Zoonotic Web of Tuberculosis

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ABSTRACT

Tuberculosis or TB is a disease of bacterial origin with an ancient history. The main causative agent of this disease in humans is *Mycobacterium Tuberculosis* or MTB. However recently it has been discovered that some other members of the genus *Mycobacterium* can also lead to TB after infection. If such agents are transmitted from animals to humans, then this type of TB is termed Zoonotic TB. This type of TB is usually more prevalent in people who come in contact with animals regularly under poor hygienic measures. Low quality of life and adaptation of poor hygienic measures are the main factors contributing to the spread of TB. In the present era, increased cases of zoonotic TB cases and the emergence of antimicrobial resistance among the *Mycobacterium* genus have caused a worldwide alarm about global health. This trend has alarmed researchers all across the world. They are now doing their level best to come up with alternatives for chemotherapy to prevent antimicrobial resistance. This situation calls for in-depth research about TB and the development of countermeasures for its control and eradication to remove this threat to global health.

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1. INTRODUCTION

TB is a pretty old disease with its history dating back to around 3 million years ago (Gutierrez et al. 2005). Zoonotic tuberculosis is the infection of the M. tuberculosis complex transmitted from an animal to a human or one human to the other (Biet et al. 2005; Quinn et al. 2011; Garcia-Jimenez et al. 2013). Zoonotic tuberculosis can be transferred from animals to humans through various sources. Raw or undercooked meat and milk are major mediums for the transfer of TB infection from animals to humans so TB thrives in the areas where milk pasteurization is rare. Similarly, inhalation of TB spores can also happen when cattle and humans come in close contact (Ashford et al. 2001).

Tb infection primarily begins spreading through the respiratory tract and leads to the production of its typical signs such as tubercles seen on the lungs during post-mortem. Although TB can affect any organ, mostly it is diagnosed as an active pulmonary infection (Pai et al. 2016; Al-Ghafli et al. 2019). Most of the time adult males are more affected by TB as compared to female adults (WHO 2021). Usually, younger patients have extra-pulmonary while older patients have pulmonary TB infections (Shannon et al. 2020).

This infection can occur in both animals and humans alike. Both wildlife and livestock animals are affected by TB. TB is not just a simple infectious disease it is a matter of global public health emergency that has re-emerged on the surface after decades of dormancy. Before the COVID-19 pandemic, TB was the single infectious disease with the maximum number of deaths on its credit (WHO 2021). These concerns were heightened as it was discovered that about half a million people were infected with rifampicin-resistant TB, making the issues of TB equally worrying for global battling TB and antibiotic resistance. Sustainable efforts will be needed to deal with this health threat and control its spread (WHO 2020).

Recently, TB has been going rampant in India due to its largest cattle population. As of 2017, there were around 21.8 million TB-infected cows in India (Srinivasan et al. 2018). The main culprit of cattle tuberculosis in India is suspected to be Mycobacterium orygis (Brites et al. 2018). The cattle population has been facing endemic tuberculosis in India leading to zoonotic infections of unknown burden. Some studies have stated that the prevalence of zoonotic TB could be up to 10 % in India (Prasad et al. 2006; Shah et al. 2006; Bapat et al. 2017). Although despite having the largest cattle populations the highest burden of animal TB is not from India but rather from Europe and the Americas. One logical explanation for these statistics might be the difference in the accuracy of studies conducted, sampling strategies and diagnostic facilities available in the Americas are much better than the ones in third-world countries (Ramos et al. 2020).

3. AETIOLOGY

Mycobacterium is a bacterial genus with a wide range of hosts and varying susceptibility and infectious pathophysiology for different hosts (Biet et al. 2005; Quinn et al. 2011; Garcia-Jimenez et al. 2013). The direct human-to-human infection is usually caused by the infection of *M. tuberculosis* which is also known as MTB. On the other hand, animal-to-human infections of TB or zoonotic TB are caused by another species known as *Mycobacterium bovis* (Fig. 1) (Morse et al. 2012; Muller et al. 2013). The *M. tuberculosis* and *M. bovis* are collectively known as the *M. tuberculosis* complex or MTBC (WHO 2020).

