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Research Article

Biological Characteristics as a Determining Factor in Evaluating the Efficacy of DOTS in MDR Tb Treatment

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Abstract

Mycobacterium Tuberculosis (MTB) drug resistance (DR) is a manmade amplification of selective pressures of genetic mutants that result from spontaneous chromosomal mutations due to poor treatment methods, despite the WHO guidelines and enforcement. MDR TB rates are higher than ever (up to 22.3% in some countries) and extensively DR, (XDR) TB has been reported by as many as 49 countries [1]. Tuberculosis incidence rates overall have decreased in proportional and absolute terms, however, multi drug resistant (MDR) TB, resistance to Isoniazid (INH) and Rifampicin (RIF), remains an issue that is on the rise, affecting four million globally. The inadequate utilization of resources, treatment, and patient noncompliance has led to worrying levels of MDR TB in many regions of the world. INH resistance is chromosomally mediated with a mutation at the *katG* gene in mycolic acid synthesis and RIF resistance reduces binding to RNA polymerase with clusters of mutations at the *rpoB* gene. The directly observed therapy short course (DOTS) program is a standardized treatment regimen, created by the WHO that includes five components of TB treatment and uses first line drugs in its treatment regimen.

Background or Current State of Knowledge

MDR Tuberculosis Definition and Transmission

DR is a fairly recent phenomenon, emerging just over 60 years ago with the development of anti-tuberculosis drugs. With RIF's extensive use between 1970 and 1990, patients who were already resistant to INH became resistant to RIF as well. With the misuse of even second line drugs, resistance has broadened to XDR TB [2,3]. MDR, resistance to RIF and INH, and XDR, MDR plus resistance to at least one injectable, resistance is a current epidemic that began its gradual progression only 15 years ago [2]. DR can be either acquired (due to prior drug treatment therapy), primary (no previous drug treatment therapy), or innate (strains are coded) [4]. Furthermore, MDR TB is associated with high death rates of 50%-80% and spans a short time (4 to 16 weeks) from diagnosis to death [5]. Tuberculosis is most commonly transmitted from person to person in miniscule droplets from sneezing, coughing, etc. The contact rate between susceptible and infectious individuals is called mass action principle, which is fundamental in understanding epidemiological curves mathematically and disease dynamics [6].

North American Epidemiology (Canada and the United States)

In 2009, 255 cases of TB were reported (9.6 cases per 100,000). While this represents a decrease of 19 cases (7%) from the 2008 total of 274 cases, it was a smaller decrease than the previous year. Ninety four percent of TB cases in 2009 were born outside of Canada (with a large proportion of foreign born originating from the Philippines, India, and China). The Philippines, India, and China, from Report Number Four of the WHO, are the highest risk countries. The proportion of Toronto's TB cases that are foreign born remains stable. The rates reported are similar to those around the world as TB disproportionately affects the foreign born population compared with the native born. There are approximately 1,600 TB cases in Canada, of which 600-700 are in Toronto with an 80% culture positive rate. Of about 200 cases, 10 develop MDR TB, or 5% fail therapy [1].

In 1993, Aboriginal Canadians accounted for 18% of the total number of cases and foreign-born residents for 53%. Until the mid-1980s, the incidence rates among the Inuit fell substantially, whereas the decline among status Indians were small, and the rates among foreign-born residents were stable. The differences in incidence rates across Canada are due to the predominance of the high-risk groups. The highest rates, in 1996, prevailed in the regions with large populations of Aboriginal Canadians, which would be the Northwest Territories and Saskatchewan [7].

The portion of active cases of TB due to reactivation has been constant, at about 10% during the 1980s. Once age 55 hits, the rates rise progressively, with steep increases among men more so than women of the same age. In 1993, just fewer than 2% of persons with active TB were residents of a long-term care facility. Active TB is uncommon in young children in Canada, except in those living on reserves; however, active disease among recently arrived foreign-born adolescents is on the rise. Most infected foreign-born children and adolescents will have acquired the infection in their

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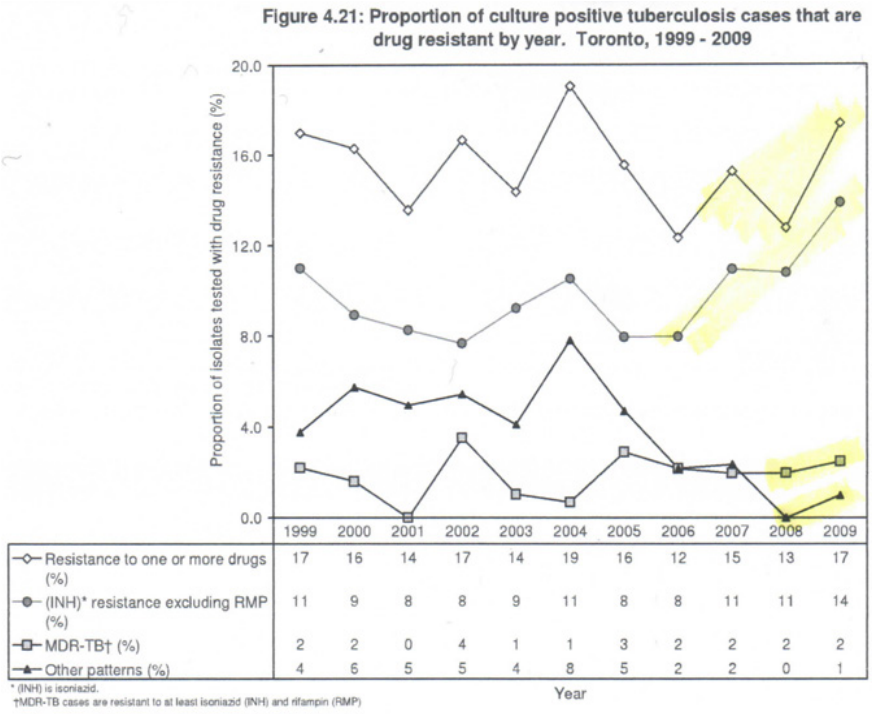

Figure 1: While TB incidence rates are slowly decreasing and sometimes remaining stable in other parts of Ontario and Canada, DR rates are rising. This is indicative of global rates as well.

Source: Toronto Public Health. "Tuberculosis Highlights." *Communicable Diseases in Toronto 2009*. Toronto Public Health, 2009. Web. 7 Apr. 2011. http://www.toronto.ca/health/tb_prevention/pdf/tb_statstics_2009.pdf.[43]

country of origin, although infection may be acquired from adult foreign-born household and community contacts in Canada [7].

Furthermore, 17% of cases reported (n=199) were resistant to one or more drugs, an increase from the 13% resistant in 2008. MDR isolates remain stable at 2% [8]. While TB incidence rates are slowly decreasing and sometimes remaining stable in other parts of Ontario and Canada, DR rates are rising. This is indicative of global rates as well [1].

In North America, prevalence of MDR is low; however, there are important outliers to consider. Since 1994, twenty one countries have reported drug resistance data as representing 93% of all TB cases in the region, but covering 48% of the countries. The population weighted mean of MDR-TB based on all countries that have reported in the Americas is 2.2% (95% CLs, 0.6-3.8) among new cases, 13.2% (95% CLs, 3.5-22.8) among previously treated cases, and 4.0% (95% CLs, 1.7-6.3) among combined cases [1].

In North America, Canada has shown low proportions of resistance and relatively steady trendsin resistance among both new and previously treated cases [1]. Tuberculosis was uncommon in Canada from 1988 to 1992, however, TB case notification has decreased since 1997 [7]. In 2005, twenty three MDR-TB cases were identified. The USA has shown decreases in overall TB notifications as well as overall numbers of MDR-TB cases since 1995. In a study on the increasing drug resistance in Ontario (2000), it was discussed that "resistance to INH and RIF developed at a rate of ~0.10-0.15 per 100 PY in the first year but was low thereafter" [9]. The US reported significant decreases in MDR among all TB cases. A total of 124 MDR-TB cases were recorded in 2005 [1].

