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Predictors of treatment outcome of Multi-Drug Resistant Tuberculosis (MDR-TB) in Egypt in the period 2007-2010

Thesis

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List of Abbreviations

ABG	Arterial Blood Gazes
AIDS	Acquired Immuno -Deficiency Syndrome
Am	Amikacin
Amx/Clv	Amoxicillin/clavulanate
BC	Before Christ
CAT I	Category I (treatment Regimen I)
CAT II	Category II (treatment Regimen II)
Cfx	Ciprofloxacin
Cfz	Clofazimine
CIs	Confidence Intervals
Clr	Clarithromycin
CM	capreomycin
CNS	Central Nervous System
CS	cycloserine
CT	Computed Tomography
DM	Diabetes Mellites
DNA	Deoxyribonucleic acid
DOTS	Directly Observed Treatment Strategy
DR-TB	Drug-Resistant Tuberculosis
DSM	Direct sputum microscopy
DST	Drug Susceptibility Testing
E	Ethambutol
ECG	Electro-Cardiography
EMB	Ethambutol
EMR	Eastern Mediterranean Region
Ethio(Eto)	ethionamide

FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FQ	fluoroquinolones
Gfx	Gatifloxacin
GIT	Gastro-Intestinal Tract
GLC	Green Light Committee
HCT	haematocrit
HCV	Hepatitis C virus infection
HIV	Human Immuno-deficiency Virus
INH	Isoniazid
IUATLD	International Union against Tuberculosis and Lung Diseases
KM	Kanamycin
Lfx	Levofloxacin
LTBI	Latent Tuberculosis Infection
Lzd	Linezolide
M. TB	Mycobacterium Tuberculosis
MDR	Multi Drug Resistance
Mfx	Moxifloxacin
MGIT	Mycobacterium Growth Indicator Tube
NRA	nitrate reductase assay
Ofx	Ofloxacin
OTC	over the counter
PA	Postero-Anterior
PAS	Para-amino salicylic acid
PCR	polymerase chain reaction
Pto	Prothionamide

PZA	pyrazinamide
R	Rifampicin
RIF	Rifampicin
S	streptomycin
SARs	Special Administrative Regions
SD	Standard Deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLD	Second Line Drugs
SM	streptomycin
SPSS	Statistical Package of Social Science software
TB	Tuberculosis
Th	Thioacetazone
Trd	Terizidone
TSH	Thyroid-stimulating hormone
UV	Ultra Violet
Vi	Viomycin
WHO	World Health Organization
XDR	Extreme (extensively) Drug Resistance
Z	pyrazinamide

Introduction

Multi- Drug Resistant Tuberculosis (MDR-TB) is a specific form of drug-resistant tuberculosis due to a bacillus resistant to at least isoniazid and rifampicin, the two most powerful anti-tuberculosis drugs.[1]

The treatment of MDR-TB requires the use of second line anti-tuberculosis drugs, which are more costly, more toxic, and less effective than first-line drugs. Since 1998, the World Health Organization (WHO) and its international partners have piloted an expanded TB treatment strategy called DOTS-Plus. This strategy promotes the programmatic treatment of MDRTB within low- and middle-income countries that have adopted the DOTS strategy.[2]

Through the Green Light Committee (GLC), which was established to lower prices of and increase control over second line anti-tuberculosis drugs, more than 20 DOTS Plus projects have been approved across the globe.[3]

Drug-resistant TB has been identified in every setting surveyed, and MDR-TB has been present in more than 95% of these; a large number of national or regional TB programs will be needed in coming years to implement the DOTS-Plus strategy. Evidence from GLC-approved projects will be critical in developing policy recommendations for MDR-TB management. To date, however, standard definitions for MDR-TB case registration and treatment outcomes do not exist. Such definitions would permit the accumulation of evidence through cross-program comparisons.[4,5]

Aim of the work

The study aims to assess the predictors of treatment outcomes of MDR-TB by studying the association and causality relationship between the risk factors & co-morbidities and treatment outcomes of MDR-TB patients' cohorts through years 2007 to 2010 in Egypt.