Another member of MTBC is *M. orygis* which was identified in 2012 however there is a lack of robust evidence regarding its zoonosis (Van Ingen et al. 2012; Lavender et al. 2013; Marcos et al. 2017; Rahim et al. 2017; Shannon et al. 2020). Some other bacteria linked to TB include *Mycobacterium caprae, Mycobacterium microti, Mycobacterium canetti, Mycobacterium mungi* and *Mycobacterium pinnipedii* (Richard et al. 2021). Still, *M. bovis* is most commonly diagnosed as the cause of zoonotic diagnosis (Duffy et al. 2020). *M. bovis* and *M. tuberculosis* cause almost the same symptoms when enter in human body. *M. bovis* causes extrapulmonary symptoms more than *M. tuberculosis*. They can be differentiated based on biochemical tests (Grange et al. 1996; Michel et al. 2010). The linkage between different TB pathogens and the symptoms caused by them is shown in Table 1.

4. GLOBAL TRENDS

Globally TB has affected 1/3 of the population (Getahun et al. 2015). The rise of COVID-19 has further increased the projection of TB and increased the expected case number to 6.3 million in the next five years with an additional death of 20% (Cilloni et al. 2020; Hogan et al. 2020; Stop TB Partnership 2020).

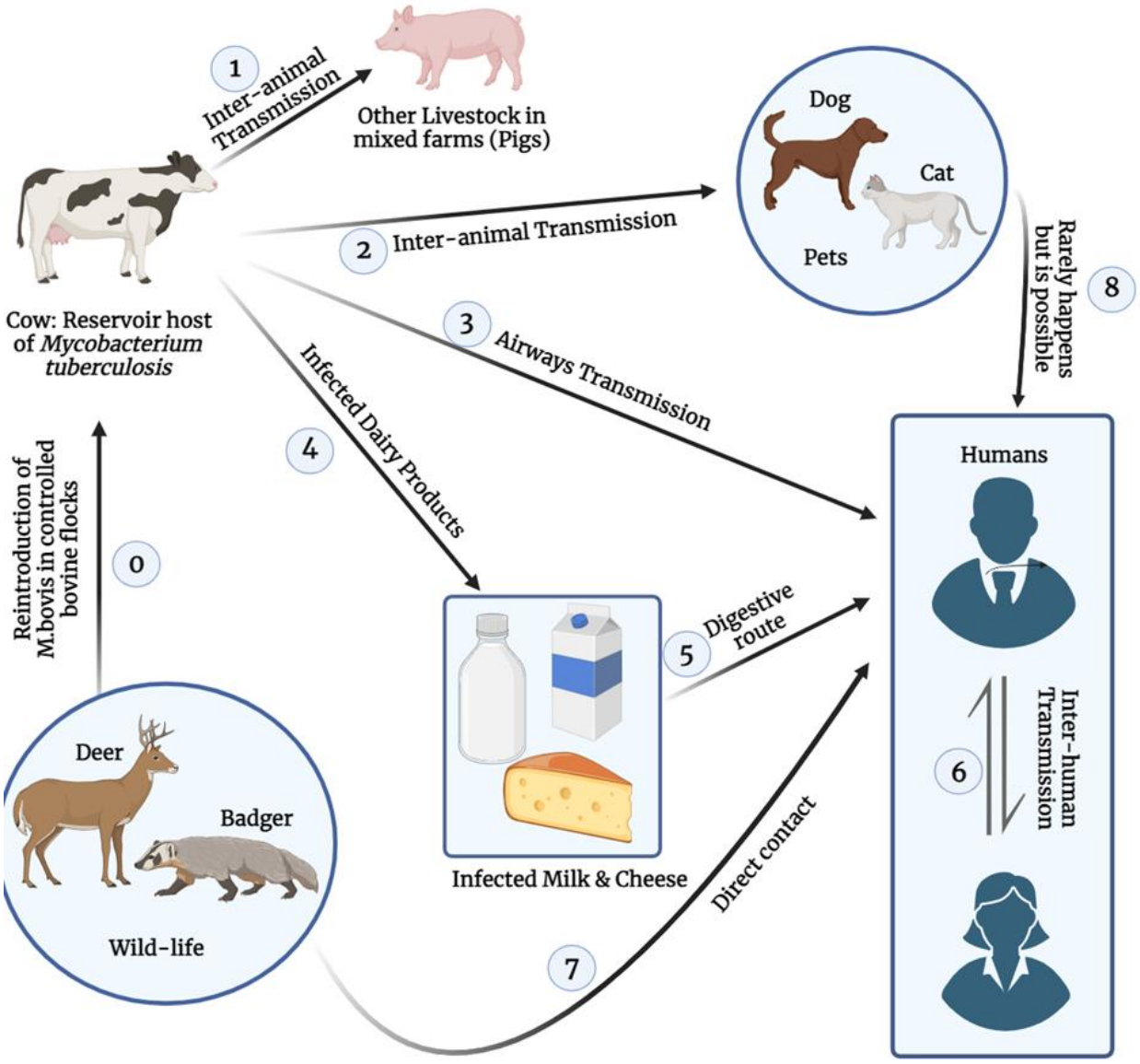

Fig. 1: Zoonotic Web of Tuberculosis.

India has the largest number of tuberculosis cases in the whole world (WHO 2021). Africa and Southeast Asia are the regions with the maximum number of cases affected by zoonotic tuberculosis (Ramos et al. 2020; WHO 2020). On the other hand TB especially, zoonotic TB is consistently declining in Europe with a prevalence of 10 cases out of 1000,000 population only. Similarly, the prevalence of zoonotic TB is less than 0.01% (Muller et al. 2013) with a few cases being caused by rare TB agents like *M. bovis* and *M. caprae* (Richard et al. 2021).

