A BASELINE SURVEY OF THE PREVALENCE OF LATENT TUBERCULOSIS INFECTION (LTBI) IN HEALTH CARE WORKERS

Thesis
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List of abbreviations

ADA Adenosine Deaminase
AFB
APC
Acid fast bacilli
Antigen-Presenting Cells
ARI
ART
ATS
ATT
Annual Risk of Infection
Anti-Retroviral Therapy
American Thoracic Society
Anti-Tubercular Therapy
BCG Bacilli Calmette-Guerin vaccination
BTS British Thoracic Society

CDC
CFP 10
Centers of Disease Control
Culture Filtrate Protein 10
COPD Chronic Obstructive Pulmonary Disease
CT Computed Tomography
DOT Direct Observed Therapy
EMB
ESAT-6
FDA
FUO
Ethambutol
Early Secretory Antigenic Target protein 6
Food And Drug Administration
Fever of Unknown Origin
HAAT
HCWs
HEPA
HIV
Highly Active Antiretroviral Therapy
Health Care Workers
Highly Efficiency Particular Air
Human Immunodeficiency Virus
INH
IFN-γ
IRS
Isoniazid
Interferon gamma
Immune Reconstitution Syndrome
LMICs
LTBI

Low-and-Middle- Income Countries
Latent TB Infection
MDR:TB
MMPs
MGIT
MMWR
MOHP
Multi-Drug Resistance-TB
Matrix Metalloproteinase
Mycobacteria Growth Indicator Tube
Morbidity and Mortality Weekly Report
Ministry of Health and Population
MT
MTB
NAA
NTM
Miliary Tuberculosis
Mycobacterium Tuberculosis
Nucleic Acid Amplification
Non-TB Mycobacteria
OSHA
OT
Occupational Safety and Health Administration
Old Tuberculin
PAS Para-Amino Salicylic
PCR Polymerase Chain Reaction
PPD Purified Protein Derivative
PZA Pyrazinamid
QFT QuantiFERON-TB
RMP Rifampicin

SM Streptomycin
TB Tuberculosis
TNF Tumor Necrosis Factor
TST Tuberculin Skin Test
UVGI Ultraviolet Germicidal Irradiation
WHO World Health Organization
XDR:TB Extensively drug-resistant tuberculosis
ZN Ziehl-Neelsen

ABSTRACT

Healthcare workers are at risk for tuberculosis exposure and infection when they care for patients. Although effective infection-control measures can greatly decrease the risk of nosocomial tuberculosis infection, the risk of tuberculosis exposure and infection among health-care workers will always be present to some extent. Therefore, screening workers for latent tuberculosis infection, using the Mantoux test, remains an integral part of tuberculosis control programs for health-care facilities. Tuberculin skin testing programs serve two important purposes: to monitor tuberculosis acquisition among health-care workers, and to identify workers with latent tuberculosis infection who need treatment.

This study was designed to assess the prevalence of latent tuberculosis infection (LTBI) in Fayoum University Teaching Hospital. It aims at determining the occupational risk of Mycobacterium tuberculosis infection among a group of 100 healthcare workers. The study showed that 32 (32%) have tuberculin skin test positive, 17 of them had radiological changes, 12 of them presented with increased bronchovascular markings and 5 with bilateral central calcified lymph nodes.

In conclusion, there is risk of tuberculosis transmission among healthcare workers at Fayoum University Teaching Hospital, mainly in internal medicine ward and the risk increase by long duration of work and by advanced age and those living in rural area

Key word: LTBI, tuberculin skin test, chest X-ray, healthcare workers.

AIM OF THE WORK

• To assess the prevalence of latent tuberculosis infection (LTBI) in Fayoum University Teaching Hospital.
• To determine the occupational risk of Mycobacterium tuberculosis infection among a group of health-care workers.

