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A Review of COVID-19 and Tuberculosis Coinfections: Epidemiological and Clinical Interactions in India

Dr. Sulagna Pattajoshi

Indian Institute of Public Health Gandhinagar, Gujarat, India
Email: *sulagnapattajoshi[at]gmail.com*

Abstract: ***COVID-19 and Tuberculosis are respiratory communicable diseases with a massive spread in the world. This review explores the interactions between COVID19 and tuberculosis TB in the Indian context, highlighting the epidemiological, clinical, and socioeconomic impacts of coinfections. Open access, English language articles published within 2011-2022 with context for Tuberculosis and COVID-19 in India, were identified comprehensively from sources like PubMed, Lit-Covid, and Google scholar, using search terms 'COVID-19' 'Tb' and 'India'. The article examines similarities in symptoms and transmission methods between the two diseases, evaluates the challenges posed by their concurrent presence, and discusses the implications for public health in India. The review further provides comparative data on the incidence, treatment, and prevention strategies for COVID-19 and TB, and offers recommendations for mitigating the impact of their coinfection. It also provides an account of the clinical and social impacts of the co-infection. It concludes on the need to continue research on each of the diseases-Tb and COVID-19 for early diagnosis, appropriate treatment, to prevent them individually as well their coinfections.***

Keywords: Tb, TB, Tuberculosis, COVID-19, coronavirus

1. Introduction

Tuberculosis is a communicable respiratory disease that is present worldwide for more than 3000 years ago. The origin of the disease is evidenced to be from Egyptian mummies and even dead bison, pigs, and cows (m. bovis).

At the end of December 2019, a new disease, COVID-19 or coronavirus disease, emerged in China, with evidence suggesting that it originated from a seafood market in Hubei, China. This disease gradually took the form of a pandemic and was declared a PHEIC by the WHO (1)

TB includes symptoms such as respiratory distress, fever, hemoptysis, fatigue, loss of appetite, weight loss, and productive cough. The disease progresses from the latent phase (no symptoms) to the tertiary phase, in which severe disease affects the heart, trachea, bronchi and other adjoining parts of the chest cavity(2)(3).

The symptoms of COVID-19 are respiratory symptoms (similar to Tb), gastrointestinal symptoms and other manifestations of different organ systems (Table 1).

Furthermore, it is described under 2 subheadings:
- Tuberculosis
- COVID-19

1.1. Tuberculosis

1.1.1 Global

An estimated 10 million (range: 8.9--11.0 million) people fell ill with TB in 2019. Geographically, most people who developed TB in 2019 were in the WHO regions of Southeast Asia (44%), Africa (25%) and the Western Pacific (18%), with smaller percentages in the Eastern Mediterranean (8.2%), the Americas (2.9%) and Europe (2.5%). From a peak of 7.1 million in 2019, Tb notifications decreased by 18% to 5.8 million in 2020, whereas in 2021, Tb notifications increased to 6.4 million. The three countries that contributed the most to the reduction in 2020 were India, Indonesia and the Philippines (67% of the global total). Compared with 2019, they achieved partial recoveries in 2021 but still accounted for 60% of the global reduction (4).Globally, in 2021, Tb deaths occurred in 54% of men, 32% of women and 14% of children (aged <15 years) in the HIV-negative population, whereas Tb deaths occurred in 51% of men, 38% of women and 11% of children in the HIV-positive population(5)

1.1.2. India

India was one of the countries with the highest TB burden—one-fourth of the total TB burden in 2013. In India, the number of notifications of people newly diagnosed with TB rose from 1.2 million to 2.2 million between 2013 and 2019 (+74%). The Tb notification numbers mostly had an increasing trend, even though a large proportion of patients were underreported and undiagnosed (2.9 million) until 2019--20. In 2021, TB accounted for 56.5% of all TB cases in men, 32.5% in women and 11% in children.(6)

The advent of the COVID-19 pandemic affected notification rates further, instilling fear of infection, stigma, etc., in people, leading to diagnostic delays and case severity. This gap is due to a combination of underreporting and underdiagnosis of people with TB and COVID-19. (7–9)

The incidence of new cases is highest in the first year and remains above background incidence for at least 5 years after exposure to a patient with TB. This chronic course of TB, the presence of comorbidities, delay in diagnosis, etc., are the factors that contribute to COVID-19 coinfection with Tb.