Pulmonary TB cases are mostly reported in rural regions linked with a lack of hygiene and awareness (O'Reilly and Daborn 1995). Additionally, bovine tuberculosis is also very common in cattle and so are the people working in close contact with cattle daily mostly rural people are into cattle farming. Consequently, the zoonotic ramifications of Tb result in a significant increase in the threat to the global public health of the human population (Shitaye et al. 2007; Legesse et al. 2011).

The main factors affecting the spread of TB are poor living standards, an unhygienic environment and many other factors that impair immunity and increase the risk of TB infection (Lonnroth et al. 2009). *M. bovis* tuberculosis is very rare in developed countries but common in developing countries because of using unpasteurized milk and having no hygienic veterinary measures (Michel et al. 2010).

Additionally, bad air quality and the prevalence of diabetes can also serve the factors ramping up the spread of TB in a region (Basnyat et al. 2018). Globally, Zoonotic TB has become a realistic concern for health security authorities as it was seen in 2019 that 140,000 cases out of 10 million TB cases were found to be zoonotic. Hence, global authorities have been trying their best to persuade country governments to make better TB control policies and accelerate development plans towards a tuberculosis-free world (WHO 2020). The global case ratio for Zoonotic TB might seem low but it is possibly due to a lack of facilities for the identification of *M. orygis* (Brites et al. 2018). It mostly happens that only *M. bovis* is detected as the cause of zoonotic TB globally along with attributed deaths and zoonotic TB burden. This methodology essentially ignores the contribution of other MTBC species in the spread of zoonotic TB (Duffy et al. 2020). That is why has been declared as a global public health emergency (Nathavitharana and Friedland 2015).

