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Epidemiological aspects of Tuberculosis in Nepal

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In April 1993 the WHO declared TB a global emergency. TB is also an alarming public health problem in Nepal. This paper reviews the current epidemiological situation of tuberculosis in Nepal. About 60% of the adult population have been infected with the tuberculosis bacillus. Every year, 20,000 people develop infectious tuberculosis, and between 13,000 and 16,000 die. One infectious patient can transmit the disease to 10 to 15 people every year. Like the common cold, and unlike TB is an airborne disease, spread by relatively casual contact. Only about 10% of patients infected with tuberculosis progress to active disease. If a person is co-infected with this increases to nearly 10% per year. Even though HIV is relatively uncommon at the moment in Nepal, the increasing trend is worrying, and will lead to an increase in attributable tuberculosis. At least 5% of newly diagnosed patients with tuberculosis have resistance to one or more drugs. This proportion is also increasing and is a matter of great concern.

Keywords: Tuberculosis, Epidemiology, DOTS, National Tuberculosis Programme, Drug Resistance, HIV

INTRODUCTION

Tuberculosis is an enormous health problem worldwide, infecting over one third of the world's population, and causing three million deaths each year.[1] In recognition of this problem, in April 1993 the World Health Organization (WHO) declared that the tuberculosis (TB) situation had become a global emergency. The main strategy for controlling TB is the treatment and cure of infectious (smear-positive) cases. The most important functions of an effective National Tuberculosis Programme are therefore passive case finding by smear microscopy to detect infectious cases, and treatment with supervised short course chemotherapy (commonly known as Directly Observed Treatment, Short Course or DOTS) to ensure that patients are cured.

An understanding of the epidemiology of TB is of great importance to the NTP, as a management tool to determine resource requirements, and as a measure of performance to monitor the trend of the disease.

Commonly used epidemiological measures of the tuberculosis situation are the prevalence and incidence of infection, the prevalence and incidence of disease, and mortality.[2] More recently other measure have also been utilized, including the prevalence of HIV in patients with TB, and the prevalence of initial and acquired resistance.

Prevalence and incidence of infection

Tuberculosis is an airborne disease, usually transmitted by people with smear-positive pulmonary TB. Aerosols of bacteria are created when a patient coughs, sneezes and breathes.

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Table I: Tuberculin surveys carried out in Nepal.

Investigator	Year	Ages surveyed	Place	Prevalence of Infection (%)	ARI (%)
Aspin	1947	14-25	Gurkha recruits	23.4	?
UMN/Iwamura	1962	5-19	Terai	72-92	?
UMN/Iwamura	1962	5-19	Hills	22-92	?
UMN/Iwamura	1962	5-19	Mountains	38-42	?
Das & Giri	1963	5-16	Kathmandu (U)	25-91	?
Worth and Shah	1965	0-14	Terai	7-48	?
Worth and Shah	1965	0-14	Kathmandu (U)	10-86	?
Worth and Shah	1965	0-14	Mountains	2-44	?
Phleps	1965	10-14	Kathmandu (U)	56	?
Phleps (Gorkha recruits)	1966	15-19	Kathmandu (U)	56	?
Phleps (Gorkha recruits)	1966	15-19	from hills	46	?
Miyamoto and Joshi	1966	All ages	Bhaktapur (U)	50.9	?
Skjerven	1973	All ages	Rolwaling (M)	43	?
Benjamin	1974	15	Hills	8	?
Giri	1976	0-5	Bhaktapur (U)	5-34	?
Giri	1976	0-5	Terai	2-11	?
Giri	1976	0-5	Mountains	0-5	?
ITSC/TBCP	1979	6-15	Jajarkot (H)	9.5	0.88
ITSC/TBCP	1979	3-14	Taplejung (H)	10.4	1.3
JICA/TBCP	1980's	?	Pokhara (U)	?	3
INF	1988	Av 9.9	Surkhet (H)	11.5	1.22
INF	1989	Av 10.2	Salyan (H)	9.2	0.95
UMN TCSP	1990/93	3-19	South Gorkha (H)	17.5	2.07
		4-18	North Gorkha (H)	10.3	1.00
		4-18	Mid Gorkha (H)	4.8	0.48
		4-18	Gorkha town (H)	19.9	1.90
NTC/JICA	1991	<15	Kathmandu (U)	37.0	5.4
NTC/JICA	1991	?	Patan (U)	41.1	4.7
NTC/JICA	1991	?	Dhading (H)	16.5	2.3
NTC/JICA	1992	?	Chitawan (T)	14.6	1.8
NTC/JICA	1992	?	Kabre (H)	20.0	2.18
UMN	1990/92	?	Okhaldhunga (H)	?	0.64
INF	1990/92	4-19	Dang (T)	9.9	0.99
INF	1993	4-19	Banke (T)	13	1.2-2.3
JICA/NTC	1993	3-15	Far West (H/T)	5.5-27	1.2-2.3
INF	1994	4-19	Bardiya (T)	?	1.2
NTC	1994	5-14	Dhanusha (T)	26.4	2.80
NTC	1994	5-14	Makwanpur (T)	35.9	4.36
NTC	1994	5-14	Nuwakot (H)	19.3	2.04
NTC	1994	5-14	Sindhupalchok (H)	15.9	1.61
NTC/JAT	1994	0-18	Morang/Saptari (T)	19.6	2.44