Global Epidemiology

On a global scale, in both developed and developing countries, tuberculosis rates have indeed risen due to the increasing prevalence of HIV, which contributes to tuberculosis. HIV infection increases the risk of reactivation of latent tuberculosis and increases the risk of progressive disease from new infection [10,7]. Fortunately, there is no evidence that the increasing HIV epidemic has had a significant impact on Canada's TB incidence rates [10].

The total number of new cases increased at 1.7%/year between 1997 and 2000, and the incidence rate per capita at 0.4%/year. The most striking increases have been seen in countries of sub-Saharan Africa and the former Soviet Union. These rises offset the fall in case numbers in other parts of the world, west and Central Europe, the Americas, and the Middle East. Industrialized countries are typically seeing fewer cases among nationals each year, but steady or rising numbers of cases among immigrants [7].

For nine Western European countries in 1999, the majority of TB patients were foreign-born or foreign citizens. The incidence

Table 2 Most frequent causes associated with selection of resistance in the community and generation of MDR-TB under epidemic conditions[17,20]

Non-implementation of DOTS and DOTS expansion strategies	Inadequate supply or poor quality of drugs	Patients: inadequate drug intake	Others
Poorly organised or funded NTPs	History of frequent shortages of drug supplies in the country	Inadequate adherence to treatment	Dominant private sector
Guidelines inadequate or lacking	Poor quality of anti-tuberculosis drugs	Adverse effects and malabsorption	Poor infection control in health centres and hospitals
Poor training	Wrong dose or combination	Social barriers	High prevalence of highly virulent MDR strains of *M. tuberculosis*
Lack of treatment monitoring		Lack of money (treatment not available free of charge)	HIV infection in some regions
Non-standardised treatment		Substance dependency disorders	

MDR-TB = multidrug-resistant tuberculosis; NTP = National Tuberculosis Programme; HIV = human immunodeficiency virus.

Figure 2: DR development has many causes.

Source: Caminero, J.A. "Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding." *International Journal of Tuberculosis Lung and Disease* 14.4 (2010): 382-390. PDF file[10].

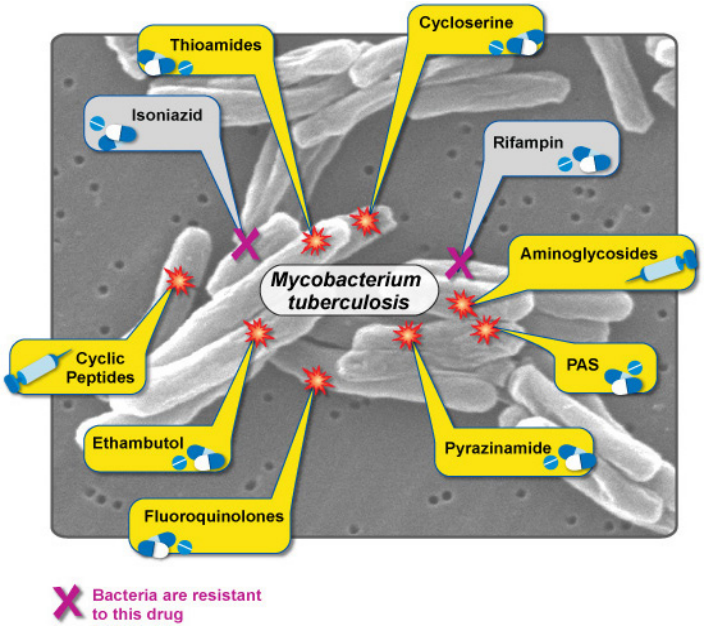

Figure 3: Diagram of How Treatment Drugs and Resistance Works

Source: Davies, Peter D.O. *Clinical Tuberculosis*. London: Arnold, 2003. Print.[15]

of smear-positive disease increased by about 50/100000/year for every 1% increase in the annual risk of infection, a result that is supported by retrospective analysis of survey data from India, and which can be recreated with mathematical models when TB is stably endemic and unaffected by HIV. Even among smear positive patients receiving anti tuberculosis drugs, the case fatality rate can exceed 10% if adherence is low, or if rates of HIV infection and drug resistance are high [7].

In India, specifically, in studies on primary and acquired resistance and response to treatment with DOTS, it was found that even with a perfectly efficient DOTS program in place, patients with no prior history of treatment or MDR TB had much higher rates of acquired resistance than initial resistance to INH and RIF [7,11,12,13]. Contrastingly, in Canadian studies of increasing drug resistance, with DOTS effectively implemented for new cases, acquired resistance decreased over time [9,8]. This interesting phenomenon might be due to a number of different factors, including different bacterium strains, hosts, immune response, environment, and exposure to others with tuberculosis amongst the different subjects. It also questions the efficacy of DOTS. In India, the rates of acquired resistance are much higher than those of initial resistance [14]. In a retrospective study at New Delhi, it was found that initial drug resistance to INH was high (18.5%), of patients who had denied any history of prior treatment and of MDR TB, and initial resistance to RIF was low (4%). In a study then conducted by the Tuberculosis Research Council (TRC), it was found that with standardized treatment in place, the frequency of acquired drug resistance increased significantly to 67% to INH, 12% to RIF, and 11% of the strains resistant to both. Similar studies around India have been conducted, revealing similar results, even with the new DOTS or DOTS plus program systematically in place [7, 13,15,16,17].

Mathematical models generate slow epidemics, which peak after several decades at an incidence rate that is typically below 1%. The early growth rate of the epidemic is governed by the basic case reproduction number, R_0, the average number of secondary infectious cases generated when one infectious case is introduced into an uninfected population. For an infection to spread, R_0 must exceed 1. Rough estimates of R_0 are relatively low among infectious diseases, of the order of 2 in untreated populations. For R_0=2, the expected doubling time of an epidemic in its early stages is the same as the M. tuberculosis generation time of 4-5 years. If transmission is concentrated within certain subpopulations at higher risk, the dynamic effect is to increase R0 locally, but to reduce the proportion of the entire population that will ever get TB. R0 is useful because it guides thinking about a wide range of

Multidrug-resistant tuberculosis treatment outcome studies from high income low-burden settings.

Country	Period	Number of patients	HIV (%)	Short-term success (%)	Long-term success (%)	TB mortality rate (%)	Follow-up (years)	Definitions of treatment success (consecutive months)	Reference
USA	1973-1983	171	0	65	56	22	1.7	≥3 CN (3)	*Goble et al* [20]
USA	1991-1993	38	89	63	55	45	1-2.8	≥2 CN (≥2 wks apart)	*Turett et al* [57]
USA	1991-1994	25	0	-	68	0	1.9#	≥2 CN (≥2 wks apart)	*Telzak et al* [55]
USA	1984-1998	205	0	85	75	12	15 (up to)	≥3 CN (3)	*Chan et al* [50]
Netherlands	1985-1998	44	0*	-	75	2	4.4	≥2 CN (≥2 wks apart)	*Geerligs et al* [54]
Canada	1986-1999	40	0	85	60	12.5	4.8	3 CN (3)	*Avendano et al* [51]
UK	1995-1999	13	0*	-	62	7.7	3.6	≥2 cons CN	*Hutchison et al* [53]
Germany	2004-2006	177	4.9 (*n*=142)	87	-	7.9	-	WHO (MDR)	*Eker et al* [49]
Denmark	1992-2007	27	7	89	100	0	8.9	WHO (MDR)	*Bang et al* [11]

* = or presumed negative; # = median; CN = culture negative; wks = weeks; WHO (MDR) treatment outcome definitions [21].