INTRODUCTION

Tuberculosis is a disease with high mortality and morbidity, approximately one third of the world population is infected with the tubercule bacillus and there are 8 million deaths annually from tuberculosis in the world. Despite the new knowledge about pathogenesis and activity of tuberculosis, it remains an important disease especially in developing countries **(Raviglione et al., 1995).**

In many developing countries attempts to control the spread of infection rely on identification and treatment of those with active disease ignoring sub clinical infection **(Rothel and Anderson, 2005).**

Determination of the prevalence of latent infection is helpful for better understanding the epidemiology of TB and for designing and evaluating TB control strategies **(Al Zahrani et al., 2000).**

In most persons, infection with M. tuberculosis is initially contained by host defenses, and the infection remains latent. However, latent tuberculosis infection has the potential to develop into tuberculosis at any time, and persons with active tuberculosis become sources of new infections. Treatment of latent infection greatly reduces the likelihood that active tuberculosis will develop. Thus, it has the potential both to preserve the health of an individual person and to protect the health of the public by reducing the number of potential sources of infection **(ATS, 2000).**

The center for disease control (CDC) and WHO recommended

screening of high risk groups as health care workers and physicians **(Jenarun et al., 2004).**

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It is desirable to undertake testing programs among those who are at risk for infection and those who are at increased risk for progression to active tuberculosis or persons whose future activities may place them at increased risk of exposure (such as health care workers) **(American Thoracic Society, 2000).**

All health care settings need a TB infection control program designed to ensure prompt detection, airborne precautions, and treatment of persons who have suspected or confirmed TB disease **(CDC, 2005).**

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EPIDEMIOLOGY OF TUBERCULOSIS

Ninety-five percent of tuberculosis cases occur in developing countries, where few resources are available to ensure proper treatment and where human immunodeficiency virus (HIV) infection may be common. It is estimated that between 19 and 43% of the world's population is infected with Mycobacterium tuberculosis, the bacterium that causes tuberculosis infection and disease **(Sudre, 1992).**

The Stop TB Department of the World Health Organization has recently projected that reduction of tuberculosis incidence, prevalence, and deaths can be achieved by 2015 in most parts of the world, but the challenge will be greatest in Africa and Eastern Europe **(Dye et al., 2005).**

Verver and coworkers demonstrated that the age-adjusted incidence rate of tuberculosis attributable to reinfection after successful treatment could be four times that of new tuberculosis in an area with high prevalence of disease, such as South Africa **(Verver et al., 2005).** This observation implies that individuals who had tuberculosis once are at an increased risk of developing the disease again when reinfected. This apparently novel concept deserves attention, as it appears to be contradictory to what would be assumed. In sub-Saharan Africa, tuberculosis remains

the top cause of HIV-related mortality. The incidence of tuberculosis in adults receiving highly active antiretroviral therapy (HAART) is lower than in untreated HIV-infected adults, but still higher than among HIV-negative adults **(Badri et al., 2002).**

The Centers for Disease Control and Prevention recently published the trends in tuberculosis (TB) incidence in the United States. In 2006, a total of 13,767 TB cases were reported in the United States, at a rate of 4.6 per 100,000, representing a 3.2% decline from 2005. The incidence of TB in 2006 was the lowest

recorded since 1953, but the rate of decline has slowed since 2000. Foreign-born persons and racial/ethnic minority populations continued to be affected disproportionately. The TB rate among the former was 9.5 times that of United States–born persons. The slowing of decline in the overall national TB rate and the inability to effectively address persistent disparities in TB rates between United States–born and foreign-born persons, and between whites and racial/ethnic minority populations, may hamper progress toward the goal of TB elimination in the United States **(CDC, 2007).**

Tuberculosis in Egypt

Egypt is ranked among the mid-level incidence countries and in Egypt it is considered an important public health problem, the annual risk of infection (ARI) represents the percentage of population that will be infected by tubercle bacilli every year.

It has been estimated that one percent of (ARI) corresponds to 50 to 60 new smear-positive tuberculosis cases per 100,000 inhabitants per year. The pulmonary form of tuberculosis represents roughly 80-85% of all cases; the remaining 15-20% is made up by cases of extra-pulmonary tuberculosis.

In Egypt there were 3 tuberclin surveys:

- In 1951, the incidence was 350/100,000 of population.
- In 1982, the incidence was 70/100,000 of population.

