to breast-feeding women, anti-tuberculosis drugs are common, as the disease is highly prevalent among women in reproductive age, necessitating long-term therapy even during lactation. Their transfer potential into

the breast milk is however not known. A number of factors can influence this transfer potential viz. physicochemical properties of the drug, maternal pharmacokinetics etc. Maternal pharmacokinetics for the drugs is known to be associated with polymorphisms in the genes encoding their metabolizing enzymes. With this background, a study has been undertaken with anti-tuberculosis drugs with following specific objectives: i) To assess transfer potential of chronically administered anti-tuberculosis drugs from maternal circulation to breast milk and ii) To assess association of their pharmacokinetic pattern with polymorphisms in genes encoding the enzymes metabolising these drugs.

An "*in vitro*" culture system based on CIT3 cells for the study of transfer potential of the drugs in terms of milk: plasma (M/P) ratios was described last year (Annual Report 2003-04, p 134). For a more precise determination of the actual transfer, multiple sampling characterising the entire concentration-time profile is essential, which will also provide additional information on the variations in pharmacokinetics in these lactating women. Quantitation methods based on HPLC have therefore been set up for accurate determination of the drugs in milk as well as plasma. Fig 96 shows the dose response curve obtained with one of the drugs viz. Isoniazid. The method is sensitive enough to estimate Isoniazid as low as 0.25 μg/ml from milk as well as plasma. Emphasis during the year was also on analysis of the gene N Acetyl Transferase2 (NAT2) as polymorphism in NAT2 has been shown to be associated with decreased metabolising capacity for the drug Isoniazid. Full length NAT2 gene was amplified using flanking intronic primers. RFLP analysis was carried out to determine polymorphisms with regard to ten restriction sites spanning the entire coding region.

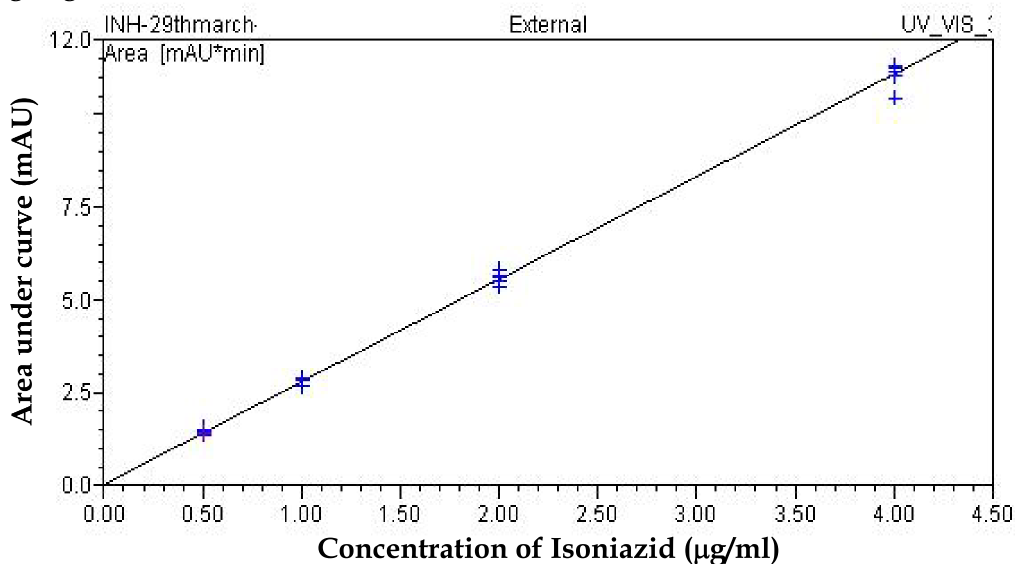

Fig. 96: Dose response curve for Isoniazid by HPLC.

Fig 97A & 96B shows restriction pattern obtained with two of the enzymes viz. Dde1 and Taq1. Analysis so far indicates polymorphism in the NAT2 gene in about 25 percent of the cases. Their association with the pharmacokinetic pattern for Isoniazid is being studied.

