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Tuberculosis: From an Untreatable Disease in Antiquity to an Untreatable Disease in Modern Times?

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Abstract

The history of tuberculosis (TB) is intricately connected to the history of humanity. The disease is considered one of the oldest infectious diseases afflicting mankind. Its history is that of colorful, often vibrant descriptions and interpretations, in the attempt of human societies to demystify the origins, causality, and course of this grave and lethal disease, and in the ultimate pursuit of finding a cure. The discovery of the tubercle bacillus on March 24th 1882, by Robert Koch, led to an unprecedented increase in international research efforts, ultimately resulting in the development of a vaccine and many potent antimicrobial agents and treatment regimens. However, the course of history is often not without some irony, commonly perceived as being unpredictable by those who find themselves immersed in history's path. In this sense, and despite the advances that were made in diagnostics and treatment during the past 70 years, TB continues to challenge mankind on numerous levels even today. The most recent emergence of multidrug-resistant and extensively-drug-resistant strains of *Mycobacterium tuberculosis* is only a small but significant reflection of the ongoing challenges in the attempt of eradicating this disease. Here we provide a review of the historic aspects of TB leading to a discussion of the current state of the approach to antituberculous treatment, including the aspects of microbiology, diagnostics, antimicrobial therapy, and public health.

Keywords: Tuberculosis; Antimicrobial drug resistance; Consumption; TB control; *Mycobacterium tuberculosis*; Public health

Introduction

Tuberculosis (TB) is an infectious disease caused by the airborne transmission of *Mycobacterium tuberculosis*, and other mycobacteria belonging to the *Mycobacterium tuberculosis* (Mtb) complex: *M. canettii*, *M. africanum*, *M. microti*, *M. bovis*, and two subspecies *M. caprae* and *M. pinnipedii* [1].

TB is associated with a significant morbidity and mortality. According to data by the World Health Organization (WHO), in the year 2011, 8.7 million people were newly infected with TB, worldwide, and 1.4 million deaths occurred due to TB [2]. While this most recent report states that the Millennium Development Goal target to halt and reverse the TB epidemic by 2015 had been already achieved, the global burden of the disease is still enormous and the emergence and increase of multidrug resistant tuberculosis has presented new challenges to the global TB control program [2,3]. TB is not only the cause of a significant global socioeconomic burden, but patients who are potentially cured of this disease often suffer lifelong sequelae with significant reduction in quality of life [4,5]. Before the era of modern antimicrobial therapy, TB was an illness feared by all of human societies. The impact of this disease is perhaps best illustrated in Rene Dubos classic work "*The White Plague: Tuberculosis, Men, and Society*", although the term was most likely first used by Oliver Wendell Holmes in the 18th century to depict the emerging tuberculosis epidemic in Europe [6,7]. With the discovery of streptomycin as an effective anti-tuberculous agent in 1944, followed by the development of many more effective antimicrobial agents and treatment regimens, tuberculosis in Western Europe and the U.S.A. began to decline [7]. Sadly enough, as the prevalence of the disease declined in these countries, so did the interest in global disease surveillance and research; tuberculosis was no longer considered a threat to developed countries [7,8]. However, by the 1980s tuberculosis could no longer be ignored, since the incidence and prevalence of TB had drastically increased in developing countries, specifically in sub-Saharan Africa, Asia, and South America [9]. By the 1990s, even in many European countries and the U.S., increasing rates of TB infection were seen, often related to immigrant populations from other endemic areas [10,11]. An equally important contributing factor to the increase in TB worldwide was the occurrence of the Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) pandemic [12,13]. Patients who are co-infected with HIV and *Mycobacterium tuberculosis* are much more likely to develop overt and rapidly progressive to fatal TB [3,12,13]. Of even greater concern at this time was the rapid emergence of antimicrobial resistance to many of the original anti-tuberculous agents. These events were considered to be so serious, that the WHO declared TB as a global health emergency in 1993 [9]. Today, 20 years after this declaration, tuberculosis and antimicrobial drug resistance remains a significant problem to the world. TB is no longer a concern of few public health workers, but has risen once again to the forefront of the public interest: popular media have as recent as March 2013 reported on the global burden of multidrug resistant tuberculosis [14], and recently information about increased cases of TB in Los Angeles, CA, and London, UK, were reported in the public media [15]. In this review, we provide a brief review of the history of tuberculosis as well as the past and current approach to treatment.

A Brief Review of History from Prehistoric Evidence to the Modern World

As stated above, Tuberculosis (TB) is one of the most deadly, but also

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curable and even preventable diseases in the world; it is perhaps as old as recorded human history, itself. Over the course of several millennia, the history of this disease is that of repeated scientific, medical, social, and political failure of societies. In this paragraph, we will briefly review the course of history of this fascinating disease with a special focus on recognition/diagnosis and approach to treatment of TB.

The earliest historical evidence of human tuberculosis dates back to approximately 8000 BC [16]. Tuberculous bone lesions have been described in fossils of vertebrae, possibly dating back to the Neolithic period [17]. Until recently, it has been a common scientific understanding that the disease in humans originated from TB in domesticated animals (namely TB in cattle caused by *M. bovis*) sometime during the Neolithic period [18,19]. However, a new, revised theory emerged when the complete genome of *M. tuberculosis* was sequenced in 1998 [20,21]. Based on this recent evidence, it seems reasonable that *M. tuberculosis* existed as a distinct pathogen approximately 35,000 years ago [22]. However, from the same studies [20-22], it appears that the ancestor to all bacilli of the Mtb complex already was a cause of TB approximately 3 million years ago. Therefore TB is likely to be a much older disease than plague, malaria, and typhoid fever [22]. It is plausible that the ancestral *Mycobacterium* affected early humans in East Africa [22,23]. Following the patterns of human evolution and waves of migration, mycobacteria may then have undergone further changes and diversification [22].

Tuberculosis was already known to the ancient Egyptians. Osseous changes found in some Egyptian mummies indicate that spinal TB likely existed as far back as 3500 BC, and TB was described in the early and the later periods of the ancient Egyptian dynasties [16,24,25]. Prominent examples of people afflicted with the disease are two pharaohs of the 18th dynasty: Echnaton (ca. 1351-1334 BC) and Tutanchamun (ca. 1332-1323 BC) [18].

