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Review Article

Drug Resistant Tuberculosis: A Major Risk to Global Health Security Treatment

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Abstract

The continuing spread of drug-resistant tuberculosis (TB) is one of the most urgent and difficult challenges facing global TB control. Patients who are infected with strains resistant to isoniazid and rifampicin, called multidrug-resistant (MDR) TB, are practically incurable by standard first-line treatment. In 2012, there were approximately 450,000 new cases and 170,000 deaths because of MDR-TB. Extensively drug-resistant (XDR) TB refers to MDR-TB strains that are resistant to fluoroquinolones and second-line injectable drugs. The main causes of the spread of resistant TB are weak medical systems, amplification of resistance patterns through incorrect treatment, and transmission in communities and facilities. Although patients harboring MDR and XDR strains present a formidable challenge for treatment, cure is often possible with early identification of resistance and use of a properly designed regimen.

Keywords: Multi drug resistant Tuberculosis, Challenges, Global health and Treatment.

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INTRODUCTION

Tuberclosis has existed since form immorial times. The oldest unambiguously detected the tuberculosis causing paliogen i.e *Mycobacetrium tuberculli* gives evidence of the disease in the remains of bison in Wyoming dated to around 17000 years ago [1]. However, wheather tuberculosis originated in bovines, then transferred to human or wheather both bovine and human tuberculosis diverged from a common ancestor, remains unclear [2]. Skeltal remains show some prehistoric humans (4000 BC) had TB and researcher, have found tubercular decay in the spines of Egyptian mummies dating 3000 to 2400 BC [3]. Besides genetic studies also suggest the presence of TB in the Americans for about 100 AD [4].

Although Richard Mortan established the pulmonary from associated with tubercles as a pattulagy 1689 [5] due to the variety of its symptoms. TB was not identified as a single disease until the 1802s. In 1819 Reve Larnnec claimed that tubercles were the cause of pulmmary tuberculosis. It was J.L Schonlein frist published the name “tuberculosis”

Robert Koch identified and described the bacillus causing tuberculosis. (*M.tuberclosis)* on 24 March 1882 [6]. He received the Nobal prize in physiology or Medicines in 1905 for the discovery. However Koch did not believe the cattle and humans tuberculosis disease were similar which delayed the recogination of infected milk as a source of infection. Koch announced a glycerine extract of the tubercle bacilli as a remedy for tuberculosis in 1890 calling it tuberculin. Although it was not effective it was later successfully adopted as a screening test for the presence of pre symptomatic tuberculosis [7].

Albert Calmette and Camille Guerin achieved the first genuine success in immunization against tuberculosis in 1906 using attenuated bovine strain tuberculosis. It was called as acilli Calmette – Guerin (BCG) and this vaccine was first used on humans in 1921 in France, but achieved widespread acceptance in the US, Great Britain and Germany only after World War II [8]. Tuberculosis caused widendespread public concern in the 19th and 20th century and it is still a great concern in the underdeveloped countries. It is an infection disease caused by *Mycobacterium tuberculi* (MTB) bacteria. It generally affect the lungs but can also affect other parts of the body. Most infections

shows no symptoms and at this stage it is called as latent tuberculosis [9]. About 10% of latent infection progress to active diseases which left untreated kills about half of those affected [9]. The typical symtpms of active TB are a chronic cough with blood containing mucos mild fever, night sweats, and weight loss [9]. It was historically called consumption due to weight loss [10] and infection of other organs can cause a wide range of symptoms.

Tuberculosis spread from one person to the other through the air, when people who have active TB in their lungs cough spit, speak or sneeze [9]. People with latent TB do not spread the disease [9]. Active infection occur more often in people with the AIDS/HIV. Diagnosis of active Tb is based on chest x-rays, as well as microscopic examination and culture of body fluids [11], where as diagnosis of latent TB relies on the tuberculin skin test (TST) or blod test [11].

Tuberculosis may infect any part of the body but favorite organs are lungs which is known as pulmonary tuberculosis [12]. When tuberculosis develops outside the lungs is called as extrapulmonary tuberculosis, although extrapulmonary signs and symptoms include fever, chills weight loss, sweats, loss of appitite, weight loss and fatigue and significant nail clubbing may also occurred [12].