Source: Five Year Development Plan for the NTP (3)
Key: U = Urban, T = Terai, H = Hills, M = Mountains

The bacteria form droplet nuclei which can then be inhaled, and lodge in the alveoli. The bacteria are then phagocytosed by macrophages in the alveoli, provoking immunological responses. The most important of these is cell mediated immunity (CMI), and it is a test of CMI - the tuberculin test - that is used as the main measure of transmission of TB. The tuberculin test is widely used to estimate the prevalence of infection in populations, as well as being used as a diagnostic test.

The tuberculin test has been standardized for epidemiological surveys, with guidelines on the sampling and testing methods.[3] Several tuberculin surveys have been carried out in Nepal, going back to 1947, mostly conducted at a district level. **(table I)**[4] However, it is only recently that testing methodologies have conformed to the recommended criteria, and random sampling methods have not been used. It is therefore difficult to interpret and compare the results of different surveys.

Attempts to collate the results of these different surveys have been made. In 1994, a joint WHO/HMG review team summarised the results nationally and by geographical region.[5] They estimated that 61% of adults aged 15-45 years and 45% of the total population is infected with TB. Incorporating the average age of the populations surveyed allows an annual incidence of infection to be calculated, commonly known as the Annual Risk of Infection (ARI). The HMG/WHO review estimated the overall ARI in Nepal to be 2.1%.[5] This is similar to the figure of 2.2% produced by Onozaki in 1992 **(table II)**[6]

Table II: Summary annual risk of infection calculated from tuberculin surveys conducted in Nepal.

Source: Region	WHO/HMG Review (1994)		Onozaki (1992)
	Mean	Median	
Terai	1.84%	1.80%	2.5%
Hills	2.03%	1.90%	1.5%
Mountains	?	?	<1%
Urban	4.49%	4.80%	4%
Population adjusteda verage	2.10%	1.98%	2.2%

Source: National Tuberculosis Programme Review (4)
National Seminar and Workshop (5)

It is interesting to note that the ARI is much higher in urban than rural areas, and higher in the terai than the mountains. Migration from the hills and rural areas to the terai and urban areas is common, and means that large numbers of people are moving between areas of low and high endemicity. Transmission of TB in the mountains may be low, but cases still occur there in seasonal migrants.[7]

Prevalence and incidence of disease

Based on the results of tuberculin surveys, it is possible to estimate the incidence of tuberculosis.[8] Using the above estimates of ARI by geographical region, and a relationship of 1 % ARI equivalent to an incidence of 50 cases of smear-positive TB per 100,000 population, about 22,500 cases of smear-positive TB will occur in Nepal in the current year (1995/96). Murray et al[9] estimated that in developing countries with an ARI of 1-2%, there are 1.22 other (smear-negative and extra-pulmonary) TB cases for each smear-positive case. If this is correct, we would expect 27,500 cases of other forms of TB in Nepal this year, and altogether a total of over 50,000 new cases of TB.

