Introduction
1. INTRODUCTION

Tuberculosis (TB) is an infectious disease primarily caused by *Mycobacterium tuberculosis*. It affects mainly the lungs but can attack any part of the body. In 1882, Robert Koch made a discovery by isolating and culturing *Mycobacterium tuberculosis* from crushed tubercles. The lessons learnt from the discovery of anthrax bacilli and tubercle bacilli were then generalized into Koch’s postulate. He also described a staining technique for tubercle bacilli, which was later modified by Ehrlich and subsequently by Ziehl. Neelsen modified the Ziehl’s technique and provided a stable staining method known as the “Ziehl–Neelsen” staining. Koch also advocated the use of heated culture filtrate of tubercle bacilli in the therapy of tuberculosis. This was soon proved to be a failure. However, Koch’s experiments with this material in guinea pigs laid the foundation for the tuberculin skin test and eventually led to the fascinating field of mycobacterial immunology.

In 1882, Edward Livingston Trudeau established the first tuberculosis sanatorium in the United States. Sanatoria were helpful in isolating infectious patients from the community. They also provided excellent natural surroundings, enforced rest, proper diet and well-regulated hospital life and thereby enhanced the healing process. A further significant advance was made in 1895 by Wilhelm Konrad von Rontgen who discovered X-rays, which helped in finding the severity and extent of a patient’s disease that could be followed and reviewed.
The chemotherapy of this infectious disease began in 1944, with streptomycin, purified from *Streptomyces griseus*, which was administered for the first time to a critically ill TB patient. Following streptomycin, chemotherapeutic drugs such as para-amino salicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962) and rifampicin (1963) were introduced as anti-tuberculosis drugs (www/undnj.edu/ntbc.web/history.html).

### 1.1. Global epidemiology of tuberculosis

According to WHO report, about one third of the world’s population (1.9 billion people) is infected with *Mycobacterium tuberculosis* and is responsible for more than 3 million deaths and 9 million new cases which occur every year worldwide. More people die of tuberculosis than any other infectious disease. Death from tuberculosis comprises 25% of all avoidable deaths in developing countries; 95% of tuberculosis cases and 98% of tuberculosis deaths are in developing countries and 75% of tuberculosis cases are in the economically productive age group (WHO 1997). Geographically, the regions with the highest prevalence and infection rate are the eastern fringe of Asia, the Indian subcontinent, the South Eastern part of Africa, South East Europe, Central America and the Western part of the South America. WHO has declared a global emergency in 1993 with respect to re-emerging menace of tuberculosis (WHO 1997).
1.2. Epidemiology of tuberculosis in India

In India out of a total population of approximately 1 billion people, each year over 2 million develop active disease and upto 5 lakhs people die annually. This roughly accounts for one sixth of the total 3 million deaths, which occur globally. It also imposes a cost on our economy in terms of current and future output loss because of premature death and ill health (WHO/TB 1997).

1.3. HIV and Tuberculosis

Human Immunodeficiency Virus has a serious effect on tuberculosis in many parts of the world. HIV infection is one of the strongest risk factor for breakdown of tuberculosis disease among those who were infected already. Tuberculosis is considered as one of the most common HIV related opportunistic infections. With the spread of HIV epidemic, several countries have witnessed a rapid increase in the incidence of tuberculosis. The dual infection of HIV and tuberculosis increases the risk factor about five folds when compared with non-HIV but tuberculosis infected persons (CDC Report, 1986). With the global increase in the spread of HIV, the increase in tuberculosis incidence rate and mortality rate are likely to occur in many developing countries including India. It has been estimated that a total of ~ 120,000 – 275,000 HIV positive cases would be breaking down with tuberculosis, if 7% to 10% break down rate to TB among HIV/AIDS positive persons remains in India (Balasangameshwara 2000). A total of 12 million people worldwide are co-infected with both TB and HIV, with the majority of them living in Southern Africa. Because of the increased spread of
HIV in sub-Saharan Africa, the number of TB cases in that region will double to 4 million new cases per year shortly after 2005. (www.aeras.org/tb/hiv/index.html). It was also reported by the National AIDS Control Policy that the dual HIV-TB epidemic with about 4 million TB cases, are existing in India. HIV/AIDS also poses a twin challenge of HIV/TB co-infection. Nearly 60% of the AIDS cases are reported to be opportunistic TB infection cases. Treatment of TB among the HIV-infected persons is a new challenge to the National TB Control Programme, which has now adopted DOTS strategy for the control TB infection(www.healthinitiative.org/html/toolkit/indperspective.html)

1.4. Global Epidemiology of Drug Resistance

One of the most alarming consequences of dual infection with HIV and \textit{M.tuberculosis} has been the emergence of potentially untreatable strains of drug resistant organisms (MDR-TB) which are resistant to two potent anti- tuberculosis agents, isoniazid and rifampicin with or without resistance to other anti-tuberculosis drugs. The levels of primary resistance to isoniazid ranged from 0-16% (Cohn DL et al., 1997). High rates of primary resistance to isoniazid have been reported from Kenya, India and Haiti, whereas it is low in South Eastern England, Melbourne and Argentina. The levels of primary resistance to streptomycin ranged from 0.1-23.5%; high rates of resistance were reported in Zaire, Pakistan and Brazil and the low levels of resistance were reported in China and Ethiopia. Primary resistance to rifampicin and ethambutol is low and it ranges from 0-3% and 0-4.2% respectively. The epidemiology of multidrug
resistance for primary drugs ranges from 0-10.8% and acquired resistance ranges from 0-48%. In surveys where there was no distinction between primary and acquired resistance it was reported to range from 0.5% to 14.3%. In general, resistance to isoniazid and streptomycin was found to be more common than to rifampicin and ethambutol (Paramasivan et al., 2004).