In case of pulmonary tuberculosis (commonly involve 90% cases). Symptoms may include chest pain and prolonged cough producing sputum. About 25% of people are asymptomatic [13]. Occassionally people may cough up blood in small amount and in very rare case the infection may erode into pulmonary artery result in massive bleeding [12]. Thus tuberculosis may become a chronic disease and cause estensive scarring up in the lobes of the lungs. The upper lung lubes are more frequently affected by tuberculosis than the lower ones [12]. The reasons is not clear but it may be due to either better air flow [14] or poor lymph drainage within the upper lungs. Where as extra pulmonary infection accounts for 15-20% (outside the lungs), such type of tuberculosis occur more commonly in people with a weekened immune system and young children but persons with HIV occur in more than 50% of cases [15]. The notable extrapulmonary infection sites include the pleura (in tuberculosis pleurisy) the central nervous system (Mennigits tuberculosis) the lymphatic system (in scrofula of the neck) The genitourinary system (in unigenital tuberculosis) and the bones and joints (in pott disease of spine) There is another potential more serious widespread form of TB is called as dessimminated tuberculosis it is also called as miliary tuberculosis. It is tuberculosis that occur when a large number of the bacteria travel the through the blood stream and spread through out the body. This type of tuberculosis makes up almost 10% of extrapulmonary cases [16].

The bacteria that cause tuberculosis (TB) can develop resistance to the antimicrobial drugs used to cure the disease. Multidrug-resistant TB (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the 2 most powerful anti-TB drugs. The 2 reasons why multidrug resistance continues to emerge and spread are mismanagement of TB treatment and person-to-person transmission. Most people with TB are cured by a strictly followed, 6-month drug regimen that is provided to patients with support and supervision. Inappropriate or incorrect use of antimicrobial drugs, or use of ineffective formulations of drugs (such as use of single drugs, poor quality medicines or bad storage conditions), and premature treatment interruption can cause drug resistance, which can then be transmitted, especially in crowded settings such as prisons and hospitals.

Today the continuing spread of MDR-TB is one of the most urgent and difficult challenges facing global TB control. In 2012, there were approximately 450,000 new cases of MDR-TB and 170,000 deaths. Globally, MDR-TB is present in 3.8% of new TB patients and 20% of patients who have a history of previous treatment. The highest MDR rates are found in countries of Eastern Europe and central Asia, where MDR strains threaten to become as common as pan-susceptible strains. In some countries, MDR strains account for up to 20% of new TB cases and well over 50% of patients with a history of previous TB treatment. In 2011, Minsk, Belarus reported that 35% of new patients had MDR-TB, as did 75% of those who had been treated previously for TB [17].

In 2006, the term extensively drug-resistant TB (XDR-TB) was coined to describe strains of MDR-TB resistant to fluoroquinolones and second-line injectable drugs. It is estimated that 9.6% of MDR-TB cases worldwide have XDR-TB [18]. Because access to second-line drug susceptibility testing (DST) is poor in many areas of the world, XDR-TB often goes unrecognized. Although patients harboring MDR and XDR strains present a formidable challenge for treatment, cure is often possible with early identification of resistance and use of a properly designed regimen.

Causes of Drug Resistance

Drug resistance is a biological phenomenon that has been observed in Mycobacterium tuberculosis since the discovery of the first anti-TB drug, streptomycin. Many patients who were injected with streptomycin were brought from the brink of death and their sputum became temporarily clear of M. tuberculosis. But despite continuing to receive treatment, they soon began to excrete bacilli that were resistant to streptomycin in the laboratory [19].

With the advent of new drugs—thioacetazone and para-aminosalicylic acid in 1948 and isoniazid in

1952—it became clear that combination chemotherapy was the key to preventing the development of resistance. Initial combination regimens required 18 mo of treatment, but the invention of rifampicin in 1957, the most powerfully sterilizing anti-TB drug, paved the way for development of the shorter and more effective isoniazid- and rifampicin-containing regimens known as short-course chemotherapy. As part of the global TB control strategy called DOTS (directly observed treatment, short-course), these regimens became the standard of care even in resource-limited settings starting in 1993.