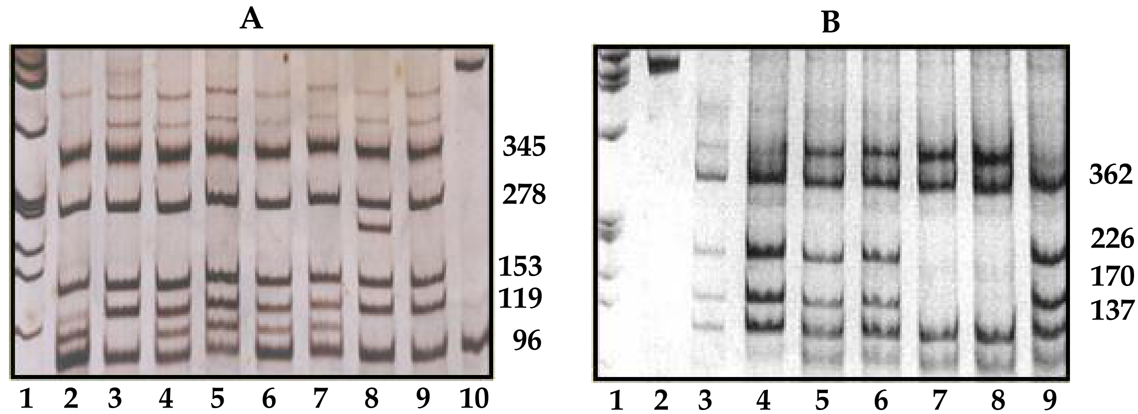

Fig. 97: RFLP screening of NAT2 gene. (A): Screening for addition of Dde1 site. Lane 1: 100 bp DNA ladder; Lane 2: Addition of Ddel site; Lanes 3-9: Wild type; Lane 10: Undigested. (B): Screening for deletion of Taq1 site. Lane 1: 100 bp DNA ladder; Lane 2: Undigested; Lanes 3-6 and 9: Homozgous wild, Lanes 7, 8: Deletion of site.

5.2 Cause of Death by Verbal Autopsy

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Duration: 2003-2005

An ICMR task force multicentre study is being conducted to assess probable causes of death in male and female population among rural and urban areas in Maharashtra, and study the socio-economic profile of the households with deaths. The study is being conducted in six selected districts - Thane, Jalgaon, Pune, Akola, Yavatmal and Bhandara. In each district data collection is carried out in two rounds with a reference period of six months. From each district, 30 villages/wards are selected from rural and urban areas by PPS sampling.

The methodology for data collection is as follows: In each population sample unit PSU (urban/rural) the population and the list of deaths was obtained from the Municipal Corporation/Gram Panchayat. In PSUs where the

population was more than 2000, the project staff with the help of ward maps in urban area and information taken from the Gram Panchayat in rural area divided the PSU geographically into five sections viz. north, south, east, west and centre. Beginning from one end the staff covered 100 households from each section. This ensured a representative sample of 500 households in each PSU i.e. approximately a population of 2000. The identification, socio-economic data and respondent's history regarding the probable cause of death were obtained. Details of the clinical signs and symptoms of the deceased were obtained in order to arrive at the most probable cause of death. The probable cause of death was then assigned using the ICD-10 codes.

In the previous annual report, data of 494 deaths pertaining to two districts, Thane and Jalgaon had been reported. The present report encompasses preliminary data on the deaths reported in all the six districts in the first round and four districts (Thane, Pune, Jalgaon and Yavatmal) in the second round. Fieldwork in Akola and Bhandara district for data collection of second round is ongoing.

As seen in Table 19, of the 1371 deaths covered, majority (89%) were adult deaths while there were only 5 percent child deaths, 3 percent neonatal deaths, 2 percent still births and 1 percent maternal deaths. Table 20 shows the clinical classification of total deaths covered.

