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CLINICAL FOCUS SERIES

Tuberculosis
Selected Problems



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CHAPTER

2 Epidemiology of Tuberculosis

Anna L Rich

INTRODUCTION

Despite being an ancient illness, with records dating back to the Egyptian mummies of 600 AD, as well as reference to an illness akin to tuberculosis (TB) in ancient Indian, Chinese, and Arabic literature; TB remains an important infectious disease and the second leading cause of death from a single infectious agent worldwide.[1] In 1993, the World Health Organization (WHO) declared a "global emergency", and set targets for the control of the disease by 2000.[2] Sadly these targets have not been met and in the 1990s, a resurgence of drug-resistant TB and subsequently multidrug-resistant TB (MDR-TB) has delayed progress in controlling the disease. At the start of the 21st century, the United Nations established eight Millennium Development Goals (MDGs) with targets set for the year 2015. Tuberculosis was included as part of MDG 6, and the targets included a fall in TB incidence, prevalence, and mortality rates. In addition, there should be an increase in the case detection rate and percentage of patients who complete treatment. Epidemiologists have used mathematical models to calculate that the requirements needed to reduce TB incidence, prevalence, and death are: a case detection rate of 70% with at least 85% of patients completing treatment. Table 1 illustrates the progress made so far.[3]

The WHO has produced a number of other documents in the past 10 years to support the implementation of Directly Observed Therapy (DOT) strategy, to help facilitate good TB control programs, and to address the problem of human immunodeficiency virus (HIV)/TB coinfection and the resurgence of drug-resistant TB.[4-6]

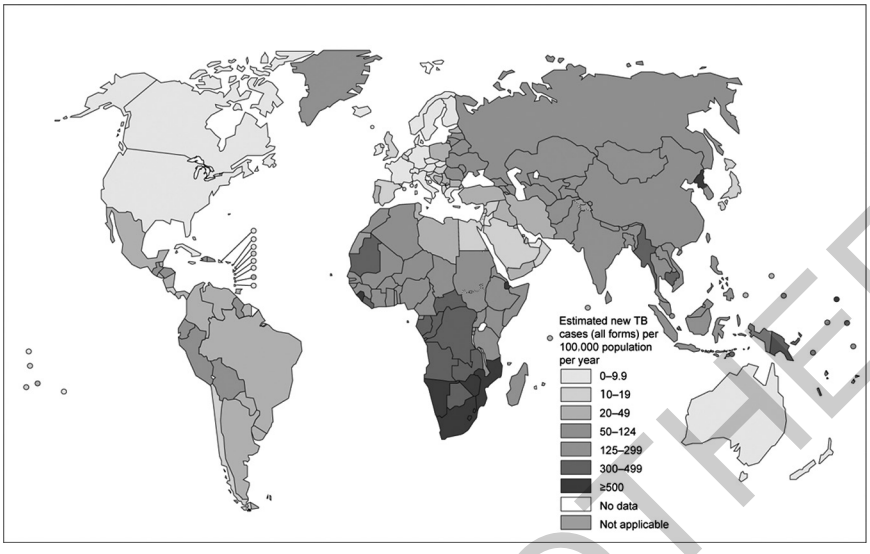
INCIDENCE AND PREVALENCE

The WHO estimates that about a third of the world's population is infected with TB, but only a few become ill with TB disease. In 2012, the WHO estimated that there were

TABLE 1 Global progress in tuberculosis care and control

	2000	*2012*
Incidence (per 100,000 population per year)	148	122
Prevalence (per 100,000 population)	263	169
Mortality (per 100,000 population per year)	22	13
Case detection rate (%)	42	66
Treatment success rate (%)	69	87

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TB, tuberculosis.