Figure 4: MTB and its Resistance to Treatment Drugs

Source: Davies, Peter D.O. *Clinical Tuberculosis*. London: Arnold, 2003. Print.[15]

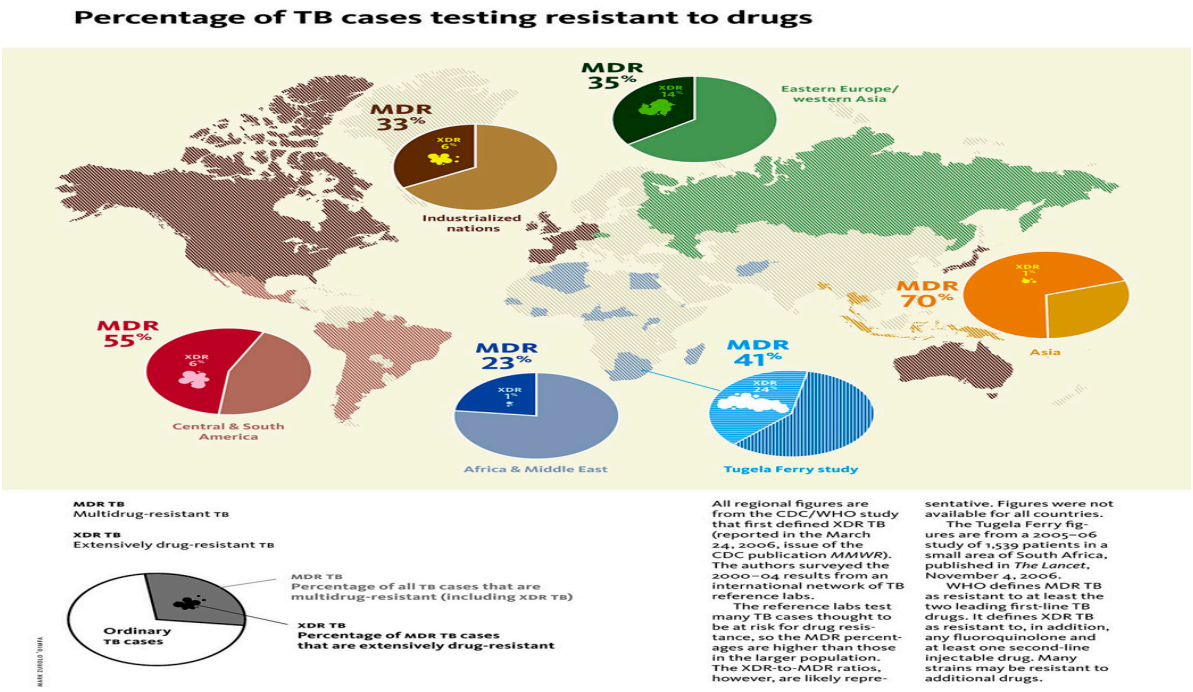

Figure 5: Percentages of MDR and XDR TB cases around the world

Source: World Health Organization. "Anti-Tuberculosis Drug Resistance in the World." *The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance*. World Health Organization, 2008. Web. 7 Apr. 2011. <http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf>.[46]

epidemiological processes, including the spread of drug resistance, and the efficacy of different control methods [7].

Immigration from high-incidence countries is part of the reason why the decline of TB in Western Europe, North America, and the Gulf States has stopped or has been reversed. TB incidence has stopped falling in east Asian countries. More cases are arising by reactivation from an ageing TB epidemic in an ageing human population. Over a much wider area in Western Europe, TB declined at 7-10%/year after drugs became widely available during the 1950s, though incidence was already falling at 4-5%/year before chemotherapy [7].

For epidemic TB, as a result of aggressive intervention following an outbreak in New York City, the number of multidrug resistant TB cases fell at over 40%/year. The epidemiological literature reports successes and failures to using IPT, with outcomes that are not always predictable. In the USA, the practice of contact tracing and IPT fall short of recommendations, some high risk groups, such as the elderly, do not receive the full benefits that IPT can provide.

IPT can be hard to manage in the groups that most need it, such as illegal immigrants, though supervision has helped drug users, and financial incentives have improved completion rates among the homeless. High levels of compliance have been achieved among immigrants to Australia, even with indirect supervision. Completion was lower among immigrants in Italy, but 80% completion among close contacts of TB cases [7].

In the 2008 global report by the WHO/Union, drug susceptibility data were collected for 90,726 patients in 83 countries and territories from 2002 to 2007. The median prevalence of resistance in new cases of TB was 11.1% for any drug and 1.6% for MDR TB, ranging from 0% in eight countries to as much as 22.3% in Azerbaijan and 19.4% in Moldova. The global proportion of MDR TB among all cases was 4.8% (95% CL 4.6-6.0) [2]. Of the half a million MDR TB cases, 5-7% are XDR [18]. The highest proportions of MDR TB in new cases were located in countries of the former Soviet Union and in China. Prevalence of initial MDR TB was higher than previously estimated. NTP are far below targets set out by the Global XDR TB Response Plan. The targets for number of MDR TB cases detected and treated have not been reached and the latest information reported indicates that at the current pace, few countries will reach the targets outlined in the Global Plan to Stop TB [1].

In all cases, India, China, and the Russian Federation were estimated to have the highest number of MDR TB cases, with India and China carrying 50% of the global burden and the Russian Federation carrying a further 7%. Twenty seven countries account for 86% of the world's MDR TB burden [2]. In a Chinese study on anti TB DR patterns and trends in a TB referral hospital from 1997-2009, it was found that during 1997-2000, the percentage of patients with any resistance (mono, poly, MDR, XDR) increased from 26.4% among MDR cases in 1997 to 56.8% in 2000 [19].

Resistances and Epidemiology

Primary drug resistance is increasing in Canada and is defined as the presence of drug-resistant isolates cultured from individuals who have not previously received treatment. Therefore, susceptibility testing for anti-tuberculosis drugs is crucial. There are four main categories for methods of susceptibility testing: the absolute concentration method, the resistance ratio method, the proportion method, and the radiometric method. The absolute and resistance ratio methods are used outside of North America. In the proportion method, colonies are inoculated into both drug containing media and control media. After incubation, the number of colony-forming units growing on the drug containing medium is compared with the number on the control medium. The proportion of bacilli resistant to a particular drug is calculated and expressed as percentage of the total population tested [7].

Clinical and laboratory studies indicate that a clinical response is unlikely when the proportion of cells resistant to a particular drug is greater than 1%. Radiometric drug susceptibility testing of MTB using the BACTEC 460. Results may be available within one week of a positive culture being obtained. A pyrazinamide test medium at pH 6.0 for PAZ susceptibility testing of MTB using BACTEC 460. Patients who have taken anti-tuberculosis drugs for one month or more at any time in the past or who come from countries with a high prevalence of tuberculosis have an increased chance of having drug-resistant TB. Patients who are not compliant with treatment could increase their chances of relapse and drug-resistance (when some drugs are selectively discontinued and others continued, taking only one active drug) [7].

The most frequent resistance has been to INH. In the 1990s, outbreaks of multidrug resistance have been documented in the US. In developing countries, where therapy is not supervised, high rates of primary INH resistance have been found. Primary RIF resistance may also be high. Administration of at least two agents to which there is demonstrated susceptibility is a basic principle in managing multidrug resistance. For INH resistance, DOTS therapy with RIF, ETH, PZA, and STR daily in the initial two month phase followed by seven months of RIF and ETH gives excellent results. For isolated RIF resistance, INH must be included instead of RIF [7].

Multidrug-resistant tuberculosis treatment outcome studies from high income low-burden settings.

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* = or presumed negative; # = median; CN = culture negative; wks = weeks; WHO (MDR) treatment outcome definitions [21].

Many such patients will be found to be resistant to the other first-line drugs and it is preferable to give at least three new drugs while the results of susceptibility studies are awaited. Each year, an estimated half a million MDR TB cases develop, of which only around 7% are, diagnosed [3].