 In 1997, the incidence was 32/100,000 of population.
In 2003, the incidence of TB infection was calculated mathematically, in collaboration with WHO, at rate of 28 TB new cases per 100,000 individual of population and modified in 2006 to 24 TB new cases per 100,000. 11 of them are smearpositive
pulmonary TB.
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In 2005, a success rate of 79% was achieved in the treatment outcome of new sputum smear-positive TB cases (cure and treatment completed rates combined).
In 2006, a total of 4, 745 new sputum smear-positive TB cases were notified **(Ministry of Health and Population, Egypt, 2007).**
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TRANSMISSION OF MYCOBACTERIUM TUBERCULOSIS

Mycobacterium tuberculosis is the bacterium that causes most cases of tuberculosis **(Ryan, 2004).** It was first described on March 24, 1882 by Robert Koch, who subsequently received the Nobel Prize in physiology of medicine for this discovery in 1905; the bacterium is also known as *Koch's bacillus*. The *M. tuberculosis* genome was sequenced in 1998 **(Camus et al., 2002).**
M. tuberculosis is nearly always transmitted through an airborne route, with the infecting organisms being carried in droplets of secretions (droplet nuclei) that are expelled into the surrounding air when a person with pulmonary TB coughs, talks, sings, or sneezes. Person-to-person transmission of *M. tuberculosis* is determined by certain characteristics of the source-case and of the person exposed to the source-person and by the environment in which the exposure takes place. The virulence of the infecting strain of *M. tuberculosis* might also be a determining factor for transmission **(ATS, 2005).**

FACTORS DETERMINING TRANSMISSION OF M.

TUBERCULOSIS

Characteristics of the source-case

• Concentration of organisms in the sputum
• Presence of cavitary disease on chest radiograph
• Frequency and strength of cough

Characteristics of the exposed person

• Previous M. tuberculosis infection
• Innate resistance to M. tuberculosis infection

• Genetic susceptibility to M. tuberculosis infection or disease or both.

Characteristics of the exposure

• Frequency and duration of exposure
• Dilution effect (i.e., the volume of air containing infectious droplet nuclei)
• Ventilation (i.e., the turnover of air in a space)
• Exposure to ultraviolet light, including sunlight

Virulence of the infecting strain of M. tuberculosis

Although much is known about factors that contribute to the risk for transmission of *M. tuberculosis* from person to person, the role of the organism itself is only beginning to be understood. Genetic variability is believed to affect the capability of *M. tuberculosis* strains to be transmitted or to cause disease once transmitted, or both. The *M. tuberculosis* W-strain family, a member of the globally spread Beijing family, is a group of clonally related multidrug-resistant organisms of *M. tuberculosis* that caused nosocomial outbreaks involving HIVinfected persons in New York City during 1991–1994 **(Kato-Maeda et al., 2001).**

W-family organisms, which have also been associated with TB outbreaks worldwide, are believed to have evolved from a single strain of *M. tuberculosis* that developed resistance-conferring mutations in multiple genes. The growth of W-family organisms in human macrophages is four- to eightfold higher than that of

strains that cause few or no secondary cases of TB; this enhanced ability to replicate in human macrophages might contribute to the organism's potential for enhanced transmission **(Barnes, 2003).**

PATHOGENESIS AND IMMUNOLOGY OF TUBERCULOSIS

M tuberculosis, the infectious agent of TB, is a thin, slightly curved bacillus that is an obligate aerobe. In comparison to other bacteria, *M tuberculosis* has a cell wall with a very high lipid content that resists staining by the usual Gram method. However, it accepts basic fuchsin dyes and is not easily discolorized even with acid-alcohol; this resistance to decolorization by acid-alcohol is termed acid-fast. As this property is shared only by members of the mycobacterial family and a few other organisms (*Nocardia*, *Rhodococcus*, and *Corynebacterium* species), it forms the basis for the simple, rapid, and relatively specific traditional technique of identification by means of an acid-fast smear **(Nolte, 1995).**