Table 1: Different types of TB pathogens leading to different symptoms.

No.	Pathogen	Origin	Symptoms	References
1.	*M. tuberculosis*	Human	Tuberculosis	(Morse et al. 2012; Muller et al. 2013)
2.	*M. bovis*	Animals	Tuberculosis with more inclination towards extrapulmonary symptoms	(Grange et al. 1996; Michel et al. 2010; Morse et al. 2012; Muller et al. 2013)
3.	*M. caprae, M. microti, M. canetti, M. mungi* and *M. pinnipedii*	Animals	Tuberculosis	(Richard et al. 2021)

5. EVIDENCE AND IMPACT OF ZOONOSIS

Zoonotic tuberculosis infection mostly happens when there is close contact between humans and animal species that have an abundant population around them such as food-based or companion animals (Johnson et al. 2020; Ramos et al. 2020). Close contact promotes unpasteurized milk consumption and aerosol spread. TB transmission also occurs from sheep and goats resulting in infection with *M. caprae*. Close contact with other non-domesticated species such as rodents, sea lions and seals, and banded mongooses consequently may lead to TB with infection from *M. microti*, *M. pinnipedii and M. mungi* respectively (Jagielski et al. 2016; Brites et al. 2018; Duffy et al. 2020). A comprehensive understanding of this vicious cycle of TB transmission can be gained from the schematic explanation provided in Fig. 2.

Tuberculosis in cattle is known as bovine tuberculosis. It is considered a major health problem of animals that is usually discovered when endemic in herds. Losses by TB are a major concern and cost up to US $ 3 billion annually worldwide (Waters et al. 2012).

Humans also get infected by TB through reverse zoonosis cycles. In reverse zoonosis, the disease spreads from animals to humans. This results in animals that are reservoirs for human disease-causing bacteria (Messenger 2014). The human infecting *M. tuberculosis* can infect a diverse range of hosts. Once infected an animal catches this infection it then begins acting as the new source for the spread of TB (Une and Mori 2007; BhanuRekha et al. 2015).

6. TREATMENT

Rifampicin, isoniazid and ethambutol are used to treat *M. bovis* tuberculosis according to the recommendation of the United States Centers for Disease Control and Prevention (American Thoracic Society 2003). This treatment regimen does not include pyrazinamide because several reviews in the past two decades, are investigated and it is concluded that all the strains of *M. bovis* are resistant to pyrazinamide. Hence, rifampicin, isoniazid and ethambutol once started, are continued for at least 9 months