Mechanisms of Resistance and How the Treatment Drugs Work

Resistance to first line and even second line drugs is a manmade amplification of a natural phenomenon [18,20], resulting from simple Darwinian pressures, brought out by the presence of antibiotics [7]. Accumulation of mutations in individual drug target genes is primarily the result of MDRTB [5]. Overexpression is the product of the MDR protein, which is one of the ABC transporters which have the ability to pump hydrophobic drugs out of the cytosol [21]. Anti TB drugs impose selection pressure so that mycobacterial mutants gradually outnumber susceptible bacilli and emerge as the dominant strains [22]. Genetic and molecular analysis of DR in MTB suggests that resistance is usually acquired by the bacilli either by alteration of the drug target through mutation or by titration of the drug through overproduction of the target [5]. New evidence suggests that a strain can revert from resistant to susceptible over time [18]. Adaptation experiments with rpoB strains have shown that after 88 generations, mutants initially less fit than the parent improve their fitness value to match and even exceed the parent [23]. As stated previously, strains can be innately resistant or acquire resistance with improper treatment methods at a low but predictable frequency, in large bacterial populations [23]. For example, naturally occurring STR resistant organisms were found in large broth cultures of H37Rv [20]. Secondary drug resistance is the main cause of primary drug resistance due to transmission of resistant strains [5]. For a list of gene locations of drug resistant MTB [18].

INH is chromosomally mediated [5,20] and relies on the bifunctional enzyme catalase peroxidase activity controlled by the *katG* gene (and an electron sink- hydrogen peroxide [5] to transform the drug from inactive to an active hydrazine derivative [5,24]. INH enters the mycobacterial cell by passive diffusion [25]. INH inhibits the biosynthesis of cell wall mycolic acids by inactivating the NADH-dependent enoyl-acyl carrier protein reductase encoded by *inhA* [25], making the mycobacteria susceptible to reactive oxygen radicals and other environmental factors [5]. A lack of mycolic acid synthesis eventually results in loss of cellular integrity and the bacteria die [24]. Its bactericidal activity rapidly reduces the sputum viable count because it is active mainly against the organisms growing aerobically in pulmonary cavities [23].

Despite being a powerful frontline tuberculosis drug, INH has the potential drawback of inducing its own stable genetic resistance in INH-tolerant persisters. With inoculums size of 10^4 bacilli, INH was found to induce resistance to itself. The minimum time required for induction of INH resistance was 5 to 6 days when incubated in liquid media. RIF did not induce RIF resistance. This finding helps to explain the higher frequency and prevalence of INH-resistant isolates than isolates with resistance to other drugs in patients [26].

The precise molecular mechanism by which *inhA* encodes the primary target of INH has been established through the coupling of specialized kinkage transduction with enzymatic analyses and X ray crystallography. *InhA* is a common target of both INH and ETH [27,28]. Single mutations in polypurine sequences (GGAAGGAA) decrease *katG* expression and confer resistance. In a study published in Molecular Microbiology, it was found that down regulation of *katG* is a mechanism of INH resistance in MTB. H37Rv expressed *KatG,* whereas the *furA-katG* mutants

Mechanisms of *Mycobacterium tuberculosis* drug resistance gene mutations.

Drug	Gene(S)	Function of the gene	Mechanism of resistance
Rifampin	*rpoB*	B subunit of RNA polymerase	Inhibition of RNA synthesis
Isoniazid	*katG*	Catalase-peroxidase	Reduces the ability to activate the prodrug isoniazid
	inhA	Enoyl ACP reductase	Reduces the binding of NADH to inhA and attack by isoniazid
	ahpC	alkyl hydroperoxide reductase	Overexpression of the antioxidant enzyme AhpC, that removes peroxide necessary for isoniazid activation
	kasA	B-ketoacyl ACP synthase	Overexpression of KasA, involved in fatty acid and mycolic acid synthesis
	ndh	NADH dehydrogenase	Increases the NADH/NAD ratio, competes with the binding of isoniazid-NAD to inhA
Ethambutol	*embB*	Arabinosyl transferase	Decreases the binding to ethambutol
Pyrazinamide	*pncA*	Pyrazinamidase	Lack of conversion of pyrazinamide to pyrazinoic acid
Streptomycin	*rpsL*	S12 ribosomal protein	Decreased binding of streptomycin to S12 ribosomal protein
	rrs	16S rRNA	Decreased binding of aminoglycosides to 16S rRNA
Amikacin			
Kanamycin	*rrs*	16S rRNA	Decreased binding of aminoglycosides to 16S rRNA
Capreomycin	*tlyA*	2′-O-methyltransferase	
Fluoroquinolone	*gyrA, gyrB*	DNA gyrase	Inhibition of DNA gyrase
Ethionamide	*inhA*	Enoyl ACP reductase	Inhibition of mycolic acid synthesis
		Flavin monooxygenase	

ACP = acyl carrier protein; NADH = nicotinamide adenine dinucleotide, reduced form

Figure 7: Mechanisms of MTB DR gene mutations.

Source: Johnson, Rabia, et al. "Drug Resistance in Mycobacterium tuberculosis." *Current Issues of Molecular Biology* 8 (2010): 97-112. PDF file [39].

NCGM2836 AND NCGM2836 Vector did not. Furthermore, a polypurine sequence in the *furA-katG* intergenic region complementary to 16S rRNA has been found to act as the *katG* ribosome binding site. Mutations altering complementarily to 16S rRNA (Inta-10c had an A to C mutation at the third nucleotide, and Intg-7a had a G to A mutation at the sixth nucleotide of the polypurine sequence) decrease the level of transcription [25].

Rarely, movement of mobile genetic elements has been associated with new resistance emerging through the inactivation of critical genes, such as with the insertion sequence IS6110 [23]. Furthermore, an INH resistant strain will have some gene mutation as an insertion or deletion that reduces its *katG* functionality [29] (loss of catalase activity [5]. These mutations are found between codons 138 and 328, with 315 the *katG* gene [24]. The *inhA* locus is proposed as the primary target for coresistance to INH and ETH. This locus is composed of two ORFs, designated *orf1* and *inhA*, separated by a 21 bp noncoding region. InhA, an enoyl-ACP reductase, more than 40% homologous to the EnvM protein, catalyzes an early step in fatty acid synthesis among enter bacteria [5]. Low level resistance can be caused by point mutations in the regulatory region of *inhA* operon, resulting in over expression of *inhA*. Sometimes bactericidal activity will not start until 1 to 4 days after taking INH [1,28].

RIF resistance is a key indicator of MDR. RIF resistance is rare, but is increasing because of widespread application and results in selection of mutants resistant to other components of short course chemotherapy [23]. Clusters of mutations are present at RRDR [10]. RIF targets the mycobacterial RNA polymerase and thereby kills the organism (that metabolizes slowly [23] by interfering in the transcription process. It kills the persisters and sterilizes the patient's sputum [23]. RIF specifically inhibits the elongation of full length transcripts and has virtually no effect on the initiation of transcription. RNA polymerase is encoded by *rpoA, rpoB, rpoC*, and *rpoD* [5,23,24].

Furthermore, RIF specifically interacts with the β subunit of RNA polymerase, thereby hindering transcription, and mutations in the *rpoB* locus confer conformational changes leading to defective binding of the drug and consequently resistance [5,23,24]. Most mutations are restricted to an 81 bp core region and are dominated by single nucleotide changes, resulting in single AA substitutions, although inframe deletions and insertions also occur at lower frequencies. Changes in the codons Ser531 and His526 have been documented in more than 70% of the RIF resistant isolates [5]. rf can be as little as 0.21 or similar to the susceptible parent at 1.05 [23].

EMB obstructs the formation of the cell wall. Increased permeability of the mycobacterial cell wall leads to increased drug uptake. Disruption of the arabinogalactan synthesis and polymerization inhibits the formation of this complex and may lead to increased permeability of the cell wall [30]. EMB specifically inhibits arabinosyltransferases, interacting with three homologous, membrane associated encoded by *embC-embA-embB* genes, leading to the notion that arabinosyltransferase is the primary cellular target for EMB [30]. Over expression of the *embB* protein has been documented to mediate resistance. The *embB* ORF lacks a potential ribosome binding site and is translationally coupled to *embA*. EMB resistant isolates generally contain missense substitutions in the conserved *embB* codon 306 that codes for methionine [5].