These figures are very crude; the estimates of ARI in Nepal are unreliable, the relationship between the annual risk of infection and the incidence of smear-positive TB has a very wide confidence interval,[9] and the relationship between smear-positive and other cases of TB is open to debate. Nevertheless, they are the best estimates we have, and will have to suffice until a more accurate method for estimating the incidence of TB is found.

Over 10,000 cases of new smear-positive TB are diagnosed and registered for treatment each year in the NTP **(table III)**. The sudden increase in reported cases in 1993/94 was due to a change in the reporting system. Inadequate reporting, with incomplete reports from some districts, and probable double reporting in others, means that it is difficult to interpret the trend in reported incidence. Assuming that a figure of 11,000 is close to the true number of new smear-positive cases registered for treatment in the NTP, then the case detection ratio in Nepal is approximately 50%. This figure excludes patients who are diagnosed and treated in the private sector. This number is unknown, but probably large, as a study of usage of anti-tuberculosis drugs demonstrated that 70% of rifampicin in Nepal was imported by the private sector (T. Hamai, personal communication). However, the widespread practice of X ray diagnosis in the private sector probably results in significant over-diagnosis and unnecessary treatment for many patients.

Table III: Reported cases of tuberculosis in Nepal.

Investigator	Year	Ages surveyed	Place	Prevalence of Infection (%)	ARI (%)
Aspin	1947	14-25	Gurkha recruits	23.4	?
UMN/wamura	1962	5-19	Terai	72-92	?
Miyamoto and Joshi	1966	All ages	Bhaktapur (U)	50.9	?
Skjerven	1973	All ages	Rolwaling (M)	43	?
Benjamin	1974	15	Hills	8	?
Giri	1976	0-5	Bhaktapur (U)	5-34	?
Giri	1976	0-5	Terai	2-11	?
Giri	1976	0-5	Mountains	0-5	?
ITSC/TBCP	1979	6-15	Jajarkot (H)	9.5	0.88
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NTC	1994	5-14	Nuwakot (H)	19.3	2.04
NTC	1994	5-14	Sindhupalchok (H)	15.9	1.61
NTC/JAT	1994	0-18	Morang/Saptari (T)	19.6	2.44

One method for confirming the validity of these estimates of incidence is to conduct prevalence surveys. In the absence of treatment facilities, the prevalence of TB is approximately double the incidence.[9] The most well known prevalence survey in Nepal was conducted in Syangja district in 1976/77.[10] In this house to house survey, 52,482 persons were contacted, of which 104 were smear-positive, giving a prevalence of 198 per 100,000. An additional 33 cases were diagnosed during the period of the study by passive case finding, giving an overall prevalence of 261 per 100,000. Halving these figures gives an estimated incidence of 99 to 130 per 100,000. This corresponds quite well to the present estimated incidence of 110 per 100,000 based on the ARI.

Mortality

In the pre-chemotherapy era, TB was a major cause of death throughout the world. It is tempting to assume that with the widespread availability of effective drugs, the number of deaths should be low, yet each year three million people worldwide still die from TB,[1] making it the single largest cause of death due to an infectious agent.[11]

Reporting systems of cause of death are often inadequate, and Nepal is no exception. One of the few routine hospital based reporting systems that includes cause of death is maintained by the United Mission to Nepal, from the four hospitals it supports. Data from this source is shown in **table IV,** which represents a tiny proportion of the actual number of patients dying from TB in Nepal. The trend in deaths from TB in UMN hospitals appears to be downward. This may be due to improved case management with the introduction of SCC in several hospitals, but may also be due to a reduction in the number of TB patients seen at the hospitals, as coverage of the NTP has increased in recent years.