Even more detailed and systematic descriptions of TB are available from the ancient Greek literature. The Greek physician Hippocrates (460- 370 BC) described some cases that have proven TB was a major cause of death at that time [16]. It was around this time that the words "phthisis" and "consumption" were first used to describe the disease state of TB. Interestingly, Hippocrates even made recommendations to other physicians of his time that they should not have any contact with their patients when in the final stages of the disease [16]. From today's perspective, it can be inferred that Hippocrates seemingly knew that he could not cure the disease and that it was highly contagious. The literature also ascribes Hippocrates to be the first to describe the presence of tubercles in tissue sections from various animals (cows, pigs, and sheep); however, he did not perform autopsies on human bodies, for that practice was prohibited in Ancient Greece [16]. Therefore, Hippocrates believed consumption to be a hereditary disease, and he failed to recognize the infectious nature. However, Aristotle (384 -322 BC), another Greek historian and physician, believed that phthisis/consumption was indeed a contagious condition, rather than a hereditary illness. Aristotle based his opinion on observations of skin lesions (later known as "scrofula") in pigs with consumption [16]. A colorful, yet dramatic description of the clinical presentation of pulmonary consumption was provided by the Greek/early Roman philosopher and play-writer Titus Maccius Plautus: "pulmoneum vomitum vomere" (meaning volatile vomiting of lung tissue) [18]. It is also remarkable that physicians and historians of the ancient world recognized tuberculosis as a disease affecting people in cities more commonly than people in rural dwellings. The theory of the infectious nature of consumption ultimately grew in popularity among Roman physicians such as Caelius Aurelianus (5th century AD) and Galen (131-201AD). The detailed information of the clinical disease provided by Aurelianus is a remarkable accomplishment for the time of his writing. Like Aurelianus, many other physicians in ancient Rome studied the patients with consumption and gathered clinical evidence to support the theory of its infectious nature [16]. Galen, another Roman physician, was also a strong proponent of the infectious disease theory of consumption. In his writings, he clearly warned against intimate contact with 'consumptives'. Despite the fact that he had no knowledge of modern pathology, as it relates to TB, his clinical observations lead him to believe that phthisis/consumption is an infectious disease rather than a hereditary condition. In summary of the data from the prehistoric and ancient time periods, it appears that TB was a well recognized illness among ancient societies in Egypt, Greece, and Rome. However, the exact pathologic basis of the disease was unknown, as reflected by the use of various terminologies such as phthisis and consumption, and the fact that there was a lack of consensus regarding the contagiousness of the illness. The existing evidence from the ancient world further supports the theory that consumption was most prevalent in highly populated, urban areas, and it is not surprising that other texts of antiquity did not mention consumption and phthisis (i.e. TB) in people living in rural areas [26]. In this regard, it is worth mentioning the *Plague of Justinian*; the epidemic most likely originated in Egypt around AD 532 and spread through the Middle East and the Mediterranean, lasting for almost 200 years [27,28]. Many infectious diseases have been suggested to have caused this great plague, including anthrax, bubonic plague (caused by *Yersinia pestis*), smallpox, and tuberculosis. While the exact cause of this epidemic plague remains unknown, to date, it seems plausible that TB was a major contributor to the repeated disease outbreaks during this time. Considering the many immigrants coming from rural northern and Eastern Europe to the ancient city of Rome, these people were most likely never exposed to TB before and had therefore no immunity. They were the perfect host and vector for repeated cycles of transmission of the causative organism [16,29].

Aside from the evidence for the existence of TB in the Old World, the disease was also believed to be present in the pre-Columbian Americas at the same time [30,31]. A particularly interesting discovery was made by Allison in 1973. The investigator and his team described the presence of acid fast bacilli in sections of a mummified child dating back to approximately 700 AD found at a site close to Nasca, Peru [30].

The end of the West-Roman Empire around 480 AD brought not only an end to art, science, and culture of the antique world, but also brought loss of knowledge in medicine and public health and hygiene. With significantly decreasing standards of living, people of the early to high medieval time period were more susceptible to infectious diseases and epidemics, including tuberculosis [18,32]. Frequently, people suffering from consumption, leprosy, and other "evil ailments" were banned from living within the limits of medieval towns and cities, and illness in general was often seen as a punishment by God [18]. During the medieval time period, a special form of mycobacterial infection was readily recognized: scrofula, also known as tuberculous cervical adenitis. This mycobacterial infection of cervical lymph-nodes commonly afflicted children, and many reports are known from medieval England and France [33]. During the middle Ages, *M. bovis* was a common cause of scrofula; today, other, non-tuberculous mycobacteria have replaced this organism as the causative organism of this disease. It was widely believed that royalty possessed the gift to cure children by a ceremonial royal touch [33,34]. The first kings believed to have this gift were Clovis of France (481-511AD) and Edward the Confessor (1042-1066AD) of England. The formal practice of this rite continued well into the 1700s.

During the Renaissance, the knowledge of science was again widely expanding. Contrary to the ancient Greek belief that consumption describes a general bodily wasting, the Italian physician Girolamo Fracastoro reserved the term phthisis for pulmonary consumption only [16]. In his famous work, *De Contagione*, he also suggested that the disease was indeed infectious and could be transmitted by a "small invisible virus". He further postulated that transmission of this "virus" occurred when one would come in contact with pus and bodily fluids, or with clothing and other fomites previously contaminated by the contagion [16]. It seems likely that this knowledge came from evidence obtained by autopsy work, which had become more commonly practiced by the physicians of the Renaissance. In fact Vesalius (1514-1564), who was one of the greatest physicians and anatomists of his time, conducted many autopsies and correlated the clinical presentation and course of disease with his findings from the autopsies of diseased bodies. By the 17th century, autopsies were regularly performed and detailed information about pathologic findings of consumption became readily available and shared among anatomist physicians of this time [16,18]. Among many writings, the text, *Opera Medica* by the Dutch neuroanatomist Sylvius de la Boë of Amsterdam, was the first to provide details about the morphology and pathology of pulmonary TB. He specifically provided descriptive information on morphology of tubercles found in the lungs and other organs targeted by this disease [18]. Along with these organ findings, he also was able to study the progression of tubercles into cavitary lesions. With his descriptions, de la Boë essentially provided the foundation to understand the pathology of tuberculosis as a disease. Ten years after de la Boë's astonishing account of consumption, Richard Morton of London (1637-1698) documented similar observations of disease progression, therefore supporting the earlier theories by de la Boë. During the 17th century, consumption (TB) was widely present in England and John Locke stated in his work *De Phthisi* that approximately 20% of all deaths in London were due to this very disease [34]. Interestingly, Morton published in 1689 very detailed descriptions and cases in his book *Phthisiologia*. There he described consumption as a disease having three major stages that eventually progressed slowly, "permitting that death would not occur right away" [16,35]. The three stages that he documented were initial inflammation, leading to the formation of tubercles, which would then ultimately manifest into ulcers and cavities. His work contains solely his own observations of the disease and he makes little if no reference to previous (e.g. Hippocrates) or other contemporary concepts of consumption. Upon reading the clinical case descriptions included in his book, and considering that Morton compiled his clinical observations without any aid of modern diagnostic technology, one can only admire the remarkable detail and accuracy of his observations and deductions [34]. But even though his findings suggested otherwise, Morton still believed the disease was of a hereditary nature. Ironically, he did not rule out the possibility of there being an infectious component as well; however, the Italian medical literature at the same time clearly suggested consumption to be of infectious nature [16].