In PZA, naturally resistant strains lack the enzyme Pzase, which hydrolyzes PZA to pyrizinoic acid, the active form of PZA [5,23]. PZA is transported as a neutral species into the cell, where it is converted into its active form. The *pncA* gene codes for the amidase, which was identified as a single point mutation that results in the substituation of His to Asp at position 57. This substitution results in the production of an ineffective Pzase. Substitution of Cys138 with Ser, Gln141 with Pro, and Asp63 with His and deletion G nucleotide at positions 162 and 288 resulted in the defective Pzase [5]. PZA is only active at a low pH, making it suitable for killing the organisms inside caseous necrotic foci. It is therefore non beneficial after the second month of therapy [23].

STR resistance emerges through mutations in *rrs* and *rpsL* that produce an alteration in the streptomycin binding site. STR binds to a ribosomal protein and 16S rRNA (encoded by *rpsL* and *rrs*) causes misreading of mRNA and faulty protein synthesis [30]. STR resistant strains grew more slowly than their wild type parents. Mutations in *rpsL* can be restrictive or nonrestrictive, being associated with an attenuation of virulence or not. In MTB, more mutants are associated with restrictive mutations [23].

FQ had mutations mainly in the *gyrA* gene at higher concentrations [23].

Mutation Rate and Rates of Transmission

The rate of resistance for each of the anti TB drugs varies. ETH is highest and RIF and quinolones are lowest. The risk of mutation for RIF, INH, STR, and ETH are 3.32 X 10^{-9}, 2.56 X 10^{-8}, 2.29 X 10^{-8}, and 1.0 X 10^{-7} mutations per bacterium per cell division, respectively. In INH and ETH, heteroresistance has been examined using PCR RFLP [23].

The probability of transmission to health care workers can be approximated by the equation: Probability of transmission=exponential of (I x q x p x t)/Q where I is the number of infectors, q=Contagiousness of each patient, p is the ventilation rate by the health care worker, t is the hours of exposure, and Q is the ventilation [7]. The goal of risk factor analysis is to try to identify out of the innumerable possibilities, the principal causal and modifiable factors in TB epidemiology [31]. The risk that an organism will develop resistance to two agents is the product of the risks of developing resistance to each separately. Risk of resistance can be calculated using the formula P=1-(1-r)n [31].

However, when mycobacteria are found in different compartments or in different physiological states, then the equation would need to be modified. Even a small deviation from the standard regimen can lead to the emergence of resistance [23].

Contributing Factors

Risk factors for resistance can be divided into two categories: 1)

Table 3. Frequency of mutations concerned with INH resistance in *katG* and *inhA* gene region detected by silver sequencing

Analyzed gene region	Location of mutation	Nucleotide change(s)	Amino acid change(s)	No. (%) of strains $n = 30$
katG-related mutations				
katG	codon 315	AGC→ACC	Ser→Thr	18 (60)
		AGC→ATC	Ser→Ile	2 (6.6)
		AGC→AAC	Ser→Asn	1 (3.3)
		AGC→ACA	Ser→Thr	1 (3.3)
	codon 279	GGC→ACC	Gly→Thr	1 (3.3)
	codon 293	GCT→ACT	Ala→Thr	1 (3.3)
katG dual	codon 279 & 315	GGC→CGC & AGC→ATC	Gly→Arg & Gly→Ile	1 (3.3)
inhA-related mutations				
inhA	-15^{th} locus	C→T	C→T	3 (10)
katG & *inhA*-related mutations				
katG & *inhA*	codon 279 & -15^{th} locus	GGC→ATC & C→T	Gly→Ile & C→T	1 (3.3)
		GGC→ACC & C→T	Gly→Thr & C→T	1 (3.3)

Figure 8 : Mutation frequency and location in INH and RIF regions

Source: Aslan, Gonul, et al. "Genotypic Analysis of Isoniazid and Rifampin Resistance in Drug-Resistant Clinical Mycobacterium tuberculosis Complex Isolates in Southern Turkey." *Japanese Journal of Infectious Diseases* 61 (Apr. 2008): 255-260. PDF file [6].

Table 4. Frequency of mutations concerned with RMP resistance in *rpoB* gene region detected by silver sequencing

Location of mutations	Nucleotide changes	Amino acid changes	No. (%) of strains $n = 14$
Codon 531	TCG→TTG	Ser→Leu	7 (50)
	TCG→TGG	Ser→Tryp	1 (7.1)
Codon 516	CAC→GTC	Asp→Val	1 (7.1)
Codon 524	TTG→TTA	Leu→Leu	1 (7.1)
Codon 545	CTG→ATG	Leu→Met	3 (21.4)
Codon 531 & 545	TCG→GCG & CTG→ATG	Ser→Ala & Leu→Met	1 (7.1)

Figure 9 : Treatment Outcomes in Asia, Europe, and US

Source: Chiang, Chen-Yuan, Rosella Centis, and Giovanni Battista Migliori. "Drug-resistant tuberculosis: Past, present, future." *Respirology* 15 (2010): 413-432. PDF file [2].

those facilitating the selection of resistance in the community and 2) the specific conditions that appear to increase some patients' vulnerability to resistance. DR is most widely due to poor treatment practices (specifically with first line RIF containing regimens) and poor implementation of control programmes [2]. In a global surveillance for Anti TB DR published in the New England Journal of Medicine, it can be further strengthened that with poor treatment strategies, resistance will be higher, with the opposite being true as well. In the Dominican Republic, no treatment strategy was implanted and resistance was 40.6%, whereas in the Czech Republic, where treatment strategies were implemented, resistance was lowered to 2.0% [4]. Recent data suggests that properly and efficiently executed NTPs can postpone and even reverse the MDR TB epidemic. Furthermore, TB is associated with depressed socio-economic conditions (especially with disadvantaged inner-city population groups). This is because there are increased opportunities for transmission in overcrowded and poor housing [7,32]. Homelessness, personal stress, younger in age [2] (25-44 years old [1]), substance abuse, poor nutrition [32], poor access to healthcare, alcoholism, cardiovascular disease, infected animals, certain occupations and other factors may contribute to the increasing prevalence of Tb [7,10,32].

In addition, limited education, low self-esteem, and disaffection with mainstream society allows the misinformed patient to not seek proper treatment. Not getting the proper help and treatment, or patient incompliance, contributes to the rise of Tb transmission. Aboriginals, immigrants or foreign-born from countries with high Tb rates who may carry inactive or latent Tb, persons co infected with TB and HIV, those with untreated or improperly treated inactive disease, and those infected with TB whose predisposing diseases, conditions, or drug use, are certain high risk individuals that could spread TB and activate inactive TB [7]. Particularly, elderly single men are at high risk [1]. For both males and females until middle age, TB rates are similar. There is an increase in prevalence after the age of 55 due to the higher prevalence of latent infection in older generations. Among Asians, there is a high incidence of TB of the

MDR-TB, multi-drug-resistant tuberculosis; NA, not applicable; XDR-TB, extensively drug-resistant tuberculosis.
Reproduced with permission from Sotgiu *et al.* [53]