FIG. 1: Estimated tuberculosis incidence rates worldwide in 2012. ***(For color version, see Plate 2)***

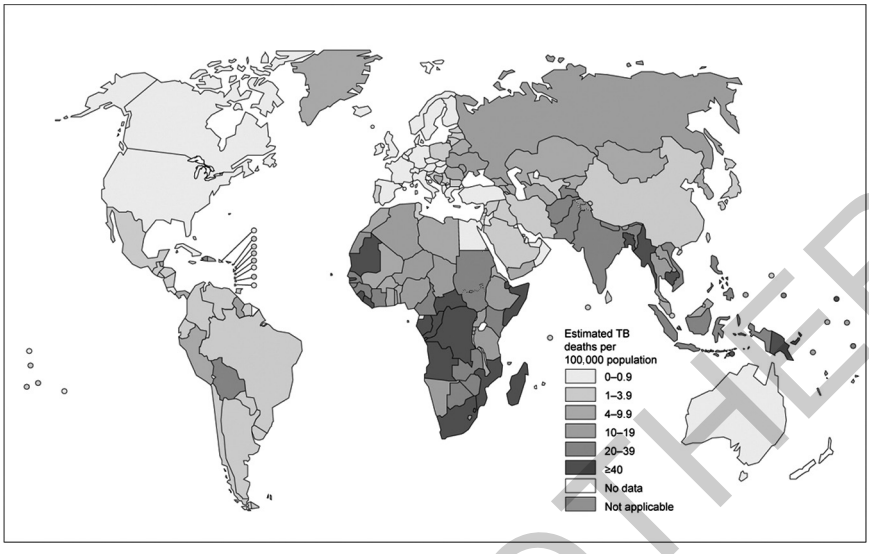
Source: World Health Organization.

8.6 million incident cases of TB, although only 5.7 million (66%) were detected and notified to national TB programs. This leaves a group of patients, almost 3 million, who were either not diagnosed with TB disease, or were not notified.[3] There is a group of 22 countries, which together represent almost 80% of the disease burden worldwide, and they are referred to as high-burden countries. These countries can be grouped by continent; in Africa—Democratic Republic of the Congo, Ethiopia, Kenya, Mozambique, Nigeria, Tanzania, Uganda, South Africa, and Zimbabwe. In Asia, the countries are Afghanistan, Bangladesh, China, Indonesia, India, Cambodia, Myanmar, Pakistan, Philippines, Thailand, and Vietnam. The remaining countries are Brazil and the Russian Federation. Figure 1 illustrates the variation in estimated incidence of TB across the world.

MORTALITY

In 2012, there were 1.3 million deaths worldwide attributed to TB, which corresponds to 20 deaths per 100,000 population, and included 320,000 deaths due to TB/HIV coinfection.[7] Tuberculosis remains one of the top three causes of death in women aged 15–44 years, and kills more women than all causes of maternal mortality combined.[8] The burden of TB-related deaths (95%) is in low-middle income countries, and it has been reported that 26% of avoidable deaths in developing countries are due to TB.[8] However, there has been significant improvement in the mortality rate over the past 25 years, and in 2012, the mortality rate had fallen by 45% compared with 1990. The MDG was for this figure to have halved by 2015, and it looks as if this will be achieved.[3] Although TB mortality rates have fallen in every region, the fall has been relatively little in sub-Saharan Africa, due to the sharp rise in HIV-related disease since 1990. As a result of this HIV epidemic, the incidence and mortality of TB in Africa only began to fall in 2004.[9] Figure 2 illustrates the variation in estimated TB mortality rates worldwide.

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TB, tuberculosis.

FIG. 2: Estimated tuberculosis mortality rates excluding tuberculosis deaths among human immunodeficiency virus-positive people, 2012. ***(For color version, see Plate 2)***

Source: World Health Organization.

AGE

In the developing world, TB is more prevalent in children and young adults, which reflects primary transmission. It can be difficult to diagnose and treat children, and this can lead to TB meningitis and miliary TB. In 2012, the WHO reported 74,000 deaths in HIV-negative children.[7] In developed countries, the rate of TB is higher amongst older adults, compared with young adults,[10] and this is thought to be due to reactivation of latent infection.[11] Reactivation may occur due to impaired host immunity with increasing age. Hochberg reported 22% of patients with TB in the United States of America were over 65 years of age, and within this population there were subgroups who were at increased risk; namely men, non-Caucasians, and those in long-term institutionalized care.[12] The elderly are known to have an increased mortality rate from TB; therefore, it is important to try and prevent reactivation in this subgroup of adults in order to prevent avoidable deaths.[10,13]