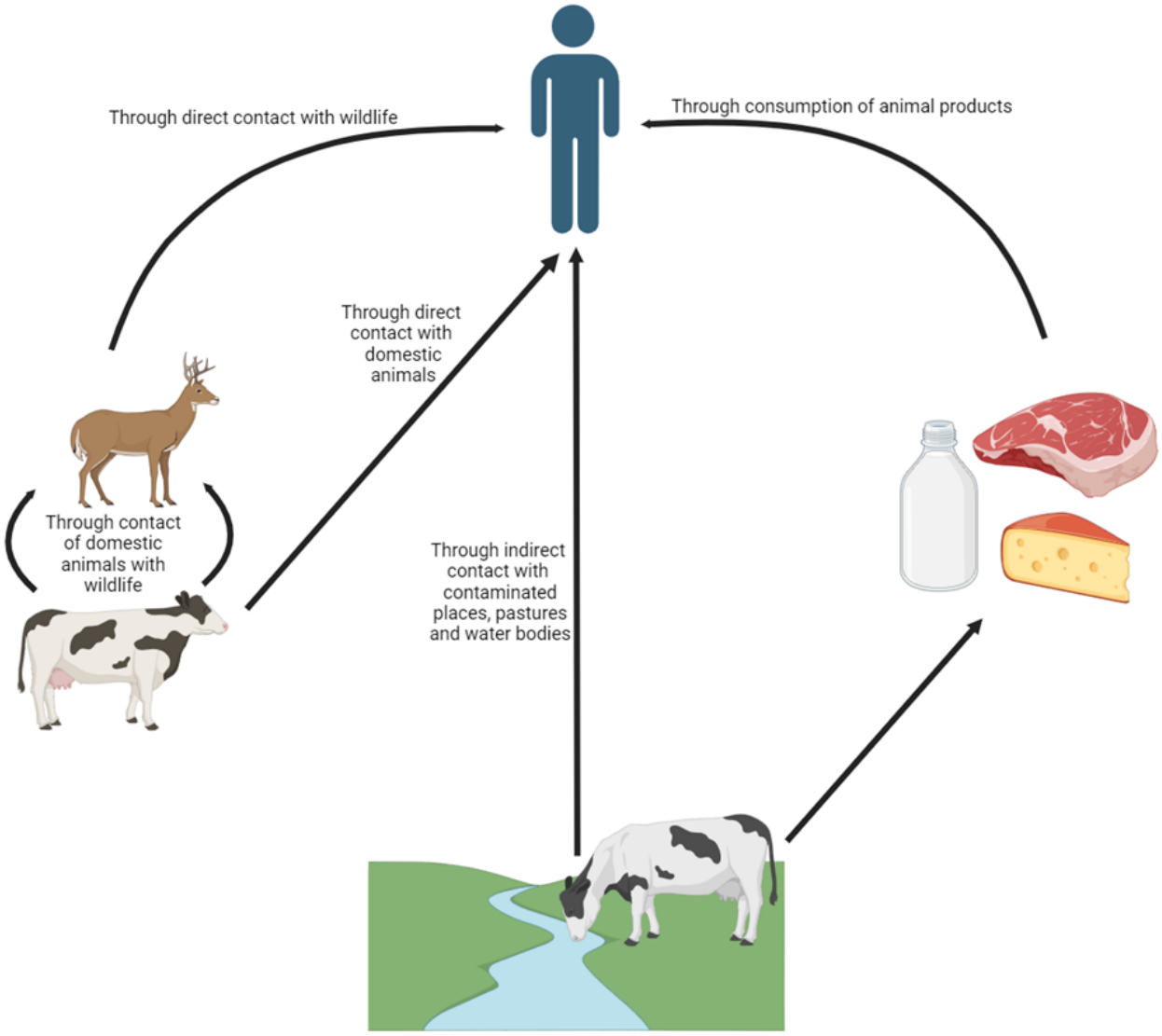

Fig. 2: Transmission Sources and Routes for Zoonotic TB Infection.

(de Kantor et al. 2008; Muller et al. 2013). No review has evaluated this treatment regimen and its outcomes in tuberculosis due to *M. bovis* (Lan et al. 2016).

Through initial database research, 985 worldwide publications are sorted for which 17 publications are selected for full-text review. The publications that did not report treatment are excluded and these are six in number. Some publications are also excluded because of different reasons as follows (Cicero et al. 2008;

Lan et al. 2016) instead of reporting 9 months of treatment, it only reported 6 months of treatment. Researchers provided the duration of treatment consisting of isoniazid-rifampicin-ethambutol varies from 4 to 12 months and it is without convincing results (Sauret et al. 1992). Researchers also include the treatment of patients who have multidrug-resistant strains of *M. bovis*, so it is also not included in our calculations (Esteban et al. 2005).

439 patients were reported with zoonotic tuberculosis caused by *M. bovis* in the United States of America, Argentina and the Netherlands from the three studies. Following are the reported facts. In LoBue studies, that were held in the United States of America for the period of 10 years from 1994-2003, the total patients were 167 out of which 7% patients were isoniazid-resistant and 1% patients were rifampicin-resistant, they were given isoniazid and rifampicin for the period of 9 months. 129 patients were cured of the disease, and 25 patients died. 12 patients lost follow-up, and in one patient there was a relapse of the disease by the same *M. bovis*. So, according to these statistics, the success rate (versus failed relapse) % is 99%. In the same way, success rate (versus fail + relapse + death + loss of follow-up) % is 77% (Grange 2001).