Table 3 Treatment outcomes of MDR-TB and XDR-TB in European and US studies

Setting	Study	Times to conversion (days)	Treatment success MDR vs XDR *n* (%)	Failure MDR vs XDR *n* (%)	Death MDR vs XDR *n* (%)	Follow up (months)
Asia	Kim *et al.*, AJRCCM 2008[55]	Not reported	615 (46.2) vs 22(29.3)	53 (4) vs 12 (16)	124 (9.3) vs 20 (26.7)	3–7 years
Europe	Migliori, EID 2007	SS: 41 vs 110 C: 58 vs 97.5 (Median)	45 (35.7) vs 0	NA	8 (6.3) vs 4 (36.4) *P* < 0.001; RR: 5.45	42 (median)
	Migliori, ERJ 2007[10]	SS: 56 vs 110 C: 60 vs 168 (Median)	165 (45.7) vs 22 (34.4)	32 (8.9) vs 12 (18.7) *P*: 0.016; RR: 2.12	43 (11.9) vs 14 (21.9) *P*: 0.03; RR: 1.84	42 (median)
	Eker, EID 2008	SS: 53.5 vs 88 C: 61.5 vs 117 (Median)	105 (59.3) vs 4 (57.1)	1 (0.6) vs 0	14 (7.9) vs 1 (14.3) *P*: 0.5; RR: 1.81	48 (median)
USA	Chan, NEJM 2008	NA	164/10	NA	Hazard ratio (XDR) 2.5 *P*: 0.07	NA
	Banerjee, CID 2008	C: 98.5 vs 195 (Median)	345 (66) vs 7 (41.2)	NA	80 (15.3) vs 5 (29.4) *P*: 0.4; RR: 1.41	NA

As the proportion of treatment outcome categories reported in the different studies we included in the table (success, failure and death) do not cover all possible outcomes (default and transferred out), the sum does not reach 100%.
C, culture; MDR-TB, multi-drug-resistant tuberculosis; NA, not applicable; RR, relative risk; SS, sputum smear; XDR-TB, extensively drug-resistant tuberculosis.
Reproduced with permission from Sotgiu *et al.* [53]

Figure 10: INH mechanism of resistance
Source: Vilcheze, Catherine, et al. "Transfer of a point mutation in Mycobacterium tuberculosis inhA resolves the target of isoniazid." Nature Medicine 12.9 (2006): 1027-1029. PDF file [10].

peripheral lymph nodes. The rate of active tuberculosis in foreign-born individuals in Canada is over 10 times higher than the rate in Canadian-born individuals. Africa, Southeast Asia, the Indian subcontinent and Central and South America are the areas with the highest prevalence of TB in the world. The risk of active disease is highest in the first five years after arrival in Canada. There is no data in Canada about the rates of TB in the homeless as of 1996. The census does not allow estimation of the denominator for this population. The homeless are at high risk of new infection because of crowding in shelters and delays in the diagnosis of active cases [7].

Moreover, residents and workers in certain environments, such as long-term care and correctional facilities, are at increased risk for TB due to exposure [7]. TB is predominately an adult disease and only 10% of incident cases are children. With low levels of transmission, the average age of TB cases increases and in industrialized countries where transmission rates are now low, the majority of indigenous TB cases are found among the elderly [10]. Physiological factors such as body weight, diabetes, silicosis, and the smoke from domestic stoves and cigarettes enhances the risk of TB as well. Genetic factors include the mechanisms of innate immunity which entail class I HLA-determined recognition of mycobacterial antigen, activation of macrophages by cytokines and vitamin D, granuloma formation, and apoptosis of bacteria infected cells. One study in India found that exposure to smoke from biomass fuel (wood or dung) accounted for 51% of active TB in persons aged 20 years or older, although there are problems with this study as there are other factors that possibly contribute to TB rates and risks are not additive. Case reports suggest that TB incidence has been steady for at least two decades in some South East Asian countries, but no such equilibrium was ever reached in Western Europe or North America. TB has been in decline up to the late twentieth century ever since rates per capita peaked in industrialized countries, probably sometime during the early nineteenth century and before chemotherapy began in the 1950s.

Prior to the emergence of HIV/AIDS, case reports and surveys of the prevalence of infection also indicated that TB was in decline, albeit a slower decline, in Africa and the Middle East. Some of this decline could be due to the natural waning of the epidemic after incidence reached a maximum, but the decline in the west seems to have been too prolonged for this to be the whole explanation. The basic model is wrong then. The 150 year decline could be attributed to the following: transmission diminished as people began to live at lower density with better ventilation [7,33] in improved housing and when patients are isolated, the caseload shifted to older people who have fewer contacts with the rest of the population, nutrition improved so susceptibility decreased (15-30% of deaths in cities of the USA attributable to TB during the early nineteenth century). Genetics and selective selection also play a part [7].

Although, natural selection and nutrition are not major factors in the decrease of TB rates. Case fatality fell drastically with the introduction of anti tuberculosis drugs in the late 1940s on. Irreversible genetic deletions appear to have produced phenotypes of MTB that are less likely to cause cavitary pulmonary disease. Contributing to the recent resurgence of TB is mainly the spread of HIV/AIDS and the social and economic deterioration in the Soviet Union [7,10]. Additionally, travel to or residence in an endemic

Figures 11: In order, table of global drug resistance, and initial and acquired drug resistance among Indian studies

Source: Paramasivan, C.N., and P. Venkataraman. "Drug Resistance in Tuberculosis in India." *Indian Journal of Medical Research* 120 (Oct. 2004): 377-386. PDF file.

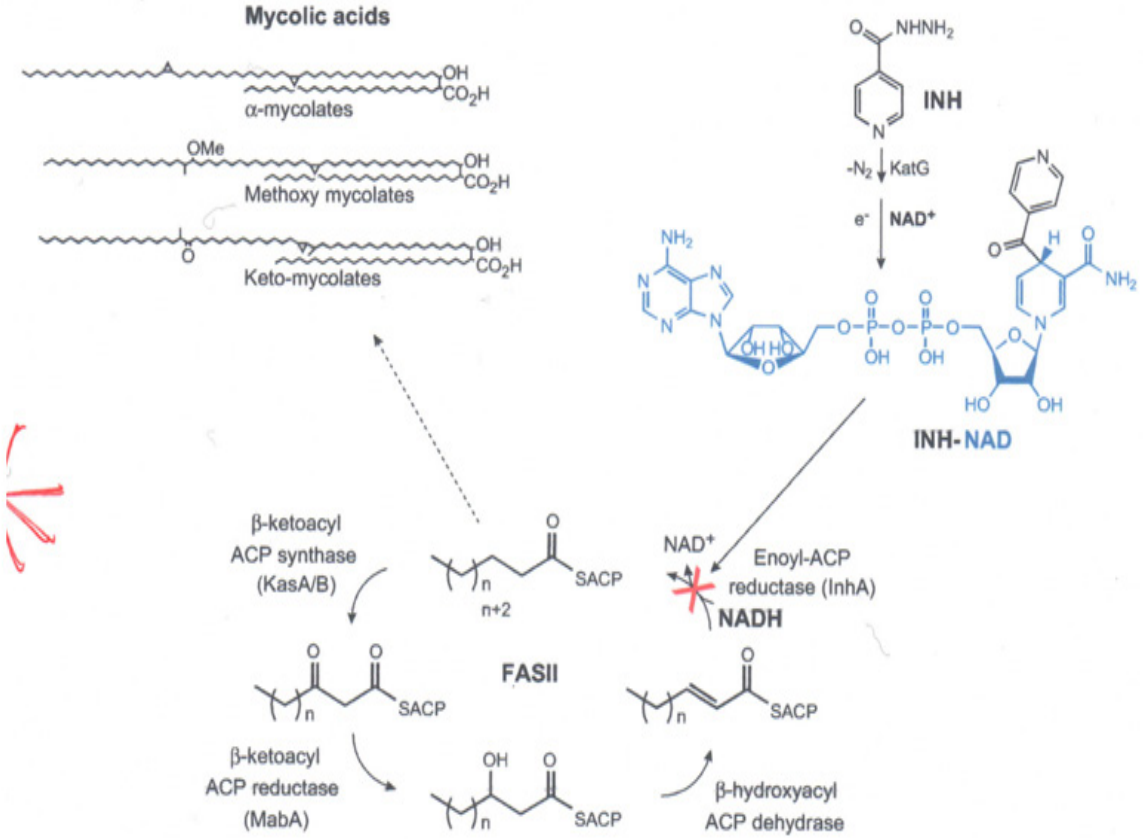

Figure 2

Mechanism of action of INH in *M. tuberculosis*. INH is activated by KatG to form the INH-NAD adduct. The adduct inhibits InhA, the enoyl-ACP reductase of the fatty acid synthase type II system (FASII), which synthesizes mycolic acids (representation of three mycolic acid classes) (50). This inhibition results in the inhibition of mycolic acid biosynthesis and ultimately cell death.