New cases of TB are attributable to five risk factors: undernutrition, living conditions, migration, HIV infection, alcohol use disorders, smoking (especially among men) and diabetes. In 2019, the estimated numbers of cases attributable to these risk factors were 2.2 million, 0.76 million, 0.72 million, 0.70 million and 0.35 million, respectively.(10)

The treatment and recovery of Tb patients is a long-term process due to the presence of other comorbidities, drug resistance or nonadherence to treatment. One meta-regression associated (OR=1.15 (1.03 to 1.28) COVID-19 positivity, public sector treatment, HIV positivity, drug resistance and tertiary health centre settings with increasing CFRs during treatment. Patient deaths after treatment may indicate either ineffective anti-TB treatment or a failure to address the socioeconomic determinants and physical environment that led to the development of a disease such as TB in the first place (11)

The Tb diagnostic pipeline appears robust in terms of the number of tests, products or methods in development. Examples include next-generation sequencing (NGS) assays for detecting drug-resistant TB directly from sputum samples and newer skin tests and interferon gamma release assays (IGRAs) to test for TB infection. Currently, there are approximately 22 drugs (MOHFW., n.d.) that are used in various combinations for different lines of treatment, and BCG vaccinations have been performed on the majority of the population.(8)

1.2 COVID-19

1.2.1 Global

COVID-19 is a newly emerged disease caused by severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), an RNA virus. Like other coronaviruses, such as SARS-CoV and Middle East respiratory distress syndrome coronavirus (MERS-CoV), the genetic material is similar to that of bats, implicating the bat as the source of this virus. The first confirmed cases were identified in Wuhan, Hubei, China, in November 2019. By the early days of July 2020, the number of cases worldwide exceeded 12 million, with fatalities in excess of 500,000. While the number of cases in the United States exceeded 3 million, Brazil had more than 1.7 million cases, and India had more than 0.7 million cases. This disease is characterized by rapid spread across the globe, and it was announced as a Public Health Emergency of International Concern on 30th January 2020 (12)

COVID-19 affects elderly individuals more, with those older than 60 years being the most vulnerable to this infection. The influence of sex is evident, since more men are affected by the infection. Studies suggest that there are many differences in the immune response to COVID-19 infection and inflammatory diseases between men and women (13,14)

1.2.2 India

The first case of COVID-19 was reported on January 30, 2020. This rose to three cases by the end of February 2020. The first case of COVID-19-related death in India was reported on March 12, 2020. By the second week of April 2020, the disease had spread to all states, with 15,712 cases and 507 deaths in India except Sikkim (Dhar Chowdhury et al,2020). By Oct 9th, the number of cases was 6977008, and the number of deaths was 107450. Currently, the number of cases is 2115100 cases (as of Jan 17th, 2022), with 7888 deaths (as of Jan 31st, 2022) (World Health Organization, 2020) that subsequently decreased to 17526 cases (as of Oct 3rd, 2022), with 1484 deaths (as of Oct 31st, 2022) (15)

Table 1: Characteristic details of effects in a multiorgan system (BL-bilateral, UL-unilateral)(16)

No.	Organ	Site of symptom	Manifestation
1	Brain	Olfactory Bulb	Hyposmia, hypogeusia, hypopsia, encephalitis and headache, cytokine storm, neurodegenerative diseases.
2	Eyes	Conjunctiva	Conjunctivitis, chemosis, swelling of conjunctiva, epiphora or overflow of tears onto the face
3	Blood and blood vessels	-	Plague, change in number of blood cells.
4	Heart	Myocardium and cardiac muscle cell	Cardiac failure or myocarditis, myocardial infarction,
5	Lungs	Pulmonary lobe, nodules, broncho-vascular bundles, alveolus	BL/UL pneumonia, thickening, ground glass opacities, thickening, irregular lesions, fibrosis,
6	GIT	Stomach & digestive organs, GI tract, liver	Anorexia, vomiting, nausea, abdominal pain, GI bleeding, liver injury, change in levels of liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT)
7	Kidney	------	Acute kidney injury, pyro ptosis and cell death

High-level commitments have galvanized global, regional and national progress towards ending TB, but COVID-19 Tb coinfection has led to the urgent need for more ambitious investments and actions required to put the world on track to reach Tb elimination targets, including coinfection (17)