In the CORDOVA studies, that were held in Argentina for the period of 12 years from 1996-2008, a total of patients 23 out of which 3% patients were rifampicin-resistant and 3% patients were isoniazid-rifampicin resistant, they were given isoniazid, rifampicin and ethambutol for the period of 8 months to a year. 14 patients were cured completely from the disease. 1 patient failed to treat the disease, and 5 patients died of the disease despite taking this drug regimen. 3 patients lost to follow-up and no patient got relapse. So, according to this data, Success rate (versus fail + relapse) % is 93%. In the same way, the success rate (versus fail + relapse + death + loss of follow-up) % is 61% (Grange 2001).

In the MAJOOR studies, that were held in the Netherlands for the period of 14 years from 1993-2007, total patients were 231 out of which 5% patients were isoniazid-resistant, 1% patients were isoniazid and rifampicin resistant. Out of which 40 patients were given isoniazid and rifampicin. 25 patients were cured completely from the disease. 1 patient failed to treat the disease, and 12 patients died of the disease despite taking this drug regimen. 2 patients lost to follow-up and no patient got relapse. So, according to this data, the Success rate (versus fail + relapse) % is 96%. In the same way, the success rate (versus fail + relapse + death + loss of follow-up) % is 63%. 110 patients were given isoniazid, rifampicin and ethambutol. 91 patients were cured completely from the disease. 7 patients failed to treat the disease, and 9 patients died of the disease despite taking this drug regimen. 3 patients lost to follow-up and no patient got relapse. So, according to this data, Success rate (versus fail + relapse) % is 93%. In the same way, success rate (versus fail + relapse + death + loss of follow-up) % is 83%. 81 patients were given other and unknown drugs. 35 patients were cured completely from the disease. 6 patients failed to treat the disease, and 25 patients died of the disease despite taking this drug regimen. 15 patients lost to follow-up and no patient relapsed (Grange 2001).

7. ADVANCEMENTS

Despite advancement, zoonotic tuberculosis has remained an important health problem for both animals and humans over the past 20 years. With the arrival of tuberculin, basic control approaches included: the detection of disease via tuberculin skin test and then isolating the flock from other animals as well as from humans. There is also the isolation of animals within infected herds such as the Bang Method and the slaughtering of infected animals (Doyle and Stuart 1958).

There has been a tremendous decrease in zoonotic TB-infected cattle in New Zealand in the previous 18 years. In June 1993 there were 1694 infected flocks, these numbers decreased to only 79 infected cattle by June 2011. These good results were achieved by controlling the brushtail possum population in addition to the slaughtering of infected cattle and by strictly isolating the herd from other animals (Buddle et al. 2011). The cross-protective strategy is also used but it failed to convey an effective and secure vaccine for

zoonotic tuberculosis. This was stopped due to safety issues because sometimes there is dissemination of infective organisms and also shedding of organisms from the infected body. Human tuberculosis vaccine can be used against cattle *M. bovis* and it was established by Calmette and Guerin when they tried to make attenuated *mycobacterium bovis* for the treatment of human tuberculosis. This was done by serial propagation of bacillus on ox bile glycerine potato medium (Buddle et al. 2011).
Behring carried out trials on extra vaccines for immunization of cattle against zoonotic tuberculosis. These included: Taurin, a too-virulent mutated strain of bovine tuberculosis. Same as there is Tuberkulase, which consists of dead tuberculous bacillus that was given chloral hydrate sedative. These efforts are not fruitful because of specific etiological prophylaxis (Murphy et al. 2008). BCG can defend the host against natural *M. tuberculosis*. This has been proved by recent studies on cattle in Mexico and Ethiopia. Moreover, BCG shows defence in multiple host species in a large number of trials. The latest bovine vaccine contains live attenuated strains and it proved very efficient.