Outbreaks of MDR-TB were initially thought to be driven by nosocomial transmission, particularly among HIV-positive patients. One of the largest and best-documented outbreaks occurred in New York in the late 1980s and early 1990s [20]. As DST laboratory capacity improved in resource-limited settings and global drug-resistant TB surveillance efforts grew, it became clear that MDR-TB was increasingly common throughout the world and a growing threat to the general public health. The causes of the global spread of MDR-TB include the following:

Chaotic treatment

Before the late 1980s, many countries were not using standard protocols for the treatment of TB and did not have systems in place to support patients. Furthermore, in many settings, TB treatment was not provided for free, contributing to poor adherence. Even today, drug-resistant TB can be created very quickly during times of socioeconomic instability if there are stockouts of anti-TB drugs or other structural weaknesses in the health care system.

Amplifier effect of short-course chemotherapy

Once drug resistance has been created, the DOTS strategy can paradoxically exacerbate the problem. In Figure 2, the initial strain has polydrug resistance, but, as a result of repeated use of short-course chemotherapy, it becomes resistant to all first-line anti-TB drugs [21]. Amplification of drug resistance patterns through repeated courses of DOTS short-course chemotherapy continues to be a major driving force of the epidemic in many parts of the world that do not have the resources to diagnose or treat drug-resistant TB correctly [22]. Amplifier effect of short-course chemotherapy. H, isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide; S, streptomycin.

Community Transmission

In the early 2000s, it was believed that resistance mutations conferred a loss of fitness, so the transmission of resistant strains would be self-limited. This has not turned out to be the case. Current models indicate that in most countries, the majority of MDR-TB patients were infected initially with an MDR-TB strain, rather than slowly acquiring resistance caused by inadequate or irregular treatment [23].

Facility-Based Transmission

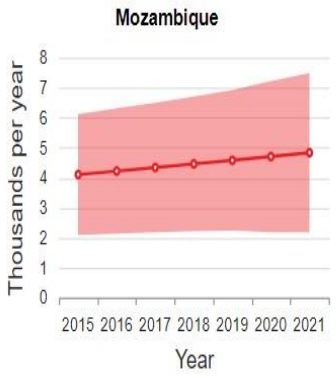
Nosocomial transmission in busy, crowded hospitals and health centers is likely an important driver of the epidemic, especially in high HIV prevalence settings. This can result in the spread of drug-resistant strains among patients receiving therapy for drug-susceptible TB as well as to the health workers [24].

Treatment

MDR-TB treatment is difficult because the second-line TB drugs are mostly weak and toxic. Most of these drugs were developed decades ago but hardly ever used because of poor side effect profiles. Because of the weak sterilizing activity of the second-line TB drugs, MDR-TB treatment generally takes 18–24 mo. In the best treatment programs, which address socioeconomic barriers and aggressively manage side effects, cure rates of 60%–80% have been reported. Globally, however, the cure rate for MDR-TB is much lower. In 2013, the WHO reported that only 48% of MDR-TB patients were cured. The global cure rate for XDR-TB is even lower: Only 20% are cured, and 44% die.

Anti-TB drugs have traditionally been divided into first- and second-line anti-TB drugs with isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin being the primary first-line anti-TB drugs. In this review, we use the WHO system, which classifies the drugs into five different groups based on efficacy, experience of use, safety, and drug class. Drugs in the same group do not always come from the same drug class nor do they have the same safety profile or efficacy.