SEX

Globally, the prevalence of TB is equal amongst men and women up to adolescence. From 15 years upward, there is a higher rate of TB in men compared with women. One suggestion is that this reflects a greater burden of disease in adult men, due to a higher number of social contacts outside the home and exposure to infection.[14] But it may simply represent a higher notification rate in men, given there is an estimated 2:1 (male:female) ratio of cases notified to public health authorities worldwide.[15] This under notification of disease in women compared to men has been observed in other infections too, including malaria and leishmaniasis.[16,17] In 2012, the WHO reported that more than half the estimated cases of TB in women went undetected, compared with less than 40% of the total population.[18]

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There is also evidence that women of childbearing age are more likely to progress from infection to disease, compared with men of a similar age;[8,19] and women are more likely to have extrapulmonary TB compared with men. Yang et al. reported the results of a retrospective case control study in Arkansas, United States, which found that 17% of the women with TB had extrapulmonary disease compared with only 9% of the men.[20] Extrapulmonary disease has been linked with a weakened immune system, which may be relevant given women are known to have a higher mortality rate from TB.[14,18] Active case finding of adult women is an important public health control measure to try and find and treat these individuals and reduce the disease burden.

RACE

Given the geographical variation in the prevalence of TB worldwide, individuals who are born or spend their childhood in countries where TB is highly prevalent are observed to have an increased likelihood of developing TB later in life. This can be most striking in low-incidence countries, like the United Kingdom and the United States of America. Almost three quarters (73%) of the patients diagnosed with TB in the United Kingdom in 2013 were born abroad.[21] Since 1986, the percentage of patients in America who were born in endemic countries has increased from 22 to 58%.[22] Asghar et al. reported an independent association between extrapulmonary TB, often a marker of disseminated disease, and origin in Southeast Asia, compared to immigrants from other areas of the world.[23] Asian patients are also less likely to be part of a cluster, which implies disease reactivation, in contrast to Black Americans who are often part of a cluster group reflecting recent transmission.[24] Fiske reported that Black men were almost six times more likely to develop extrapulmonary TB than non-Black men.[25] Black Americans developing TB were more likely to be young, from an inner city background (reflecting low socioeconomic status), be HIV-positive and have drug-resistant disease.[24] Mexicans account for 25% of the migrant TB population of America. Joseph et al. reported an ethnographic study looking at the sociocultural aspects of TB in this population.[26] They reported significant misconceptions regarding disease transmission, low perception of risk and stigma amongst those who had TB. Tuberculosis control programs need to be aware of these cultural differences and how they might lead to barriers in accessing health care and completing treatment.

In 2013, Tollefson published a literature review to summarize the burden of disease amongst indigenous people. The United Nations defines an indigenous group as being any group of people who self-identify as indigenous. The majority of the published literature relates to the Aborigines of Australia, the Inuits of Canada, and the Indians of North America. However, there are indigenous people in every continent of the world. Although there is a paucity of data, and some papers are more than 25 years old; it does appear as if the rate of TB in indigenous people is often higher than the nonindigenous people in the same country.[27] The reason for this is unclear, and more research is required.

SOCIOECONOMIC STATUS

Tuberculosis has long been regarded as a disease of the poor, with overcrowding, malnutrition, and poor sanitation contributing to its prevalence. Efforts to improve these social factors have led to success in reducing the prevalence rate, but they rely on political and cultural change. The role of the health service, and in particular the TB control program, has been highlighted in New York and the United States of America as a whole.[28] In the 1980s, the incidence of TB had been falling for several decades, and TB services had been cut back. However, what followed was a steep rise in the

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incidence, which peaked in 1992. This was attributed to a number of factors, including the epidemic of HIV/AIDS, immigration of individuals from endemic countries, and the dismantling of public health infrastructure. Since 1992, there has been a substantial reduction in the incidence of TB in the United States of America, which has been achieved by improved public health efforts, infection control measures, and the use of DOT, as well as public education programs.[29,30] In Eastern Europe, a socioeconomic crisis followed the dismantling of the former Soviet Union, and this led to struggling public health systems which have undoubtedly contributed to the increase in the incidence and prevalence of TB including MDR-TB.[6]