8. CONTROL AND PREVENTION

After decades of neglect and ignorance, serious efforts to control TB were initiated in 1991. It was the time when WHO declared TB a major public health issue globally (WHO 1991). Although WHO wasn't satisfied with the efforts of the countries, consequently it moved forward and declared TB as a global health emergency in the year 1993 (WHF 1993). A control regimen based on DOTS (directly observed therapy strategy) was released in 1994 in an attempt to limit the spread of TB (WHO 1994). Stop TB partnership between WHO and global advocacy organization launched the Global Plan to Stop TB 2001 (2001-2005) which was then succeeded by the Stop TB Strategy 2006-2015 in 2006. The Stop TB Strategy mainly focused on a patient-centred care approach to focus on TB patients (Raviglione and Uplekar 2006). Later on, the World Health Assembly devised the End TB Strategy in 2014. WHO launched this programme in 2015 (Uplekar et al. 2015).

9. RECENT TREND

Even in this age of modernization limited point of care (POC) diagnostics and insufficient reporting have reduced the reliability of data for determining the trend of incidence and prevalence of zoonotic tuberculosis in certain regions. Hence, it cannot be determined if TB prevalence and incidence are going up or down. However, one suggestion in this regard is to provide farmers and veterinarians with rapid test kits for quick diagnosis of TB, enabling them to make spot decisions about the fate of animals about quarantine or slaughtering. So there has been an increase in demand to educate the farmers and spend budget on research and development of quick diagnosis kits for TB (Duffy et al. 2020).
Recently another trend has emerged over the horizon of the medical industry to manufacture a vaccine against TB by Ag85 nanoparticles. Researchers and making tireless efforts to formulate a DNA-based vaccine against TB to put a preventive cure in the blood of people before this awful malady can reach them (Zhu et al. 2005).

10. UPCOMING TRENDS

More than a century ago, an approach was accepted worldwide for the diagnosis of bovine or zoonotic tuberculosis by checking the cell-mediated immune response of the host body against intradermal injection of tuberculin (de la Rua-Domenech et al. 2006). This test has weak results because the purified protein derivatives used in the tuberculin test are obtained from heat-killed specific strains of *mycobacterium bovis* on glycerol broth (Yang et al. 2012; Good et al. 2018). In certain regions where there

is high exposure of *M. bovis* in the environment, the tuberculin test case has larger induration which makes the test less sensitive (de la Rua-Domenech et al. 2006). Moreover, there are certain cross-reactive antigens are also present between pathogens and vaccines which also artificially increase the induration and make the test less sensitive (Yang et al. 2012; Good et al. 2018). According to modern studies, an in vitro interferon-gamma release assay (IGRA) is introduced as a secondary test to increase the overall sensitivity of the tuberculin test (Wood and Jones 2001; EFSA 2012).

In the past 20 years, a specific *M. bovis* antigen has been searched by comparative genomics and transcription that has the DIVA (Differentiating Infected from Vaccinated Animals) capability. This means it can identify or differentiate between BCG-vaccinated and not-vaccinated animals in a mixed flock. These antigens include ESAT-6, CFP-10 and Rv3615c. These are present in field strains of *M. bovis.* These are not present in BCG vaccines based on this it can differentiate between vaccinated and not vaccinated animals (Vordermeier et al. 1999; Young and Robertson 1999; Vordermeier et al. 2016).

11. IN VITRO SUSCEPTIBILITY AGAINST MOXIFLOXACIN

There is no available data that sheds light on moxifloxacin's effects on *M. bovis*. That's why a retrospective move was made for research by taking the cultures of sputum, pleural effusion, and nasal exudates from 33 patients for about 18 years from 1993-2011. The drug sensitivity test was performed by using *M. bovis*-BCG using MTBC genotype assay. The results were excellent, all 33 cultures showed susceptibility to moxifloxacin at less than 1 microgram per millilitre (Gumbo 2010).