Table 19: Category wise distribution of total deaths covered

Area	Number of deaths covered	Still births	Neonatal deaths	Child deaths	Adult deaths	Maternal deaths
Male	827	19	29	36	743	--
Female	544	8	18	33	479	6
Total	1371	27	47	69	1222	6

As seen in Fig 98 the deaths were most in the age group 60 and above both in males and females. However female deaths were more (56%) in this age group as compared to males (43%). In the age group 25-44, male deaths were more (19%) as compared to females (13%) also in the age group 45-59 male deaths were more (27%) as compared to females (13%). In the age group 0-1 (including still births) male deaths were more (8%) as compared to females (4%).

As seen in Fig 99, deaths due to diseases of circulatory system (Heart diseases & stroke) were almost equal among males and females. Deaths due to Infectious and Parasitic diseases were more in males (18%) as compared to

females (14%). Deaths due to Digestive system were more among males (8%) as compared to females (2%) as Alcoholic liver disease contributed to a large proportion of male deaths. Deaths due to Cancers & Endocrine, Metabolic & Nutritional disorders were more in females (4%) as compared to males (2%).

Table 20: Clinical classification of total deaths covered

Sr. no.	Categories of deaths	Number	Percentage
1	Circulatory system	333	24
2	Infectious and parasitic diseases	222	16
3	Injury and poisoning	131	10
4	Respiratory system	99	7
5	Cancers	83	6
6	Digestive system	84	6
7	Causes related to pregnancy and infancy	65	5
8	Endocrine, nutritional and metabolic diseases	37	3
9	Nervous system, mental & behavioral disorders	37	3
10	Genito-urinary system	44	3
11	Others*	236	17
	Total	1371	100

**Congenital malformations, fever of unknown origin, senility, undetermined, diseases of musculo-skeletal system.*

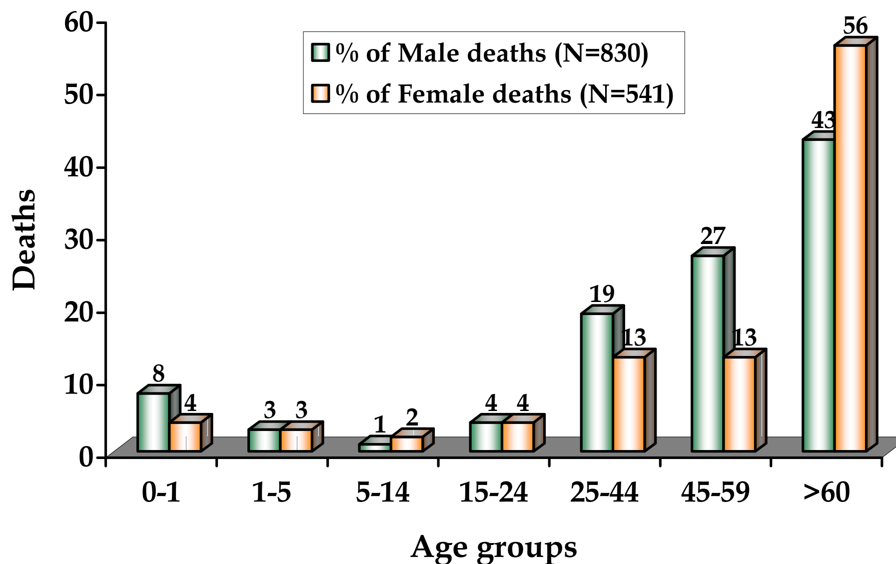

Fig. 98: Age and sex specific classification of deaths.