There is evidence that aspects of an individual's socioeconomic status will affect the likelihood of them developing TB, and these include wealth, education, smoking, alcohol consumption, and drug use. However, many of these factors are related, and often an individual with a poor education record, will find themselves unemployed or homeless, resulting in malnutrition, perhaps overcrowding and at risk of coinfections. Khan et al. reported that those individuals below the poverty line were twice as more likely to develop TB than those above it, and those with less than a high school education were also more likely to develop TB than those with higher education.[30] A systematic review by Lonnroth reported an almost threefold increased relative risk of developing TB if an individual had an alcohol-related disorder, or drank more than 40 g of alcohol per day.[31] However, it is not possible to determine whether this is a direct link between excess alcohol and a reduced immunity or the social implications of drinking excess alcohol, such as an increased likelihood of smoking cigarettes, and low income. Several papers have reported a link between tobacco smoking and an increased likelihood of developing TB.[32-35] Lin performed a prospective cohort study, and reported an almost twofold increased odds ratio amongst those who smoked, compared with nonsmokers.[33] The greater the tobacco consumption, the higher the odds ratio for developing TB. Bates et al. performed a meta-analysis and discovered that smoking is a risk factor for TB infection and disease, but there was no definite increased mortality from TB amongst tobacco smokers.[34] Individuals who use recreational or illicit drugs are at increased risk of developing TB, and they put themselves at risk of coinfection with hepatitis and HIV, and require specialist management in terms of drug interactions.[36-38]

The prison community is the perfect setting for an outbreak of TB, with large numbers of usually young men living in close communities, and often with concomitant risk factors, such as HIV infection, smoking, malnutrition, etc. Several studies from Africa have looked at this setting and confirmed that there is a high prevalence of HIV infection, 25–27%, and that prospective case finding has identified between 4 and 8% of the prisoners screened had active TB.[39,40] Screening for latent TB infection (LTBI) has also been studied, and rates vary depending on location; 73% of inmates in a Brazilian prison were tuberculin skin test (TST)-positive.[41] Two studies from Europe, in Switzerland and Spain, used the TST to assess prisoners on arrival and found between 40 and 47% had LTBI; and the rate was greatest amongst those originally from sub-Saharan Africa.[42,43] In order to prevent outbreaks of active TB in prisons, screening for LTBI should be routine practice, and chemoprophylaxis given.

Malnutrition profoundly affects cell-mediated immunity which is the principle mechanism employed in the defense against TB. Individuals who are underweight are more likely to develop TB than those with a good nutritional status, and are more likely to die of the disease.[44,45] Patients who have had gastric surgery, including jejunoileal

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bypass are reported to have an increased risk of developing TB,[46] as are those with celiac disease.[47] The mechanism for the latter association may be related to malabsorption.

PREDISPOSING HUMAN FACTORS

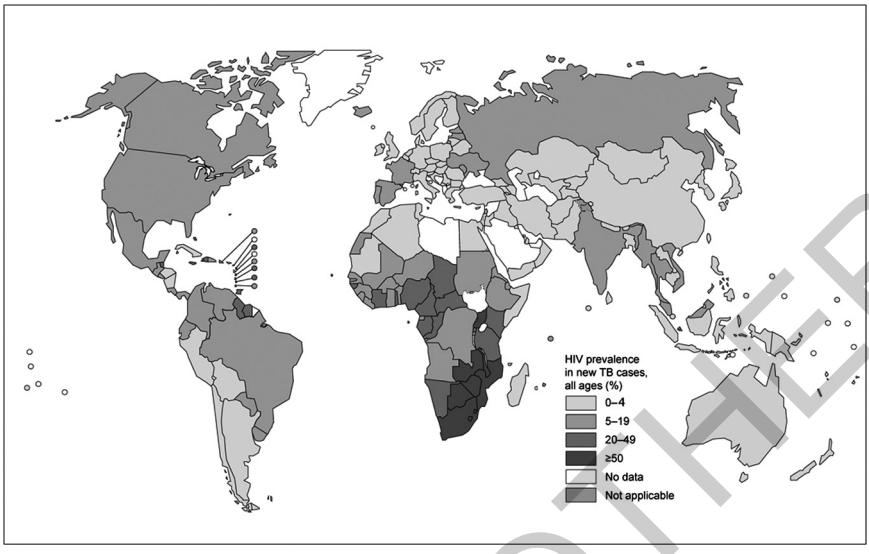
There are a number of conditions which are linked to an increased risk of developing TB, which are usually attributed to a change in the host immune system and reactivation of latent infection. Diabetes is one such disease and poor diabetic control along with an increasing number of complications secondary to diabetes have been linked to an increased likelihood of developing TB.[48-51] Jeon et al. reviewed 13 observational studies and reported a threefold increased risk of developing TB in those individual with diabetes.[49] Chronic renal disease is another condition related to a significant increase in the likelihood of developing TB. In 2003, Hussein et al. summarized the published literature to date, and reported a range of 5.9–52.5 increased risk of developing TB in individuals with chronic renal disease.[52] The association is greatest in those patients on hemodialysis. Liver cirrhosis has also been reported as an independent risk factor for TB, and one with a poor prognosis. A cohort review of patients entered into the Danish registry with liver cirrhosis revealed that over a 16-year period, and more than 20,000 patients, 151 cases of TB were identified. This equated to an incidence rate of more than 160/100,000 person-years. Sadly the 30-day mortality for those with TB was very high at 27%.[53] Individuals with cancer are also thought to be at increased risk, but this risk is not uniform. Hematological malignancies or those of the head and neck have been found to be particularly relevant to the development of TB. Kamboj et al. performed a 25-year review of cancer patients in the United States of America, and reported a rate of TB in those with a hematological malignancy as more than 200/100,000. This is 40 times the rate in the general population. Among patients with cancer of the head and neck, the rate was more than 100/100,000; whilst no increased risk was observed in solid tumors that were not in the head and neck.[54]