The shaded area represents the 95% uncertainty interval.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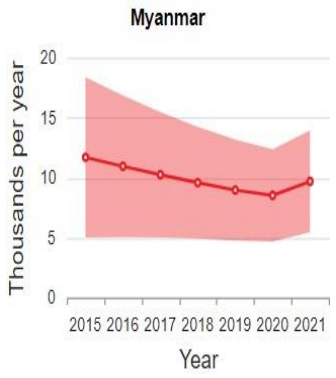
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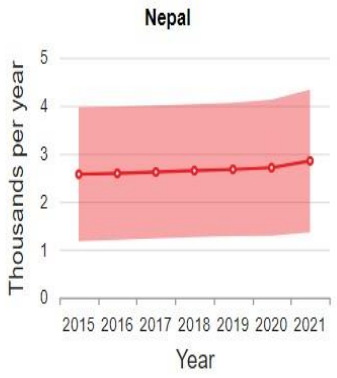
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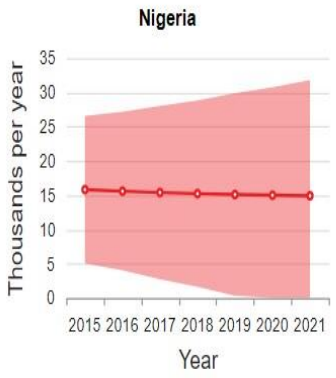
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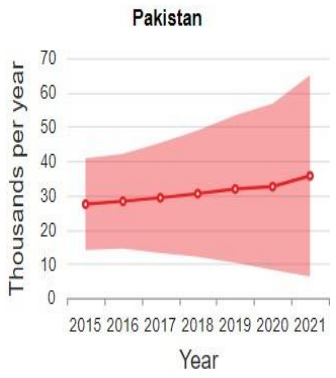
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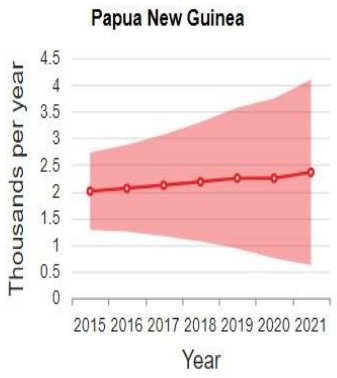
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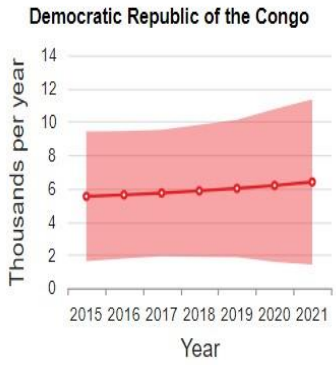