In 1720, Benjamin Marten (1704-1722) published his book *A New Theory of Consumptions, More Especially of a Phthisis or Consumption of the Lungs* [36]. Although the idea of *animalcules* ("small living cells") causing infections in people grew in popularity after Leeuwenhoek's invention of the microscope and discovery of bacteria in 1676, Marten's theory was the first in history to state that consumption was caused by an infection of the lungs [36]. Marten suggested that these *animalcules*, once entering the body, are the direct cause of tubercles and other classic lesions of consumption. 163 years after this remarkable proposal, it was Robert Koch who experimentally verified the infectious nature of TB. Marten further introduced the concept of transmissibility of consumption, particularly when one came into close contact with an infected person. He also noticed in his clinical observations that not every contact immediately resulted in disease, but that rather close contact and "airborne transmission" lead more frequently to the rapid development of disease in the previously healthy [16,36].

While by the end of the 18th century, microscopy and systematic evidence from autopsies provided the foundation for a better and well developed understanding of consumption, it was not until the 19th century that true scientific research on TB emerged. Rene Theophile Hyacinthe Laennec of Paris (1781-1726) believed that the multiple forms of consumption were one single infectious entity. On the contrary, Giovanni Battista Morgagni of Padua (1682-1771) and Rudolf Virchow of Berlin (1821-1902) remained strong supporters of the idea that tubercles, scrofula, and consumption were different disease entities. Finally in 1834, the German physician Johann Lukas Shönlein of Würzburg (1793-1864) coined the unifying term Tuberculosis, describing the pathologic afflictions with tubercles [37,38]. However, he did not support the theory of a unitary disease, and like many other German physicians and pathologists used the terms scrofula, phthisis (pulmonary consumption), and tuberculosis to describe different disease entities, the latter term denoting a form of extrapulmonary TB [37]. While the debate between the German school and the French school over the unity of TB as a disease continued for several more decades, it was Robert Koch's discovery of the tubercle bacillus in 1882 that marks the turning point in the understanding of this deadly disease [39]. In prior years, Louis Pasteur had introduced the germ theory (1862), and Robert Koch had already demonstrated the life cycle of *Bacillus anthracis* providing proof for the first time in history that a microorganism can cause a single disease (1876) [40]. In 1877, Cohnheim had experimentally inoculated rabbits with tuberculosis; Tappeiner had shown that dogs could contract TB by inhalation of droplets obtained from infectious material [40,41]. It was then on March 24th 1882 that Robert Koch announced his discovery of the tubercle bacillus at the meeting of the Berlin Physiological Society. Seventeen days later, he published his lecture "Die Ätiologie der Tuberkulose" in the Berliner Medizinische Wochenzeitschrift [42]. Immediately after Koch's lecture, a young physician at the Berlin Charité hospital, Paul Ehrlich (1854-1915), who was inspired by Koch's presentation, began to work on improving the staining methods for tubercle bacilli. Ehrlich had already developed other stains for tissues and bacteria, and now experimented to apply these stains to visualizing Koch's tubercle bacilli [40]. He initially applied aniline water, fuchsin, and gentian-violet, shortened the staining time and also applied 30% nitric acid and alcohol for better decolorization of the tissues surrounding the tubercles, but it was only by accident that he discovered the benefit of heating the slides prior to staining [40]. The same year, Ziehl introduced the use of carbolic instead of aniline for the stain, and later Neelsen introduced the use of sulphuric acid instead of nitric acid [40,43]. With these modifications, the staining method for tubercle bacilli became known as the "Ziehl-Neelsen" or the "acid-alcohol fast bacillus" stain [40]. It should also be mentioned that Robert Koch after the discovery of the tubercle bacillus continued research on tuberculosis and was determined to identify a cure or vaccine for the disease. In 1890, at the 10th International Medical Congress in Berlin, he announced the discovery of a substance that inhibited the growth of tubercle bacilli [40,44]. In 1891, he published his findings in the *British Medical Journal* [45]. His announcement lead to a tremendous excitement worldwide and many people travelled to Berlin in search for a cure for TB. At The Johns Hopkins Hospital in Baltimore, USA, Professor William Osler had received two small

bottles of tuberculin that were sent by Robert Koch himself [40]. With all the international excitement at that time, tuberculin was widely used; however, tuberculin administration to patients with advanced tuberculosis resulted in many severe reactions, turning the initial enthusiasm for a cure into a grave disappointment [44]. Despite these setbacks, Robert Koch continued his research on tuberculin; in fact, tuberculin subsequently proved to have no therapeutic value, but its utility in the diagnostic setting gained wide acceptance and is still used in today's TB monitoring programs. For his contributions to science and medicine and his work on tuberculosis in particular, Robert Koch received the Nobel Prize for Medicine in 1905 [40].

The Changing Field of Anti-Tuberculosis Treatment

In the previous section we discussed the historic aspects leading to a better understanding of a disease, namely TB that since earliest recorded human history exhibited some of the most devastating effects on peoples and societies. Ever since Robert Koch's remarkable breakthrough discovery of the tubercle bacillus in 1882, a steady increase in TB research associated with substantial financial support led to the development of a vaccine (Bacille *e* Calmette *et* Guérin, BCG) as well as effective anti-tuberculous agents for treatment and prevention. Regrettably, 60 years after the discovery of the first effective anti-tuberculous drug, streptomycin, there are currently more cases of TB worldwide than there were at any previous time in history [7,46]. In the following section, we will discuss the discovery and evolution of the most common anti-tuberculous agents, their clinical utility, and the development and mechanisms of drug resistance, as this information is crucial in developing an understanding of the "re-emergence" of tuberculosis as a societal health problem.