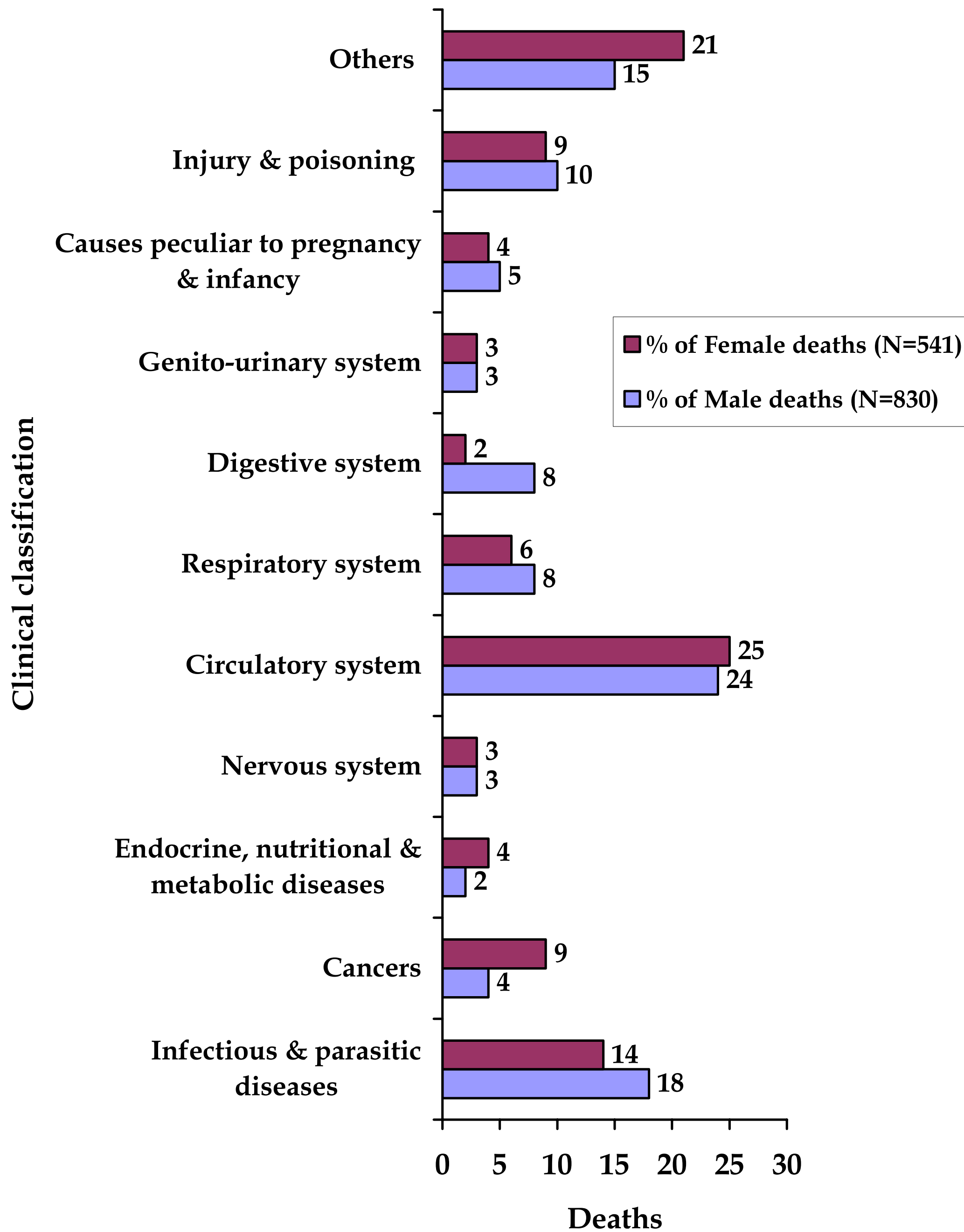

Fig. 99: Sex-specific clinical classification of deaths.

As seen in Fig 100, deaths due to diseases of circulatory system (heart diseases and stroke) were more in urban (30%) as compared to rural areas (20%). Deaths due to causes related to pregnancy and infancy were more in rural (7%)

as compared to urban (2%). The data collection of second round in Akola and Bhandara district will be completed by June 2005.