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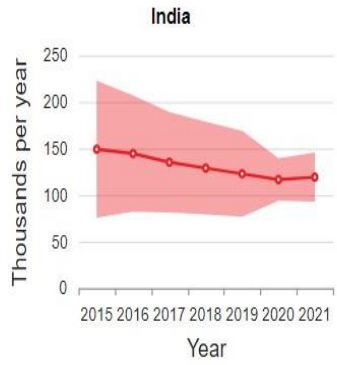
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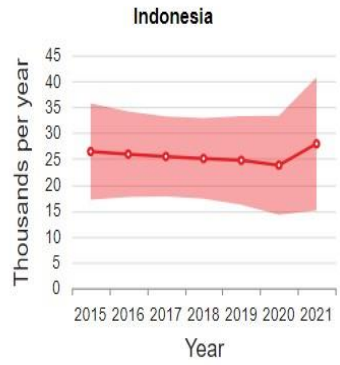
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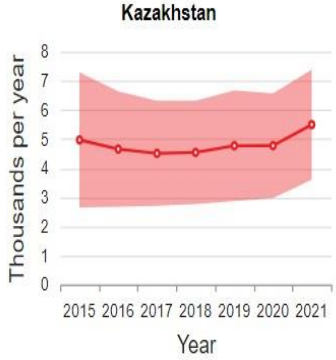
Kazakhstan
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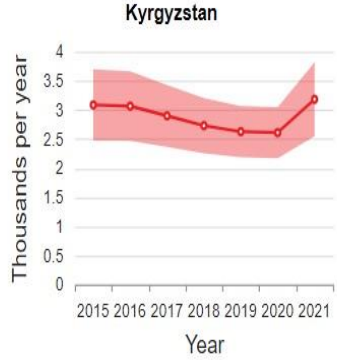
Kyrgyzstan
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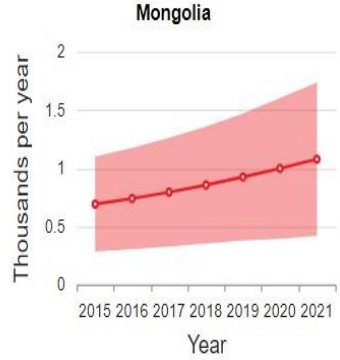
Mongolia
Thousands per year
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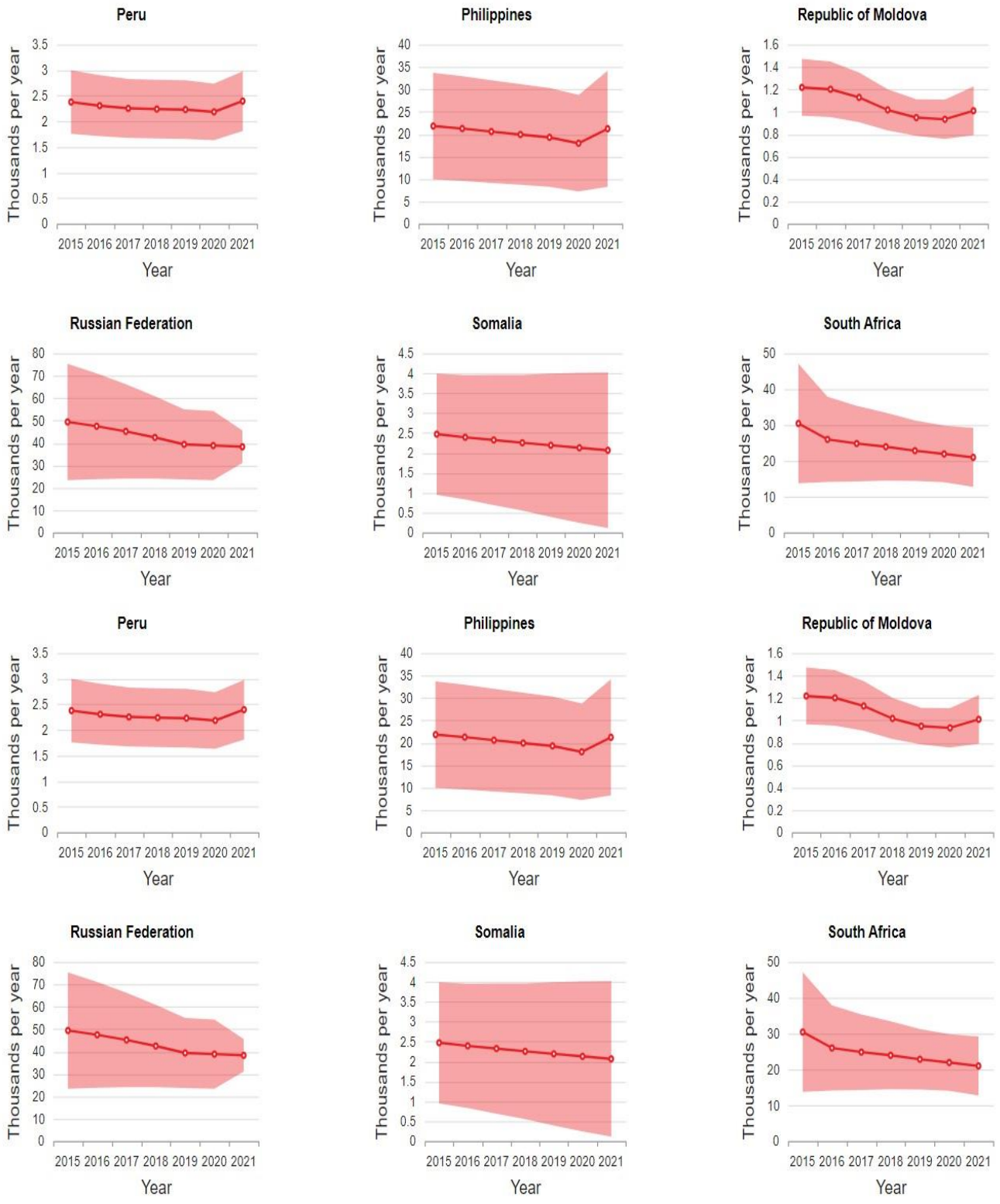
2015 2016 2017 2018 2019 2020 2021
Year