12. VACCINES BASED ON NANOPARTICLES AGAINST *M. BOVIS* INFECTION

The latest vaccine is produced against *M. bovis* by genetically engineering the bacteria. This vaccine is formed by nanoparticle polyester inclusions. The control of tuberculosis is achieved by presenting, mycobacterial antigens, Ag85A and ESAT-6 on the surface of bio-beads. These bio-beads were extracted from host production bacteria, *E. coli* and GRAS bacterium. GRAS is generally accepted as a safe bacterium for removing bio-beads. Earlier published worldwide studies depicted that vaccination with Ag85A and ESAT-6 causes an increase in levels of antigen-specific interferon gamma, interleukin 17A, interleukin 6, tissue necrosis factor-alpha and interleukin 2 in the cells of the spleen. But there is no remarkable rise in interleukin 4, interleukin 5 or interleukin 1. However, the latest worldwide studies showed that CD4 and CD8 + T cells in mice which was vaccinated with the Ag85A and ESAT-6 bio-beads induced the release of antigen-specific interferon-gamma. These test mice had a remarkable decrease in bacterial count when treated with Ag85A and ESAT-6 bio-beads alone or given in combination with the BCG vaccination. These mice were previously exposed to aerosol *M. bovis* and these were compared with the control group which was not exposed to *M. bovis* (Zhu et al. 2005; Xi-Dan et al. 2009; Natalie et al. 2014). This nanoparticle-based vaccination has proven very cost-effective and efficient for the protection of cattle against *M. bovis*.

13. COMBINED DNA VACCINES

The immunological responses of diseased and healthy animals were calculated based on increased interferon-gamma in the whole blood. The interferon gamma is produced by T cells in response to the combined DNA vaccines including Ag85A, MPT64, and MPT83 or with PPD of the BCG vaccine (Xi-Dan et al. 2009).

A study is carried out to get the results that which vaccination method is more efficient. Experimental studies carried out over the previous 10 years of the BCG vaccine against *M. bovis* show that there is variation in the efficacy of this vaccine. Th1 response is the crucial step in the process of BCG vaccine because *M. bovis* is an intracellular organism. In DNA vaccine we changed the immune response of the affected organism from partially effective to absolutely effective because it can kill the bacteria (Zhu et al. 2005).

Vaccination in which plasmid DNA that expresses the HSP65 portion of *M. bovis* is introduced in mice followed by chemotherapy was proved very effective when the organism is introduced with *M. bovis* intravascularly (Xi-Dan et al. 2009).

In summary, it is concluded that combined DNA vaccines have better results than the traditional BCG vaccine for the prevention of *M. bovis* infection that causes zoonotic tuberculosis.

14. CONCLUSION

In summary, the present recommendations for the treatment of zoonotic tuberculosis caused by *M. bovis* have very little evidence. Still, it is a potential risk that needs attention for cure, treatment, prevention and eradication. So, thoughtful action plans should be implemented to counter and control it and prevent the emergence of drug-resistant TB.

According to the available data, although it is limited, the presently used regimen includes isoniazid-rifampicin or isoniazid, rifampicin and ethambutol are adequate and enough. The benefit we get by adding ethambutol to the regiment is not clear at all. For better results, this drug regimen should be continued for at least 9 months. Strict care and consistency should be maintained to get the best results out of this regimen while eliminating the risk of anti-microbial resistance at the same time.

HIV infection along with *M. bovis* infection has tremendously increased the mortality rate and causes limitations in the interpretation of results gained by these treatment regimens. Hence it proves that TB prevails among the immuno-compromised patients. So special care should be given to immuno-compromised people. They should be educated to follow proper dosing routines to prevent relapse of TB and control its spread.

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