It was about 60 years after the discovery of the tubercle bacillus, in 1943, that the first effective anti-tuberculous agent, streptomycin, was discovered by Selman Waksman at Rutgers University, NJ. Subsequently, in 1944 the first TB patient was successfully treated with streptomycin and ultimately declared to be cured of the disease [47]. Following this initial success, several other individual and/or anecdotal cases of successful administration of streptomycin followed, until in 1948 the British Medical Research Council (BMRC) conducted the first large-scale clinical trial for use of streptomycin in TB patients [48,49]. This trial was the first of its kind and is considered to have set the methodological standard for all modern randomized, controlled clinical trials [47]. It was concluded that streptomycin monotherapy was efficacious, significantly reduced immediate mortality, and resulted in striking improvements based on chest X-ray findings and microbiologic sputum evaluation [48]. But it was in the same year that Crofton and Mitchison reported the first streptomycin resistance in *M. tuberculosis* [50]. Ultimately, the 5-year follow-up data from the initial BMRC trial showed that there was a significant relapse rate among patients treated with streptomycin; essentially no statistically significant difference in 5-year survival rates was seen between patients who received streptomycin and those who did not receive treatment [51]. *Mycobacteria* isolated from patients who had relapsed showed resistance to streptomycin [50]. At the time of this first clinical trial, another anti-tuberculous agent had been developed: para-aminosalicylic acid (PAS) [47]. When this newer drug was given together with streptomycin to TB patients, the rate of cure was higher and antibiotic resistance rates were lower [52]. Within the following 10 years several more anti-tuberculous agents were discovered and/or developed: isonicotinic acid hydrazide (isoniazid, INH) (1951), pyrazinamide (PZA) (1952), cycloserine (1952), ethionamide (1956), rifampin (1957), and ethambutol (1962) [47]. Given the experience from the earlier clinical studies of streptomycin and PAS, the BMRC conducted additional trials with isoniazid as a single agent or in combination with streptomycin and PAS [47,52]. During a 2-year surveillance study of drug resistance in the United Kingdom, the investigators identified that anti-tuberculous drug resistance almost always affected only one of the three available drugs [53]. These findings ultimately led to the implementation of treatment approaches using a three-drug regimen, consisting of streptomycin, PAS, and INH [47]. During the following decades, as more clinical trials with the newly developed anti-tuberculous drugs emerged, the WHO and many other government organizations worldwide implemented various guidelines for short-term and long-term multi-drug regimens for the treatment of active and latent TB. The discussion of these various programs and approaches is beyond the scope of this review, and the authors refer to the relevant literature for further detailed information [2,54].

Currently, there are 10 drugs approved by the Food and Drug Administration (FDA) available in the U.S. for the treatment of TB [54]. A summary of currently available anti-tuberculous agents and suggested regimens is listed in Table 1. As recommended by the Centers of Disease Control and Prevention (CDC), there are four regimens available for treatment of patients with TB caused by drug-susceptible *M. tuberculosis* [54]. Of the FDA-approved drugs, INH, rifampin, ethambutol, and pyrazinamide are considered first-line anti-tuberculous drugs. These 4 agents are the core components of the initial phases of every treatment regimen [54]. Each regimen consists of an initial treatment phase (2-months duration), followed by a continuation phase (variably 4-7 months duration). For the vast majority of patients in the U.S., the option of a 4-month continuation phase is currently used. The 7-month continuation phase is recommended if patients meet at least

Category	Indication for use in TB treatment	Dugs
1	First-line, oral antituberculous agents	Isoniazid (INH)
		Rifampin / Rifampicin
		Ethambutol
		Pyrazinamide
		Rifabutin
2	Injectable antituberculous agents, second-line antituberculous agents	Streptomycin #
		Kanamycin
		Capreomycin
		Amikacin
3	Fluoroquinolones, second-line antituberculous agents	Levofloxacin
		Moxifloxacin
		Gatifloxacin
4	Oral bacteriostatic, second-line antituberculous agents	Ethionamide
		Prothionamide
		Cycloserine
		p-Aminosalicylic acid
		Terizidone
5	Antituberculous agents with unclear efficacy and/or role	Linezolid
		Clofazimine
		Clarithromycin
		Thioacetazone
		Imipenem
		Amoxicillin/ clavulanate
		Dapsone

*adapted from [87-89]

#denotes first-line antituberculous agent/drug

Abbreviations: TB: Tuberculosis

Table 1: Anti-tuberculous agents currently available for treatment*.

one of the following criteria: 1) presence of cavitary pulmonary TB due to drug-susceptible organisms, and positive sputum culture at the time of completion of the initial phase; 2) treatment during the initial phase did not include PZA; and 3) treatment during the initial phase was once weekly INH and rifapentine, and positive sputum culture at the time of completion of the initial phase [54]. Special guidelines for treatment regimens are considered for special patient care situations, e.g. HIV infection, children, pregnant and/or breastfeeding women, and cases with extrapulmonary TB [54]. However, it is important to recognize that according to all these guidelines, the completion of treatment (i.e. a full course of treatment) is not based on the duration of therapy, but rather determined by the total number of doses taken [2,54]. The primary goal of anti-tuberculous therapy has always been the rapid elimination of viable organisms from lesions in order to prevent future relapses of the disease. In more recent years, the additional goal of preventing the development of antimicrobial drug resistance has also risen to the forefront of concerns voiced by physicians and public health officials. To place these treatment goals and guidelines into a more international context, it is necessary to understand the different treatment approaches and implementation in high-incidence, low-income countries. While TB steadily declined during the first half of the 20th century in Europe and the U.S., the prevalence remained high in many other parts of the world, and by the mid-20th century, TB outcomes had diverged along the fault lines of the global economy [3,47,49,55]. On September 6th 1978, perhaps inspired by the eradication of smallpox in the prior year, the delegates of the *International Conference on Primary Health Care*, convened at Alma-Ata (today's Almaty) in Kazakhstan, and gave their support to the goal of "Health for all by the year 2000"; their commitments and affirmations included a firm statement on combating infectious diseases, perhaps aiming at the possibility to eradicate TB [47,56,57]. However, only a few years later, with decreasing financial support for the goals of Alma-Ata, many policymakers and supporters of international health embraced a new concept: selective primary care. In order to balance the enormous financial need for TB eradication programs and other international public health measures, the focus was shifted to development of discrete, targeted, and inexpensive interventions [47,58]. In 1993, the World Bank, a major financial supporter of international public health programs, reassessed its metrics to evaluate the decision process to determine the distributions of funds for such programs [59]. The assessment of "disability-adjusted life-years", a measure of morbidity and mortality by age, was introduced to evaluate the "cost effectiveness" of any given health intervention/program in order to be deemed worthy of funding. Truly effective treatment of TB in the 1950s and 1960s typically required extensive antimicrobial chemotherapy for 18-24 months, and even with regimens shortened to 9 months, it was quickly evident that a major obstacle to the cure of patients in resource-poor settings and developing countries lay in the patients' compliance with the lengthy treatment regimens, allowing interruptions of drug administration for various reasons [49]. With the intent to maintain the efforts of international TB programs, the WHO recognized this report as an opportunity to develop a new approach to anti-tuberculous therapy: short-course chemotherapy for TB was declared a highly cost effective intervention [47]. As this new approach gained momentum, the WHO developed and promoted the "directly observed therapy, short course" (DOTS) strategy for treatment of tuberculosis [47,60]. It should be noticed that the concept of directly-observed-therapy, however, had emerged from BMRC clinical trials in India and Hong Kong some 30 years earlier [61]. Since 1995, the WHO has been encouraging many countries to implement the DOTS strategy, and directly-observed-therapy has even gained popularity in developed nations as a measure to assure compliance with still cumbersome treatment regimens. Although directly-observed-therapy and DOTS remain appealing to many health care providers and public health officials, it will be necessary to continuously evaluate the ramifications and effects of this treatment approach: patient behavior and compliance, available resources, and the centrality of directly-observed-therapy are only a few of the possible challenges to be considered [61-63].