History of Tuberculosis

Tuberculosis (TB) has a long history. It was present before the beginning of recorded history and has left its mark on human creativity, music, art, and literature; and has influenced the advance of biomedical sciences and healthcare. Its causative agent, *Mycobacterium tuberculosis*, may have killed more persons than any other microbial pathogen. [6]

TB was documented in Egypt, India, and China as early as 5,000, 3,300, and 2,300 years ago, respectively. Typical skeletal abnormalities, including Pott's deformities, were found in Egyptian and Indian mummies and were also depicted in early Egyptian and pre-Colombian art. [7]

Identification of genetic material from *M. tuberculosis* in ancient tissues has provided a powerful tool for the investigation of the incidence and spread of human TB in historic periods. It also offers potential new insights into the molecular evolution and global distribution of these microbes. Research on ancient DNA poses extreme technical difficulties because of the minute amounts of DNA remains, their oxidation/hydrolysis, and the extremely high risk of contamination with modern DNA. [8]

The term phthisis (Greek word means consumption) appeared first in Greek literature. Around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times. It most commonly occurred between 18 and 35 years of age, and was almost always fatal. [7]

Hippocrate warned physicians against visiting consumptives in advanced stages of the disease, to preserve their reputation! Although some Greek physicians considered the disease to be contagious, most Greek authors believed it to be hereditary, and a result, at least in part, of the individual's mental and moral weaknesses. Clarissimus Galen, the most eminent Greek physician after Hippocrates, defined phthisis as an ulceration of the lungs, chest or throat, accompanied by coughs, low fever, and wasting away of the body because of pus. He also described it as a disease of malnutrition. [9]

History of TB epidemics:

The TB epidemic in Europe, later known as the "Great White Plague", probably started at the beginning of the 17th century and continued for the next 200 years. By 1650, TB was the first leading cause of mortality. The high population density and poor sanitary conditions that characterized the enlarging cities of Europe and North America at the time, provided the necessary environment, not met before in world history, for the spread of this airborne pathogen. The epidemic spread slowly overseas by exploration and colonization. [7]

TB existed in America before Columbus' arrival but was rare among the natives. The major outbreaks of TB among the native people of North America began in 1880, after they were settled in reservations or forced to live in barracks in prison camps. Death rates increased rapidly, and by 1886, reached 9,000 per 100,000 people. [10]

It is presumed that the genus *Mycobacterium* originated more than 150 million years ago. An early progenitor of *M. tuberculosis* was probably simultaneous and co-evolved with early hominids in East Africa, three million years ago. The modern members of *M. tuberculosis* complex seem to have originated from a common progenitor about 15,000 - 35,000 years ago. [11, 12]

In the 18th century, TB was sometimes regarded as vampirism. These folk beliefs originated from two observations: firstly, following the death from consumption of a family member, household contacts would lose their health slowly. This was attributed to the deeds of the recently deceased consumptive, who returned from the dead as a vampire to drain the life from the surviving relatives. Secondly, people who had TB exhibited symptoms similar to what people considered to be vampire traits, such as red, swollen eyes, sensitivity to bright light, pale skin, and a blood-producing cough. They "wasted away" and "lost flesh" and at the same time remained active, and conserved a fierce will to live. [11]

The discovery of the tubercle bacillus:

The earliest references to the infectious nature of TB appeared in 17th century Italian medical literature. [12] In the publication of *"A New Theory of Consumptions"*, in 1720, the English physician Benjamin Marten was the first to guess that TB could be caused by "minute living creatures", which, once they had gained entry to the body, could generate the lesions and symptoms of phthisis. He further stated that consumption may be caught by a second person by lying in the same bed, eating and drinking or by talking together so close to each other. On the evening of March 24, 1882, in Berlin, Robert Koch made his famous presentation