There are certain situations in which the immune status of an individual is directly suppressed, either deliberately or inadvertently. The risk of HIV coinfection with TB is discussed in a separate section below. Patients who have had a solid organ transplant are deliberately immunosuppressed to avoid rejection of the donor organ, but screening should be done before this, in order to treat LTBI and avoid reactivation.[55,56] Several chronic systemic diseases have previously relied upon long-term use of glucocorticoids, which are known to increase the risk of TB reactivation;[57] and now use anti-tumor necrosis factor (anti-TNF) agents as disease-modifying drugs, and these patients should be screened and treated for LTBI, before anti-TNF agents are started.

HUMAN IMMUNODEFICIENCY VIRUS/TUBERCULOSIS COINFECTION

The WHO reports that a third of the 35 million people living with HIV worldwide are infected with LTBI. Those diagnosed with HIV have a significantly increased risk of acquiring primary TB infection and reactivation of latent infection. The size of the risk of acquiring TB in those who are HIV-positive has been reported between 9 and 30 times the risk in HIV-negative individuals.[58-60] There is strong evidence that a fall in CD4 count and a rise in viral load are risk factors for disease, and antiretroviral therapy (ART)

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HIV, human immunodeficiency virus; TB, tuberculosis.

FIG. 3: Human immunodeficiency virus prevalence in new cases of tuberculosis in 2012. ***(For color version, see Plate 3)***

Source: World Health Organization.

reduces the risk of TB.[61,62] Tuberculosis is the most common presenting illness in individuals living with HIV, with and without ART. There were 1.1 million new cases of TB in HIV-positive patients in 2012, and 75% of these were in sub-Saharan Africa.[60] Approximately, 1 in every 15 new patients with TB is already HIV-positive.[5] Figure 3 illustrates the variation in estimated HIV prevalence in new cases of TB across the world.