While the advent of the HIV/AIDS pandemic presented the first major challenge to sustained efficacy of antituberculous treatment regimens, the most recent events of emerging and growing antimicrobial drug resistance are presenting a second wave of challenges to the public health community and TB programs. Drug-resistance in TB is not a new phenomenon, but was first recognized following the introduction of streptomycin as a treatment option in 1944; in later years with the introduction of other antituberculous agents, resistance to these agents was also seen [64,65]. As mentioned above, two of the major contributors to the emergence of drug resistance in TB are the use of inappropriate treatment regimens (e.g. monotherapy) or patient non-compliance with prescribed treatment [66,67]. However, spontaneous mutations that result in drug-resistance in *M. tuberculosis* also occur at predictable rates [64]. While the rate at which resistance develops is different for each of the antituberculous agents, it is worth mentioning that it is highest for ethambutol and lowest for rifampin and fluoroquinolones [64]. Detailed information regarding the clinical and molecular concepts of resistance development in *M. tuberculosis* is available elsewhere in the literature and beyond the scope of this review [64,65,68]. Here we will specifically discuss the most recent issues of multidrug resistant and extensively-drug resistant TB (MDR-TB and XDR-TB). Resistance of *M. tuberculosis* to more than one primary antituberculous drug was reported in the medical literature as early as 1970 [69]. An outbreak of a highly virulent strain of *M. tuberculosis*, resistant to multiple drugs in New York City was reported by Steiner et al in 1970, and subsequently other reports followed throughout the 1980s and 1990s [47,69,70]. MDR-TB, defined as resistance to isoniazid and rifampin, has been recognized with increasing frequency, worldwide, since the earliest reports in the 1970s [2,49,54]. Since the 1990s, MDR-TB has been a significant and growing problem in sub-Saharan Africa and India. However, even in Europe and the U.S., MDR-TB has become a major public health problem [71-75]. Specifically, reports of the rapid emergence and spread of MDR-TB and challenges to anti-TB therapy in India have been a concern to local and global public health [74-76]. Highest rates of MDR-TB are reported from countries within the area of the former Soviet Union (Azerbaijan, Moldova, Uzbekistan), India, and China; in fact 62% of the estimated global incidence of MDR-TB is accounted for by three countries, China, India, and the Russian Federation, and the incidence and prevalence are globally increasing at an alarming rate [71,72]. The treatment of MDR-TB requires the use of 2nd-line drugs including fluoroquinolones. At the time of increased efforts by the WHO to facilitate treatment efforts of MDR-TB in resource-limited countries, the emergence of resistance to 2nd-line and other alternative anti-tuberculous agents was noticed in various regions of the world [77-79]. XDR-TB is defined as resistance to INH and rifampin, with the addition of resistance to at least 1 of 3 injectable 2nd-line drugs (amikacin, kanamycin, or capreomycin), and any fluoroquinolone (FQ) [80]. From the review of these reports, it is evident that XDR-TB is now present worldwide, is associated with worse treatment outcomes when compared to MDR-TB, and therefore poses a significant threat to global public health. As of 2011, 19% of countries/territories reporting to the WHO TB surveillance program have documented more than 10 cases with XDR-TB within a single year. The highest rates for XDR-TB were reported in Azerbaijan (12.7%),

Belarus (11.9%), Estonia (18.7%), Latvia (12.6%), Lithuania (16.5%) and Tajikistan (21%) [2]. XDR-TB, however, is not only a disease in countries with limited resources for public health and TB programs, but has been recognized in Europe and The U.S., as well [79,81,82]. Two studies in 2006 and 2008 reported that worldwide approximately 10% of MDR-TB strains eventually acquire additional resistances to become XDR-TB [72,82]; however, within the last few years some even more alarming resistance trends have emerged. The first study was published in May 2007; the investigators reported 2 patients with a longstanding history of tuberculosis who had received three different treatment courses for over 30 days, before they were admitted with suspected MDR-TB to a specialty hospital [83]. Both patients were young, native Italian females, and at least one patient had a history of close contact with another confirmed MDR-TB patient. The organisms isolated from cavitary lung lesions in both patients were resistant to all of the following drugs: streptomycin, rifampicin, isoniazid, ethambutol, pyrazinamide, ethionamide, amikacin, para-aminosalycilic acid, capreomycin, kanamycin, cycloserine, all fluoroquinolones, rifabutin, clofazimine, dapsone, clarithromycin and thiacetazone [83]. In fact, one of the investigators had raised concerns about the possible occurrence of "*extremely drug-resistant TB*" (XXDR) in several European countries [84]. A second study from Iran, published in 2009, reported 16 patients with a prior history of pulmonary TB who now presented complicated drug-resistant TB; the patients were from the following countries: Iran, Afghanistan, Azerbaijan [85]. The strains of *M. tuberculosis* recovered from these patients tested resistant to all of the following drugs: isoniazid, rifampin, streptomycin, ethambutol, pyrazinamide, amikacin, kanamycin, capreomycin, cycloserine, ethionamide, ofloxacin, and prothionamide. The investigators referred to these new strains of M. tuberculosis as "*totally drug-resistant*" (TDR) or "*super XDR isolates*" [86]. The final study reported 4 cases from India, all of whom had previously known TB and received intermittent, erratic, and unsupervised treatment with 1st-line and 2nd-line antituberculous drugs, often using incorrect dosing regimens [86]. Organisms isolated from these 4 patients tested resistant to all 1st-line and 2nd-line drugs.

These most recent reports about further increasing antituberculous drug resistance are highly alarming. It is important to note, that these new strains of "TDR-TB" did not only emerge in unrelated geographic regions, but also afflicted patients from all strata of society. It is also important to recognize that all patients either resided in regions with a high prevalence of MDR- and/or XDR-TB, or had close contact with other confirmed TB patients. All three papers raised further concerns regarding appropriate and timely diagnosis, implementation of appropriate antituberculous therapy, public health and infection control measures, and lastly more standardized guidelines for antimicrobial susceptibility testing (AST) to determine a more accurate definition of "TDR-TB". Regarding the latter issue, more readily available access to AST and timely reporting was also considered imperative to optimize the clinical care for these patients. The characteristics of drug-resistance in TB are summarized in Table 2.