M tuberculosis is transmitted via airborne droplet nuclei that are produced when persons with pulmonary or laryngeal TB cough, sneeze, speak or sing **(CDC, 1994).**

The particles, which measure 1–5 μm in size, can be kept airborne by normal air currents for prolonged periods of time, resulting in dispersion throughout a room or building. The presence of acid-fast bacilli in the sputum smear is the main indicator of potential for transmission; other source patient characteristics that increase the probability of transmission include positive sputum culture for *M tuberculosis*, presence of cavitation on the chest radiograph, presence of TB laryngitis, and high-volume and watery respiratory secretions **(ATS, 1992).**

Infection occurs when a susceptible person inhales droplet nuclei that contain tubercle bacilli. As the distribution of inhaled droplet nuclei is determined by the ventilatory pattern and volumes of the various lung lobes, the site of implantation

preferentially occurs in the middle and lower lung zones, although any lobe may be affected **(Allen, 1995).**

Once lodged in the alveolus, *M tuberculosis* is ingested by alveolar macrophages. Resistance to establishment of tuberculous infection is known to be under genetic control **(Ellner, 1997),** and the course of infection depends on the interaction between the inherent microbicidal power of the alveolar macrophage and the virulence of the ingested bacillus **(Dannenberg, 1991)**.

If the alveolar macrophage cannot destroy or inhibit *M tuberculosis*, the bacilli multiply within its intracellular environment, causing the host macrophage or its progeny to burst. The cycle continues as released bacilli are ingested by other alveolar macrophages and monocytes are recruited from the blood. During this period of rapid growth, tubercle bacilli are spread through lymphatic channels to regional hilar and mediastinal lymph nodes and through the bloodstream to more distant sites in the body. The logarithmic phase of bacillary growth is arrested with the development of cell-mediated immunity and delayed-type hypersensitivity at 2–10 weeks after the initial infection **(Bass, 1990).**

Development of specific immunity is usually adequate to limit further multiplication of the bacilli; the host remains asymptomatic; and the lesions heal **(Bass, 1990).**

Some of the bacilli remain dormant and viable for many years, and this condition—referred to as latent TB infection—may be detectable only by means of a positive purified protein derivative tuberculin skin test or radiologically identifiable calcification at the site of the primary lung infection or in regional lymph nodes **(CDC, 1994).**

In approximately 5% of infected individuals, immunity is inadequate and clinically active disease develops within 1 year of infection; in another 5% of the infected population, endogenous reactivation of latent infection occurs remote from

time of initial infection **(Bass, 1990).**
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Co-infection with HIV and *M tuberculosis* is the strongest known risk factor for both immediate and delayed progression from infection to active TB **(Telzak, 1997).**
The risk of progression to disease for co-infected persons is 5%–10% per year compared with a 5%–10% lifetime risk for HIVnegative
persons **(Allen, 1992).**
Other known risk factors for development of active TB include conditions that are associated with defects in T-lymphocyte and/or macrophage function, such as malnutrition, drug and alcohol abuse, coexistent medical conditions (e.g. chronic renal failure, diabetes mellitus, silicosis, jejunoileal bypass, and subtotal gastrectomy), and corticosteroid or other immunosuppressive therapy **(Bates, 1995)**.
Postprimary TB occurs in a person who has previously been infected and has retained a degree of acquired immunity; it can result from endogenous reactivation or, less commonly, exogenous reinfection **(Small et al., 1993).**
Although delayed progression of latent infection may occur at any seeded site in the body, lung foci account for the majority of cases **(Bass, 1990).**
Predilection of postprimary disease to involve the upper lung zones is likely due to a combination of factors including the relatively higher oxygen tension and impaired lymphatic drainage in this region. Local control and resolution of pulmonary TB is always accompanied by some destruction of involved tissues **(Allen, 1995).**
While cell-mediated immunity controls TB by activating macrophages to kill ingested bacilli, delayed-type hypersensitivity causes caseous necrosis that results in killing of bacilli-laden macrophages at the expense of destruction of nearby tissues **(Dannenberg, 1991).**
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