Table IV: Deaths from TB in UMN hospitals.

Year	Deaths from TB
1990/91	94
1991/92	64
1992/93	54
1993/94	49
1994/95	48

Source: Health Services Office, United Mission to Nepal.

With grossly incomplete recording of cause of death, mortality from TB can only be estimated based on assumptions arising from observations in other parts of the world. These mortality assumptions are: 60% in untreated sputum positive cases; 50% in partially treated sputum positive cases; 40% in untreated other TB cases, and 30% in partially treated other TB cases.[9,12] Assuming 20,000 new cases of sputum positive TB and 25,000 cases of other forms of TB arise each year, that 50% are diagnosed, and 50% go on to complete treatment, then 15,375 people die from TB each year in Nepal. Increasing case finding to 70% and case holding to 85% would reduce this number to 8,000, i.e. a reduction of nearly 50%. However, these figures ignore patients treated in the private sector. If we assume that a further 20% of patients are diagnosed and treated in the private sector, and that 40% of these complete treatment, then the revised estimate of deaths is 13,425.

Assuming that 33% of these deaths occur in women between the ages of 15 and 45, the number of deaths due to TB (about 4,500) can be compared with the number due to maternal causes (about 6,300; based on a total population of 20 million, crude birth rate of 38 per 1000, and maternal mortality rate of 830 per 100,000 live births.[13] Achieving the global targets of 70% case finding and 85% case holding in the NTP would have a similar impact on deaths in women as a 30% decrease in maternal mortality.

HIV and Tuberculosis

The growing pandemic of HIV threatens to overwhelm TB control programmes throughout the developing world. A person infected with TB has a 10% lifetime risk of developing TB disease.[2] However, this risk increases to nearly 10% per year if he or she is co-infected with HIV,[14] the risk being greatest if TB infection follows HIV infection. This diabolical duet has resulted in a rapid increase in the incidence of TB in many countries, particularly in sub-Saharan Africa, but also more recently in some countries of Asia, for example Thailand. Globally, the number of new cases of TB attributable to HIV was estimated to be 300,000 in 1990, equivalent to 4% of total new TB cases. This proportion is projected to increase to 14% by the year 2000.[1]

There are two ways of looking at the epidemiological relationship between HIV and TB. The first is to look at the prevalence of HIV in patients with TB, and the second is to study the prevalence of TB in people with HIV. As TB is now a diagnostic marker for AIDS, patients with HIV and TB disease by definition have AIDS.

The number of HIV and AIDS patients diagnosed in Nepal continues to increase, (**table V**). The first case of AIDS in Nepal was diagnosed in 1988, and in the last year a case of perinatal transmission was reported. This is a rapid progression through the epidemiological stages of the AIDS epidemic, suggesting very rapid spread of HIV in Nepal. However, it is possible that this has arisen because of the high proportion of female cases of HIV and AIDS in the early stages of the epidemic, which is an unusual feature.

Table V: Reported cases of HIV and AIDS in Nepal.

	HIV	AIDS
Male	189	22
Female	160	29
Total	349	51

Source: National Centre as of 29th Feb. 1996 for AIDS and STD Control As of 29th February 1996

An epidemiological study of the burden of HIV in Nepal conducted in 1994 estimated that 0.07% of adults aged 20-49 years were infected with HIV, equivalent to a total of 5,000 people. A survey of 300 TB patients at the NTC in 1993 failed to identify any with HIV. This is not surprising, given the low prevalence of HIV. However, the prevalence of HIV is projected to rise rapidly over the next few years, to reach 0.25% (22,000 people) by the year 2000.