At this point of the discussion, we want to briefly mention, that

Drug-susceptible TB [71]	**Multidrug-resistant TB (MDR-TB)** [71,72]	**Extensively drug-resistant TB (XDR-TB)** [77-81]	**Extremely drug-resistant TB (XXDR-TB) or totally drug-resistant TB (TDR-TB)** [82-86]
Susceptible to all 1st-line antituberculous drugs (note: AST for 2nd-line antituberculous drugs is not routinely performed)	Resistance to at least isoniazid and rifampin	Resistance to isoniazid and rifampin, *PLUS* any fluoroquinolones and at least one of three injectable 2nd-line drugs (amikacin, kanamycin, or capreomycin)	Resistance to all 1st-line (isoniazid, rifampin, rifabutin, ethambutol, pyrazinamide), and 2nd-line (streptomycin, amikacin, kanamycin, capreomycin, fluoroquinolones, *p*-aminosalicylic acid, ethionamide, cycloserine), and any other drug in category 5 (clarithromycin, dapsone, thioazetazone, clofazimine, linezolid)

TB: Tuberculosis; MDR-TB: Multidrug-Resistant Tuberculosis; XDR-TB: Extensively Drug-Resistant Tuberculosis; XXDR-TB: Extremely Extensively Drug-Resistant Tuberculosis; TDR-TB: Totally Drug-Resistant Tuberculosis; AST: Antimicrobial Susceptibility Testing

Table 2: Definitions of antimicrobial drug resistance in tuberculosis.

Drug class	**Investigational drug**	**Stage of clinical development#**	**Drug target and/or mechanism of action**	**Drug activity against**			
				Drug-Susceptible TB	**Drug-resistant TB**	**Replicating *M. tuberculosis***	**Non-replicating *M. tuberculosis***
				data based on *in-vitro* AST			
Oxazolidinones	Sutezolid (PNU-100480)	Phase II	Inhibition of protein synthesis	✓	(✓)	[0]	[0]
	AZD-5847	Phase II		✓	✓	✓	✓
Diarylquinolone	Bedaquiline TMC-207	Phase II	Inhibition of ATP synthase	✓	✓	[0]	[0]
Nitroimidazo-oxazines	PA-824	Phase II	Production of NO and Inhibition of mycolic acid synthesis	✓	✓	✓	✓
	Delamanid (OPC-67683)	Phase III		✓	✓	✓	✓
	TBA-354	Preclinical		✓	✓	✓	✓
Ethylenediamine	SQ109	Phase II	Inhibition of cell wall synthesis	✓	✓	[0]	[0]
Pyrroles	LL-3858	Preclinical	Unknown	[0]	[0]	[0]	[0]
Benzothiaziniones	BTZ043	Preclinical	Interferes with cell wall synthesis by epimerase inhibition	✓	✓	[0]	[0]

*adapted from references [87-90] (list of new antituberculous agents is not all inclusive and information on novel drug-combination regimens are not shown here)

#Phase of drug development based on Working Group on New TB drugs website [87]; accessed April 28, 2013

[0]: denotes no drug activity or no data available for sufficient assessment

Abbreviations: TB: Tuberculosis; AST: Antimicrobial Susceptibility Testing; ATP: Antimicrobial Susceptibility Testing;; NO: Nitric Oxide

Table 3: Selected new anti-tuberculosis agents*.

despite these alarming developments in TB drug resistance and the fact that no new 1st-line drugs are commercially available, there are exciting new candidate compounds from several different drug classes currently in development. Some of these compounds are summarized in Table 3, and more detailed information is available on the "Working Group on New TB Drugs" [87]. The two most important reasons for developing new anti-TB drugs are to shorten the duration of therapy for drug-susceptible TB and to improve treatment for drug-resistant TB. In addition, the search for safer, more efficacious drugs, useful also in special patient populations has become an important component in the search for new anti-TB drugs. Some of these newer compounds include oxazolidinones, nitroimidazopyrans, diarylquinolones, pyrrols, ethenylenediamines, ethylenediamides, and benzothiaziones. [88-90]. Linezolid, a broad spectrum antibiotic that inhibits protein synthesis by interfering with mRNA binding to the ribosome is currently in phase II trials for the treatment of MDR-TB [87,88]. Although no large clinical trials have been conducted to date, several small studies indicated that treatment regimens that include Linezolid can be used to successfully treat infections due to MDR-TB [88]. Sutezolid (PNU100480) and AZD5847 are other, newer oxazolidinones that are also in phase II studies [87]. Some preliminary evidence suggests that these drugs may have a better bioavailability and may be better tolerated by patients [88]. In addition, the two fluoroquinolones moxifloxacin and gatifloxacin are currently in phase III clinical trials [87]. Limited but promising data are available for diarylquinolones. These drugs reduce adenosine triphosphate (ATP) levels by selectively inhibiting the mycobacterial ATP synthase [87-89]. However, they do have little to no effect on other bacteria or eukaryotes. Bedaquiline (TMC207), a diarylquinolone, is currently undergoing phase II evaluation for the treatment of drug-susceptible TB, with promise of being a new 1st-line treatment choice [87]. Although there are currently no phase I clinical trials, at the time of preparation of this manuscript, there are 8 new anti-tuberculous compounds in various stages of preclinical evaluation [87].

Diagnosis and Treatment: Implications for Public Health

There is a consensus among public health officials and the TB community that the emergence of drug-resistant tuberculosis poses a significant threat to the prior achievements in combating this disease [84].

In 2007, Udwadia et al. published a brief communication on the issues of MDR- and XDR-TB in which they raised an important question: how important are descriptive names of drug resistance when there is little consensus on the approach to AST and even lesser hope for treatment? [91] Ascribing the extent of drug resistance and therefore the choice of terminology (MDR-TB, XDR-TB, TDR-TB) remains a microbiologic diagnosis. In the previous sections, we described the historic events leading to defining tuberculosis as an infectious disease and the development of anti-tuberculous therapy. In this final section, we will explore the past and present approach to TB diagnosis, with a few comments on possible future directions.