Table I. Global antituberculosis drug resistance situation

Drug	Range (%) of drug resistance during the period					
	1994-1997		1996-1999		1999-2002	
	Initial	Acquired	Initial	Acquired	Initial	Acquired
Isoniazid	1.5-31.7	5.3-69.7	0.0-28.1	0.0-81.3	0.0-42.6	0.0-71.0
Streptomycin	0.3-28.0	0.0-82.6	0.3-32.4	0.0-52.4	0.0-51.5	0.0-73.1
Rifampicin	0.0-16.8	0.0-57.9	0.0-15.8	0.0-50.0	0.0-15.6	0.0-61.4
Ethambutol	0.0-9.9	0.0-29.6	0.0-11.1	0.0-32.1	0.0-24.8	0.0-54.2
MDR (range)	0.0-14.4	0.0-58.0	0.0-14.1	0.0-48.2	0.0-14.2	0.0-58.3

MDR, multi drug resistance
Source: Ref. 9

Table II. Summary of studies on initial drug resistance among *M.tuberculosis* isolates in India

Location	Period	No. of isolates	Any resistance (%) to				
			S	H	R	SH	HR
9 Centres-ICMR I[13]	1964-65	1838	14.7	12.5	ND	6.5	ND
9 Centres-ICMR II[14]	1965-67	851	13.8	15.5		NA	ND
GCI-SH, Chennai[20]	1976	254	14.2	15.4	ND	4.7	ND
Bangalore[18]	1980's	436	5.7	17.4	3.0	3.9	1.1
Wardha[21]	1982-89	323	14.9	21.4	8.0	8.0	5.3
Gujarat[22]	1983-86	570	7.4	13.8	0.0	4.2	0.0
Bangalore[19]	1985-86	588	4.8	17.3	2.9	3.0	1.4
North Arcot[15]	1985-89	2779	11.6	21.3	1.7	8.0	1.6
Pondicherry[15]	1985-91	1841	8.1	10.8	1.0	3.7	0.8
Kolar[19]	1987-89	292	5.1	32.9	4.4	4.1	3.4
Raichur[15]	1988-89	244	11.4	19.3	3.3	6.6	3.3
North Arcot*	1989-90	241		12.9	2.5		1.7
North Arcot*	1989-98	747		19.0	11.8		4.4
Jaipur[23]	1989-91	1009	7.6	10.1	3.0	1.7	0.9
New Delhi[25]	1990-91	324	ND	18.5	0.6	ND	0.6
Military Hosp, Pune[26]	1992-93	473	8.2	3.2	4.0	2.1	1.0
Tamil Nadu state[11]	1997	384	6.8	15.4	4.4	4.4	3.4
North Arcot[12]	1999	282	12.4	23.4	2.8	8.5	2.8
Raichur[12]	1999	278	7.2	18.7	2.5	4.0	2.5
Wardha**	2000	197	7.6	15.0	0.5	3.0	0.5
Jabalpur**	2002	273	7.0	16.5	1.8	2.6	1.1

*Tuberculosis Research Centre, unpublished data
**Tuberculosis Research Centre, interim findings, unpublished data
S, streptomycin; H, isoniazid; R, rifamicin; ND, not done

Table III. Summary of studies on acquired drug resistance among *M. tuberculosis* isolates in India

Location	Period	No. of isolates	Any resistance (%) to		
			H	R	HR
Gujarat[22]	1980-86	1574	47.7	28.3	—
Gujarat[22]	1983-86	1259	81.1	33.0	30.2
Wardha[21]	1982-89	302	47.0	12.6	9.6
North Arcot[16]	1988-89	560	67.0	12.0	10.9
Raichur[17]	1988-89	111	52.3	17.1	17.1
New Delhi[25]	1990-91	81	60.5	33.3	33.3
Tamil Nadu (4 districts)[27]	1996	162	—	—	20.3
Tamil Nadu State[11]	1997	16	(50.0)	(25.0)	(25.0)
North Arcot[12]	1999	16	(81.0)	(69.0)	(69.0)
Raichur[12]	1999	11	(100.0)	(100.0)	(100.0)
Wardha*	2000	9	(78.0)	(78.0)	(78.0)
Jabalpur*	2002	31	87.1	80.6	80.6

Brackets indicate that the percentage is based on isolates less than 25
*TRC, unpublished interim findings
H, isoniazid; R, rifampicin
Superscript numerals indicate reference nos.

area is the most commonly reported exposure setting in 2009 (94% of TB cases in Toronto- n=236). In 2009, only 2% of those cases reported a shelter as an exposure setting for acquiring TB [8]. Not only do the efficacy of management practices contribute to MDR TB prevalence, but it is also reliant on transmission: the virulence of the DR strain, the susceptibility of the population [2,29], and the relative fitness of DR MTB. Furthermore, patients with a large bacillary load (usually 10^9 will contain several mutants resistant to any one anti TB drug [5] have an increased risk of developing DR, as suggested by mathematical modeling [23]. This is because more spontaneous mutations occur in a large population of bacteria [18]. With poor management, the most frequent causes associated with DR can also be poor training of the health care workers, inadequate supply or poor quality of drugs, inadequate drug intake in the patients due to adverse side effects or non compliance, poor infection control in hospitals, and HIV co infection [4,34].

Risk of MDR has been studied to be up to 10 times higher in previously treated cases than in never treated ones [4,34]. Sometimes these factors are due to lack of monetary resources, as DST is complex and expensive, especially with second line drugs [2,3,4,18]. Accurate and rapid diagnosis for this same reason is usually not carried out, threatening appropriate control measures and clinical management [35]. Even in high income countries, like Denmark, that can afford all of the necessary resources and can implement proper treatment methods, NTPs are failing to curtail the TB burden further and the disease remains a health problem of concern. While short term success is high in high income low burden countries, long term success is low [18]. In a study observing high incidence of hospital admission with MDR and XDR TB among health care workers, by the American College of Physicians, it was charted that MDR and XDR rates increased drastically and this was true with HIV positive and previously treated cases. Of the median of 6 drugs used in treatment, resistance was found in half or all of the drugs used [3].

Current Treatment

Several studies have reported on outcomes of MDR TB treatment and the proportion of patients with favorable outcome ranges from 97% to <40%. There are many factors to explain such outcomes, as discussed in the "Contributing Factors" section [14]. The Bacillus Calmette-Guerin vaccination can protect against infection of Tuberculosis and is used in North America for groups of people who live and work where there is an unavoidable risk of exposure. Chest radiography could be used to detect unilateral pleural effusion and without identifiable parenchymal lesions. Tuberculin Skin Test is positive in 90% of patients with TB, but in patients with AIDS and malnutrition, the skin test could return as negative. A diagnosis of pulmonary tuberculosis can be confirmed in most individuals by direct microscopy and culture of the sputum [7].

Use of the auramine stain combined with fluorescence microscopy demonstrates acid-fast bacilli in clinical specimens. A PCR kit uses specific genetic markers to directly detect the presence of the homologous microorganism in clinical specimens such as sputum or spinal fluid. rRNA target amplification assays for directly MTB directly. RNA and PCR hold promise for the future for rapid and routine methods of detecting MTB, but are costly. In the 1990s, a standardized method for DNA fingerprinting of strains of MTB, also known as RFLP typing for detection of strain-specific markers, provides a more powerful tool for epidemiologic studies of TB than phage typing [7].