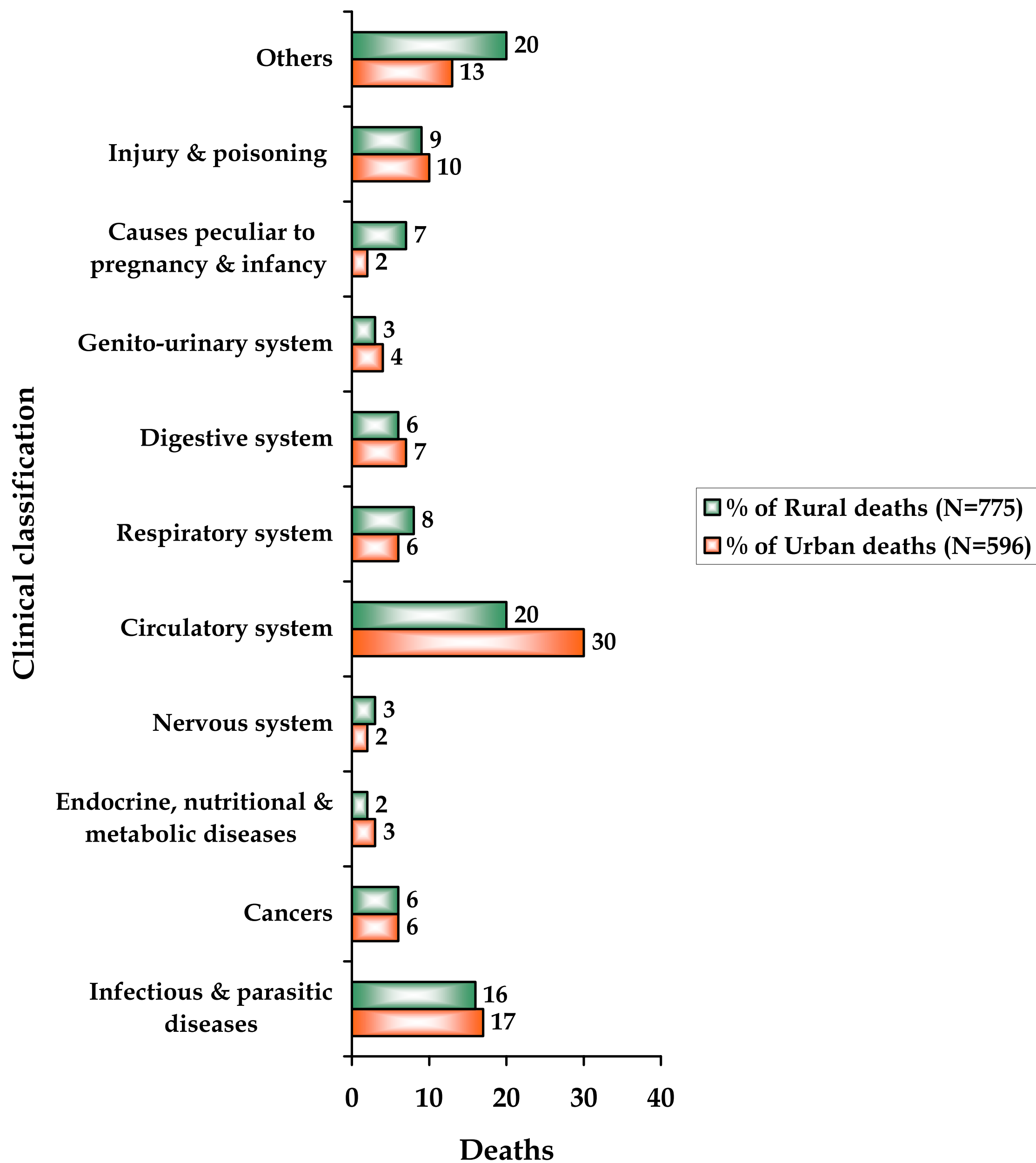

Fig. 100: Area wise clinical classification of deaths.