The traditional approach to the diagnosis of TB has been based on clinical parameters and culture-based evidence of the organism coupled with other laboratory tests [92]. From a clinical perspective, pulmonary TB is mainly defined by dry or productive cough, fever, sweating, anorexia, weight loss, and malaise, with persistent cough being the most common symptomatology [92]. In many regions of the world, patients presenting with symptoms suspicious of TB will be ultimately receive a confirmatory diagnosis by chest radiograph, positive tuberculin skin test (TST), or direct microscopy of sputum coupled with isolation of *M. tuberculosis* in the laboratory [92]. With regard to the diagnostic approach, one must clearly consider the state of the patient's clinical disease; current TB control programs in many parts of the world have focused on reducing the burden of active TB. It is important, however, to recognize the fact that the global TB burden is not simply defined by the incidence and prevalence of active disease, but also by the prevalence of latent tuberculosis infection (LTBI). Unfortunately, the diagnosis of LTBI, in the absence of good animal models to gain a better understanding of its pathophysiology, has been largely based on TST, the latter often being confounded by BCG vaccination. The increase in knowledge of immunology, together with newer laboratory tests such as interferon-gamma (IFN-γ) release assays (IGRAs) has provided opportunities to redefine the natural history of TB and LTBI in particular. Detailed information about these advances is available elsewhere in the literature and beyond the scope of this review [93,94]. Considering, however, the increased recognition of global drug-resistance in TB, it is important to understand and diagnose LTBI in the context of this emerging drug resistance trend. The recent emergence of more complex and extensive drug resistance in *M. tuberculosis* could perhaps also result in a larger drug-resistant LTBI burden in future years. In fact the recent case reports from Italy, Iran, and India may suggest that such events have already happened [83,85,86]. In that case, one might postulate that these case reports would only be the "tip of the iceberg". Therefore, the importance of accurate and timely diagnosis of MDR-TB and XDR-TB has been the driving force behind the development of more rapid diagnostic tests.

Here we will further discuss the utility of various diagnostic approaches in both developed and developing countries for both active and latent TB. A summary of common diagnostic test methods is provided in Table 4. Sputum-smear microscopy using an acid-fast stain remains in many resource-poor settings the sole laboratory method for TB diagnosis. Unfortunately, this method often lacks sensitivity, as it is dependent on the organism burden in sputum samples [95]. Furthermore, classic culture-based methods to confirm the presence of *M. tuberculosis* using either liquid or solid culture media are cumbersome and lengthy and often performed only in specialty hospitals [92,96-98]. This is particularly the case in countries with resource poor settings. Even more difficult are procedures for AST, as those, too, require the use of special media and drugs for testing. Detection of TB and AST using culture-based methods can take 6 weeks or longer because of the slow growth of mycobacteria. In recent years, with the improvement of molecular diagnostics, several newer test methods for rapid detection and AST in TB have been developed and are commercially available [97,98]. With the advances in molecular technologies specifically during the past 10 years, several molecular test methods for the detection of *M. tuberculosis* and select resistance genes are now available. Commonly used approaches employ nucleic acid amplification tests (NAAT), which typically rely on the amplification of a short DNA or RNA sequence of the organism. The most frequently targeted sequence in *M. tuberculosis* for these assays is the insertion sequence IS*6110* [92]. Rapid, molecular detection methods can be either applied to identify the organism in culture, or to directly detect TB from primarily respiratory specimens. NAAT applied to diagnostic specimens has the potential to reduce the TAT for the laboratory diagnosis of TB by at least 2-4 weeks compared to the traditional methods, based on mycobacterial growth detection [98]. Several "home-brew" as well as five commercial assays are available (Table 4); however, many of these tests require complex laboratory settings and may not be readily applicable to resource-limited settings [98]. Various techniques

	Diagnostic test	Methodology	Clinical sample	TAT	Sensitivity (%)		Comments / references
					Smear-positive samples	Smear-negative samples	
Traditional, conventional diagnostic tests	Microscopy (acid-fast stain)	Observation of acid-fast bacilli by Ziehl-Neelsen or other AFB stain	Sputum	30 minutes	Low (5,000 to 10,000 bacilli/mL in samples needed to give positive result)		While still used as the sole laboratory diagnostic in low-resource settings, test has low sensitivity [92, 95]
	Traditional culture	Isolation and identification of *M. tuberculosis* (use of LJ or Middlebrook 7H11 agar)	Sputum	3-8 weeks			[92, 96]
	Enhanced culture technology	MGIT; BACTEC MGIT960 automated detection system	Sputum	5-12 days			[92, 96]
Molecular test methodologies	Amplicor PCR (Roche Molecular Systems, Pleasanton, CA)	PCR	Sputum	2-3 h	90 – 100	50 – 95.9	[92, 98] FDA Approved
	Amplified MTD (Gen-Probe, Inc., Beford, MA)	Transcription-mediated amplification	Sputum	2.5-4 h	91.7 – 100	65.5 – 92.9	[92, 98] FDA Approved
	BD Probe Tec (Becton, Dickinson & Co., Franklin Lakes, NJ)	Strand-displacement amplification	Sputum	5 h	98.5 – 100	33.3 – 85.7	[92, 98]
	GenoType Mycobacteria Direct (Hain Lifescience, Nehren, Germany)	Transcription-mediated amplification	Sputum	6 h	85.7 – 94.6	33.3 – 65.4	[92, 98]
	Inno-LiPA Rif TB (Innogenetics NC, Ghent, Belgium)	LPA	Sputum, *M. tuberculosis* isolates	≤ 24 h	96%	no data available	[92, 98,101]
	LAMP (Eiken Chemical Co., Tokyo, Japan)	Loop-mediated isothermal amplification	Sputum	2 h	97.7	48.8	[92, 98]
	Xpert MTB/RIF (Cepheid Inc., Sunnyville, CA)	Real-time PCR	Sputum	≤ 2 h	100	86.3	[92, 98, 104-106]
Immunodiagnostics	TST	Cell-mediated response to intradermal injection of tuberculin	intradermal	72 h			[92]
	QuantiFERON-TB Gold In-Tube (Cellestis Ltd., Carnegie, Australia)	IGRA (measure IFN-gamma release)	Whole blood, heparinized	24 h			Similar sensitivity compared to TST; additional studies necessary to further delineate clinical & predictive value [92]
	T-Spot, TB assay (Oxford Immunotech Inc., Oxford, UK)	IGRA (measure peripheral blood mononuclear cells to detect T-cell response & IFN-gamma release)	Peripheral blood mononuclear cells	24 h			May have higher sensitivity compared to TST; additional studies necessary to further delineate clinical & predictive value [92]

*adapted from [92,98]

Abbreviations:

TB: Tuberculosis; TAT: Turn-Around-Time; AFB: Acid-Fast Baci; LJ: Löwenstein-Jensen agar;

MGIT: Mycobacterial Growth Indicator Tube (Becton, Dickinson & Co., Sparks, MD); LPA: Line probe assay; IGRA: Interferon-gamma release assay; shaded area indicates "*not applicable*" or "*no data available*"

Table 4: Current laboratory approaches and methods for the diagnosis of tuberculosis*.