Effective chemotherapy taken over an adequate period of time is the treatment for all forms of tuberculosis. All isolates of MTB are tested for anti-tuberculosis drug susceptibility. The five first-line medication drugs should be used in treatment. Three to four of these drugs are recommended, in addition to second line drugs. Newer drugs, such as the quinolones (ciprofloxacin and ofloxacin) have some demonstrated activity against MTB. Treatment is divided into two phases, the initial or intensive phase and the continuation phase. During the initial phase, three to four drugs are given daily and the bactericidal effect leads to rapid bacteriological sputum conversion and lessening of clinical symptoms. During the continuation phase, when fewer drugs are given, either daily or twice weekly, the sterilizing effect of therapy eliminates the remaining bacilli and prevents subsequent relapse [7].

Furthermore, patients are best treated with DOTS either in the home or clinic, in which the prescribed dose of medication is administered under direct observation, designed to prevent and not cure MDR TB. Patient compliance with therapy is an absolute must. Depending on the treatment option, treatment could last for 6-9 months, if followed correctly [7]. Standard short-course regimens can cure over 90% of new, drug-susceptible TB cases. DOTS plus is used for more complex strategies for control where rates of drug resistance or HIV infection are high, in which second line drugs are used and MDR TB is trying to be cured [10].

In Toronto, 77% of the TB cases (n=212) beginning treatment in 2008 were enrolled in the DOT program, which is an increase from the 69% enrolled in 2007. It is concerning to note, however, that of the reported cases in 2009, 75% (n=212) of incidences were successfully treated with DOT and 78% (n=55) were successfully treated not using DOT. It seems that DOT is not as effective as patients and the WHO Global Surveillance Goal would like it to be [8]. With good NTP practices, resistance rates are low. On the other hand, with poor NTP practices, resistance rates are high [2]. Automated liquid culture systems and molecular probe assay are recommended by the WHO as the 'gold standard' for first line DST only due to good reliability and reproducibility [2, 3].

Currently, some new and improved diagnostics have been made more affordable and feasible, for developing countries, although management practices are still poor or are not being implemented [36]. The WHO recommends the monitoring of treatment progress in smear positive or culture positive patients through sputum smears and cultures: at 2 months, at 5 months, and at the end of treatment. When MDR is suspected, a minimum of five or six drugs are suggested to be used initially and injectable agents. FQs improve treatment outcomes, especially when used with injectable drug Am. When full DST is known, a minimum of four drugs is appropriate [18].

MDR has limited treatment options. The WHO suggests a minimum of 18 months MDR TB treatment after culture conversion and DOTS throughout treatment [18]. In a study conducted by the New England Journal of Medicine, it was found that patients who were undergoing treatment had significantly higher resistance rates than patients undergoing no treatment, 36%, with MDR at 13% to 9.9%, respectively [4]. Using the anti TB drugs in conjunction reduces anti TB therapy from 18 months to 6 months [5].

Treatment of patients is most successful within a comprehensive framework of five points recommended by the WHO: government commitment, case detection by sputum smear microscopy, standardized treatment regimen of six to eight months, a regular uninterrupted supply of all essential anti TB drugs, and a standard recording and reporting system [24]. Recently implemented, DOTS plus is a revision or improvement of DOTS [24].

In more extreme cases, surgical procedures from segmental resection to pleura-pneumonectomy may be implemented. Operations can be performed with low mortality (<3%), but the complication rates are high with BPF and empyema being the major complications [11,12]. Further exploration is required regarding the use of immunotherapy [37].

What Needs to be Done

Diagnostic services, including radiography, should be accessible. Sufficient staffing resources should exist to provide optimal supervision of patients. Testing the sputum for MDR Tb should be readily available and if necessary, "on the spot" or "on the street". Taking these measures will rapidly confirm the diagnosis in a high percentage and define the infectious cases. Survey campaigns could close the gap between an estimate of the prevalence and annual incidence rate derived from passive case-finding. Long term regular observation or cross-sectional screening in those of high risk may contribute to early diagnosis [7].

As stated above, staff and resources might be unavailable or limited, and with the rapidity of the disease, careful evaluation and observation are a must. Some patients might not develop signs of TB until weeks or months into the onset, making proper diagnoses early and limited transmission not easy. TB needs to be taken care of immediately in this case, as the patient is just diagnosed at his or her most infectious point. This is where maintaining an appropriate awareness of TB among physicians is critical to reducing transmission and initiating early prevention and treatment. Thus, an effective, well-defined, well-informed and alert public health component in the control program of TB is absolutely essential. To help avoid the problem of multidrug resistance and its spread, especially, clinicians should give patients fixed-dose combinations adjusted for body weight whenever the drugs are self-administered, more of an individualized therapy [7].

The investigation of close contacts of cases has been found to be highly cost effective in Montreal, Canada (the screening of prospective immigrants much less so). Studies among contacts of active cases have demonstrated that 12 months of daily isoniazid gives 30-100% protection against active TB, and yet IPT is not widely used [7,10]. Due to inaccurate or incomplete DR data in many countries, there is a great need for more straightforward methods for surveillance of TB resistance [2].

Challenges

Patients who do not comply with their treatment regimens pose challenges to the health care workers. Also, the enormous cost of meeting the new standards, especially for environmental controls, is difficult. For example, adequate indoor and outdoor ventilation reduces transmission; however hospitals cannot keep their windows open continuously. Hospitals at a lower risk of contraction may not run into these financial difficulties of adequate ventilation [7].

The main challenge to a tuberculosis control program is the development of efficient, effective, and economically sound strategies to make the best use of available resources. A team approach is an integral part of developing such strategies [7]. As stated previously, there are problems with inaccurate and incomplete (or lack of) death registration and recording of cases in many countries [2,10].

Active TB can arise via three different routes, and typically, with a considerable time delay after infection, it is not straightforward to calculate an exact value of R_0. Misdiagnosis and non-rapid DST are problems as well in trying to effectively control MDR. Furthermore, active diseases must be excluded before isoniazid is taken alone, and side effects include a hepatitis risk of 1%/year. Some do not actually start IPT (35%) and of those that started, only 23% completed at least 6 months of treatment. The challenge, in sum, is to find ways in which active case finding and preventive therapy can significantly boost the of DOTS programmers. Success is most likely in groups at high risk of infection or where active disease can be identified, and where treatment compliance is high [7,10].

Additionally, duplicate isolates pose a problem when susceptibility testing because epidemiological studies will be inaccurate and might skew results [9]. The organism has a long generation time and a capacity for dormancy, when its low metabolic activity makes it a difficult therapeutic target [23]. As previously stated, modeling epidemics of MDR MTB of heterogeneous fitness has found that even when the rf of a strain is low and an well-functioning control program is being implemented, high rf strains can outcompete both the drug susceptible organisms and the less fit MDR organisms [14,22].

In sum, the main challenges are the following: human resource development for the diagnosis and management of MDR and XDR is needed, especially in countries with a high burden of MDR TB, capacity of laboratory needs to be strengthened and a laboratory network established for the detection of resistance, treatment remains difficult and expensive, XDR could develop, if MDR is not treated, improper regulation, and non-adherence of patient and health care worker to proper standards of care and control [7,14,22,23].

New Treatments in Queue

A series of compounds containing a nitroimidazopyran nucleus

that possess anti TB activity have been considered as new drug treatment. After bioreductive activation by a mechanism dependent on F420 cofactor, nitroimidazopyrans inhibited the synthesis of protein and cell wall lipid and exhibited bactericidal activity against both replicating and static bacilli [11,12]. This drug is currently undergoing Phase II clinical trials for drug sensitive TB [30]. Additionally, a new drug, diarylquinoline TMC207, has been tested to significantly reduce the time to sputum culture conversion to negative [22].

Cost effectiveness

In a cost effectiveness study, treatment of MDR TB using second line drugs was found to be highly cost effective in Peru. Strategies depend on incidence, burden, and budget. Simulation results suggested that individualized regimens would be cost effective in a wide range of situations. This study provides evidence that DOTS plus strategies are likely to be cost effective in lower middle income settings with at least 1% MDR TB [38].

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