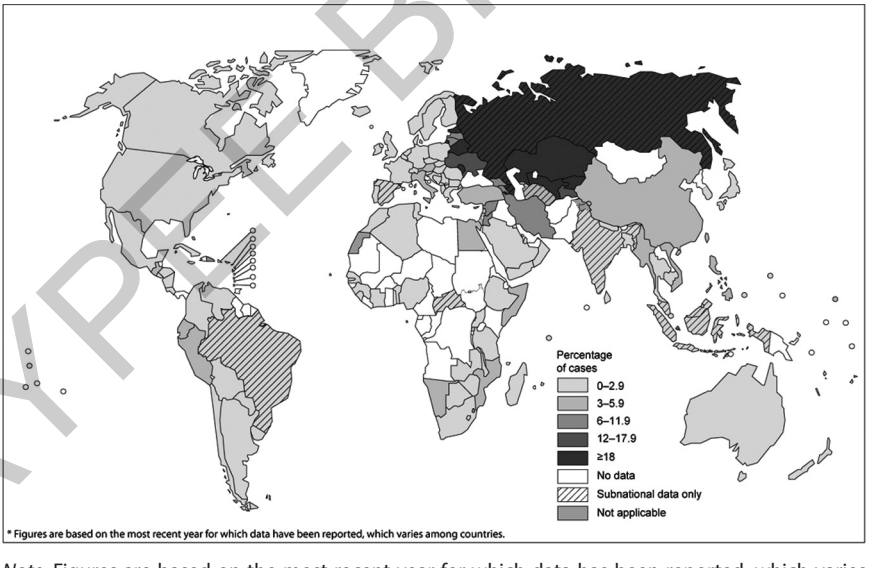
Tuberculosis is the leading cause of death for individuals with HIV, and it accounts for 20% of HIV-related deaths, and the reverse is also true. An extra 25% of deaths amongst patients with TB is attributable to coinfection with HIV.[63] A retrospective cohort study from Ethiopia, comparing the mortality rate in HIV-positive compared with HIV-negative patients, confirmed the increased mortality rate in those with coinfection, but reported that this was more likely in the self-administered continuation phase, rather than the initiation phase which was under DOT.[64] Globally, there is no difference between men and women with regard to HIV/TB-related deaths; but in sub-Saharan Africa, there is a female predominance.[60] In response to the synergy between HIV and TB, leading to increasing levels of disease and death, the WHO has set several targets related to HIV/TB coinfection—universal HIV testing amongst patients with TB, provision of ART to HIV-positive patients with TB, and the provision of chemoprophylaxis to those people living with HIV.[3] The data currently suggests that less than 50% of patients with TB are tested for HIV infection (46% in 2012); and only 57% of the TB patients know to be HIV-positive were receiving ART, although 80% were had been enrolled on to a program of cotrimoxazole preventive therapy.[60]

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MULTIDRUG-RESISTANT TUBERCULOSIS

The primary cause of MDR-TB is inappropriate, incorrect, or inadequate use of anti-tuberculous therapy to treat susceptible TB. Cases have been reported in every country but there are certain areas which have a higher percentage of the TB burden who are multidrug resistant. This is illustrated in figure 4, which identifies the former Union of Soviet Socialist Republics, and parts of Eastern Europe, and China as being the worst affected areas. The WHO is concerned that there is significant underreporting of cases with MDR-TB and that clinical outcomes are very poor in this patient group, with a high-mortality rate, and successful completion of treatment in only 50% of patients.[3] Makinen et al. report a population-based study in the Murmansk region of the Russian Federation between 2003 and 2004.[65] In total 1,226 patients were diagnosed with TB, of whom 688 (56%) had MDR-TB. The majority of the patients with MDR-TB had been treated for TB in the past. Of those previously treated for TB, 73% had MDR disease, in contrast to 26% of those who had not been treated before. This highlights the need for good education and support from a designated key worker, or TB specialist nurse, to ensure compliance with the regime and high TB treatment completion rates first time. The WHO reports that global treatment success rates in MDR-TB are less than 50%, due to the high-mortality rate and large numbers of patients who are simply lost to follow-up.[3]

In 2006, it became clear that a new problem had emerged, extensively drug-resistant TB (XDR-TB). This is defined as resistance to rifampicin and isoniazid, but in addition resistance to a fluoroquinolone and also to an injectable agent. A mission hospital in



Note: Figures are based on the most recent year for which data has been reported, which varies among countries.

FIG. 4: Percentage of new cases of tuberculosis with multidrug-resistant tuberculosis. ***(For color version, see Plate 3)***

Source: World Health Organization.

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Tugela Ferry, KwaZulu-Natal province, South Africa reported 53 cases with XDR-TB, all of whom were coinfected with HIV. Sadly the mortality rate was 98%, and the median survival time from sputum collection was a mere 16 days.[66] Since then the situation in Tugela Ferry has improved. There have been a total of 463 patients with XDR-TB between 2005 and the end of 2008, of whom 69 have survived more than 6 months. This subgroup of survivors had less advanced TB at diagnosis, and it was more likely to be their first episode of TB. Although rates of HIV coinfection were similar between the survivors and those who died, the CD4 count was significantly higher in the group that survived.[67] There was no significant variation in sex or age in these two patient groups. Although South Africa remains a country severely affected by drug-resistant disease, cases of XDR-TB have been reported in almost 100 countries.[3]

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