are used for detection of *M. tuberculosis*: polymerase chain reaction (PCR), transcription-mediated amplification, strand displacement amplification, and loop-mediated isothermal amplification (LAMP). In various studies, summarized in a review by Parsons and colleagues, these tests have been shown a sensitivity of 86% - 100% in smear-positive samples and 33% - 93% in smear-negative samples [97]. Although most of these tests can be performed within 8 hours, it is important to recognize that initial steps of specimen (sputum) processing are still necessary. Furthermore, these tests also require strict compliance with quality assurance standards and good laboratory practice, therefore perhaps limiting the applicability to many low-resource settings [98-100]. Detection of drug resistance in TB can employ either traditional, broth or agar-based AST methods or molecular methods; similar to the issues mentioned for general detection of *M. tuberculosis* in patient specimens, traditional phenotypic methods are time-consuming and require stringent quality assurance standards [98]. Through gene-sequencing studies, it was found that antimicrobial resistance in TB occurs by spontaneous mutations in genes that are either encoding the target site for the drug or enzymes for drug activation [98]. No single genetic determinant for multidrug resistance has yet been described. Therefore the selection of a molecular test method for detection of drug resistance may be challenging. Molecular detection methods for TB resistance include line probe assays (LPA) and real-time PCR. Two LPA methods (Inno-LiPA Rif TB test, Innogenetics NV, Ghent, Belgium) and the DNA strip assay (Hain Lifescience, Nehren, Germany) detect rifampin resistance; the DNA strip assay also reliably detects resistance to isoniazid [98,101]. The most recently introduced rapid molecular test method is based on real-time PCR technology using hybridization with fluorescence-labeled beads. The ability to run the assay within a closed system is a major advantage of this technology over other molecular methods, since the chance of external contamination is significantly diminished [98,102]. The Cepheid GeneXpert®, (Cepheid Inc., Sunnyville, CA) is a single-reaction tube, molecular beacon-based, real-time PCR method, developed by Cepheid Inc. in collaboration

with the *Foundation for Innovative New Diagnostics* (FIND), for the detection of *M. tuberculosis* and associated rifampin-resistance [103]. This test method is simple and less time-consuming (TAT ≤ 2 h), requires no special molecular-laboratory expertise or biosafety requirements, when compared to other molecular technologies [98]. Based on a few studies to date, the Xpert MTB/RIF test has demonstrated good performance standards for the detection of *M. tuberculosis* and associated rifampin resistance [104-106]. In one study, the Xpert MTB/RIF had the following performance characteristics: 100% sensitivity, 91.6% specificity for smear-positive sputum samples; 86.3% sensitivity, 93% specificity for smear-negative sputum samples [105]. Another study demonstrated that the introduction of the Xpert MTB/RIF could substantially decrease morbidity and mortality of TB by improving case-finding and treatment [105]. Considering TB case-finding approaches, an accelerated control of TB also requires improved control measures. So far we have discussed various approaches to TB diagnosis; as stated above, the use of traditional methods, i.e. sputum smear microscopy and culture, may be inexpensive, but also time-consuming and lack sensitivity, potentially missing up to 40% of all TB cases in certain regions of the world [107]. Conversely, more sensitive test methods are also more costly, and may be prohibitive in some countries with limited resources [108]. In this regard, the introductions of biomarkers that reliably diagnose active TB, latent TB, or even predict the risk of progression, are an appealing concept to public health officials. Widely used "screening tests" that are currently in use are TST and IGRA; however, neither one of these tests can reliably differentiate between LTBI and active TB. In fact, in countries and regions of high TB incidence, approaching 100%, both tests are of practically no value in diagnostic algorithms [109]. While several biomarkers are currently under consideration, no one single biomarker is likely to become available within the next decade as a simple, low-cost, point-of-care test for diagnosis of TB [110,111]. Finally, some promising new technologies that are currently in development for TB diagnosis are a urinary test for detection of *M. tuberculosis* antigen, lipoarabinomannan (LAM) and breath analysis for detection of several volatile organic compounds (VOC) in patients with TB [98]. Continued research efforts to further understand the mechanisms of latency and immune-evasion in TB as well as research on the development of antimicrobial resistance in TB is necessary to further improve therapeutic approaches necessary to achieve the WHO target to eliminate TB by 2050.

Conclusions

In 1907, John B. Huber stated "The tubercle bacillus is an index by inversion of the real progress of the human race. By it the claim of civilization to dominate human life may fairly be judged. Tuberculosis will decrease with the substantial advance of civilization, and the disease will as surely increase as civilization retrogrades" [112]. These words are as true today as they were in 1907. In today's times, tuberculosis remains among the top 10 leading causes of death, worldwide. The WHO estimates that globally 2 billion people, one third of the world's population, are infected with *M. tuberculosis*, and that there are approximately 9 million new cases of active TB, annually. Estimates from the WHO data further suggest that almost 2 million people die annually because of TB; 25% of these deaths occur in patients who are co-infected with HIV. The history of tuberculosis changed numerous times and quite dramatically during the past 2000 years of human civilization. The most dramatic change occurred after the introduction of the first drug with anti-mycobacterial activity. Until that point, TB was considered an ultimately fatal disease only treatable in sanatoria. With the advent of anti-tuberculous agents in the 1940s, TB was considered an ailment that could be managed and even cured with antibiotics. With the support of national governments, civil society, private foundations, financial donors, the corporate sector, and under the auspices of the WHO, significant progress was made to decrease the global incidence. When the WHO declared TB as a "global health emergency" in 1993, the initial response from the international community was slow and inadequate; however, the global increase in TB prevalence, complexities of the HIV/TB co-infection, and the emergence of the early MDR-TB strains in various regions of the world had brought the global tuberculosis and public health community once again closer together. Today, the WHO Millennium Development Goal (MDG) to halt and reverse the TB epidemic by 2015 was said to have already been achieved [2], yet the global burden of tuberculosis is still enormous, and the recent emergence of XDR-TB and TDR-TB once again pose a great threat to the health of all human societies. In order to maintain the status of the MDG or perhaps achieve the goal of eliminating TB altogether, the WHO is clearly the principal agency to provide guidance for determining the best approach for successful TB control programs. However, at the present time of economic austerity, we find ourselves again at a crossroads in TB care and control. Zumla and Grange [12] stated that "the ultimate answer to the global emergency of tuberculosis lies in a revolution of human conduct and a replacement of the present world order with one based more equitably on natural justice." This statement written 14 years ago and prior to the emergence of XDR-TB and TDR-TB is still applicable today. Unless one wants to accept the fact that TB could once again become an untreatable and dreaded malady, mankind must globally combine all possible resources (governments, non-governmental organizations, corporate sector/industry, private foundations, and civil society) in order to fully support the efforts and research in microbiology, drug development, and clinical care to combat the emerging threat of TDR-TB and to ultimately achieve WHO's target to eliminate TB by 2050.

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