Assuming that 60% of adults aged 20-49 are infected with TB, that 0.07% of people infected with TB are also infected with HIV, and that 8% of dually infected persons develop TB each year, about 300 new cases of TB attributable to HIV will arise annually, i.e. 0.6% of all new cases of TB in Nepal. If the prevalence of HIV rises to 2.5% as predicted, then the number of cases of HIV attributable TB will increase to about 1,300 by the year 2000, i.e. 2.4% of all cases of TB expected at that time.[4]

Tuberculosis is the commonest infection in patients with HIV/AIDS in developing countries. About 75% of the AIDS cases diagnosed so far in Nepal have had TB. This is similar to reported figures of 60 to 80% in other countries of the region.[15]

Drug Resistance

Drug resistant TB is a major threat to the National Tuberculosis Programmes. In a colony of tubercle bacilli there will be a small number of naturally resistant mutants. If only one drug is given, or drugs are given in adequate doses, the sensitive bacteria will be killed, but the resistant ones remain and multiply. Inadequate TB therapy therefore selects out resistant strains, resulting in secondary or acquired resistance.[16] If these resistant bacteria then infect another person, causing disease, then the patient will be resistant from the beginning of treatment. This is known as primary resistance, and frequently results in treatment failure, the patient remaining smear-positive 5 months or more after commencing treatment. It is often difficult to differentiate between true primary resistance and undisclosed acquired resistance. For this reason the term initial resistance is often used.

Drug resistance poses a major problem, because it is difficult and expensive to treat successfully. It most commonly arises as a result of poor treatment regimens, often because doctors have failed to follow national treatment guidelines. A study from India on patients treated in the private sector discovered that 100 private practitioners used a total of 80 different treatment regimens for patients with TB - most of which were both inappropriate and expensive.[17] Not surprisingly, drug resistance and treatment failure are common in some parts of India.[18]

Testing for drug resistance is too expensive for routine use, and is usually restricted to epidemiological surveys, and patients who have failed on a Category 1 regimen. Several epidemiological surveys of primary resistance have been carried out in Nepal[19,20,21,22,23] but the lack of standardization of sampling, testing and reporting methods has made comparisons difficult. Most of the patient studied have come from the Kathmandu valley, where drug resistance is likely to be most common, due to the widespread availability of anti-tuberculosis medicines. A summary of these surveys was prepared by the WHO/HMG review. It concluded that primary drug resistance to at least one drug was present in 5-24% of new cases. There appears to be an increasing trend of resistance. A sentinel site study of drug resistance is currently in progress in Nepal, based on an internationally agreed protocol.[24]

The NTC has also carried out several studies of acquired drug resistance. In 1994/95 345 samples from patients with suspected resistance were examined. Of these, 175 cultures were positive for mycobacteria. Results of these tests are shown in **table VI**. The extremely high prevalence of drug resistance is very worrying, even in this selected population of patients. In analysing these results it was not possible to differentiate between named patients, so some of these samples may have come from the same patient. Of these samples, 88 (51%) were resistant to isoniazid and rifampicin. Multi-drug resistance, defined as resistance to at least rifampicin and isoniazid,[25] is here in Nepal.

Table VI: Drug sensitivity patterns in patients with suspected drug resistance at the National Tuberculosis Centre.

Culture	Number	Resistance	Number
Negative	157 (46%)	Fully sensitive	15 (9%)
Positive	175 (51%)	1 drugs	27 (15%)
Contaminated	13 (4%)	2 drugs	26 (15%)
		3 drugs	41 (23%)
		4 drugs	38 (22%)
		All drugs	27 (15%)
Total	345 (100%)		175 (100%)

Source: NTC Laboratory 2051-4-1 to 2052-3-30. Cultures tested for resistance to Streptomycin, Isoniazid, Rifampicin, Ethambutol and Thiacetazone.

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