Peru
Philippines
Republic of Moldova
Russian Federation
Somalia
South Africa
Peru
Philippines
Republic of Moldova
Russian Federation
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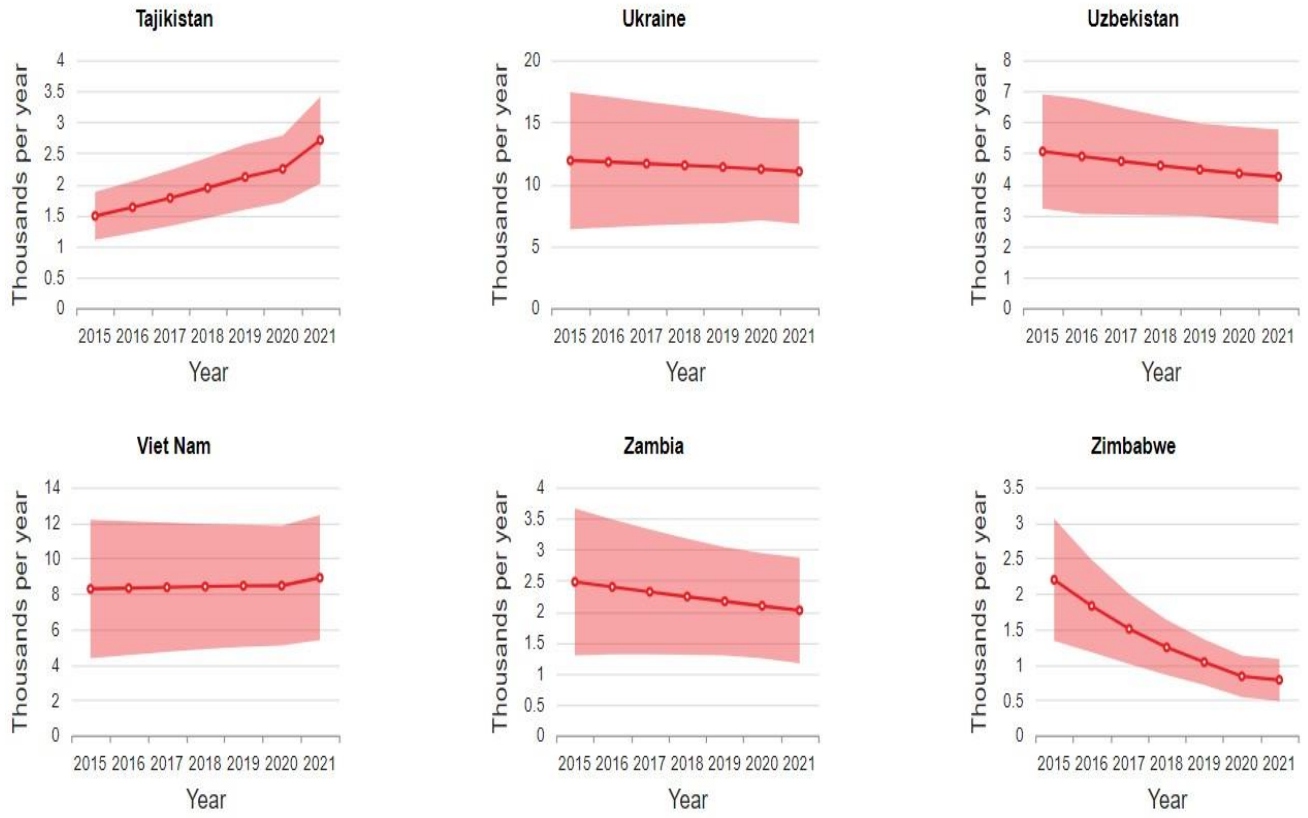

Fig. 1: Regional trends in the estimated number of incident cases of MDR/RR-TB, of different countries of world from 2015–2021

The countries with the largest share of incident cases of MDR/RR-TB in 2021 were India (26% of global cases), the Russian Federation (8.5% of global cases) and Pakistan (7.9% of global cases)

CONCLUSION

Despite advances in diagnostics and treatments we still have to find and treat two thirds of the drug resistant cases that go undetected and therefore go untreated each year. Control of TB and elimination will only occur if cases are detected, diagnosed and treated promptly.

The continuing spread of MDR-TB is one the most urgent and different challenges facing global TB control. The main cause of spread of resistant TB strains are weak medical system, amplification of resistance through incorrect treatment and ongoing transmission at community level. Of course, new molecular methods of DST have revolutionized the diagnosis of MDR- TB, but they are still not widely available. The community based programmes can improve treatment outcome by allowing patients to be treated in their respective places.

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