2. Rationale

Currently, infections are most common and are transmitted from one person or one organism to another. Similarly, both tuberculosis and COVID-19 are respiratory diseases caused by microorganisms affecting lungs with similar symptoms. Both are infectious diseases transmitted by droplets of cough and sneezing. The radiographic features of both of these diseases even appear similar. Some studies have shown that TB disease is a precursor to COVID-19, as TB-recovered patients have weak lungs to COVID-19((18) and vulnerability to TB-COVID-19 coinfection. Some studies have shown that after Tb patients are coinfected with COVID-19 or vice versa, the impact on individuals, society and the country is to a large extent. This study is significant because it sheds light on the dual burden of COVID19 and TB in India, providing critical insights into the management and prevention of these diseases in a resource limited setting. Therefore, this review takes into

account the similarities and differences, the TB-COVID-19 coinfection alongside the Indian context in order to suggest solutions to prevent it.

3. Aim and Objectives

3.1 Aim

To describe the interactions between Tb and COVID-19 in the Indian context

3.2 Objectives

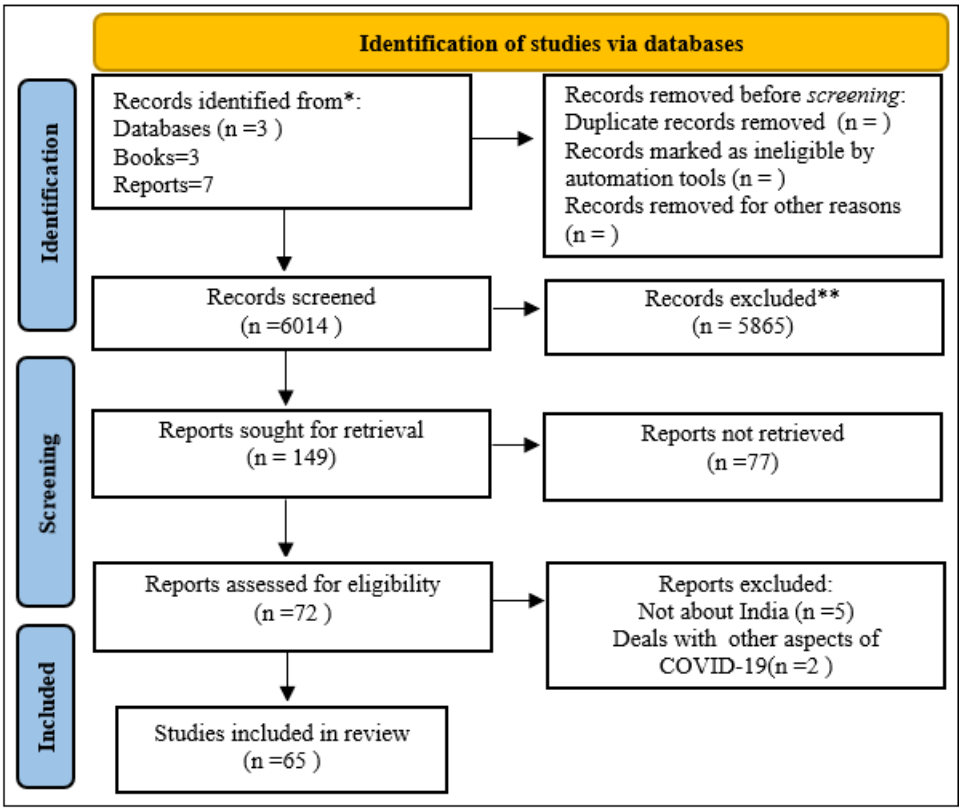
1) To review evidence of Tb-COVID-19 coinfection in an Indian context
2) To compare tuberculosis and COVID-19 on the basis of annual/monthly cases, mortalities and epidemiology, transmission, etc.
3) To provide suggestions for preventing TB-COVID-19 coinfection

4. Methodology

The review was conducted via a comprehensive search strategy on databases such as PubMed, Lancet, Lit-COVID and Google Scholar.

The search terms included 'Tb' ,'tuberculosis' , COVID-19, 'coronavirus' and 'India' combined with the Boolean operators 'AND' and 'OR'. Articles were included on the basis of their relevance to the Indian context, publication in English, and availability of full text between 2011 and 2022.

Secondary data on COVID-19 and Tb were collected from authentic sources such as the WHO, ourworldindata.org, worldometers.info, and global and Indian Tb reports from 2019 & 2020.



5. Results

Table 2: Comparing Epidemiological Characteristics of TB & COVID- 19 in India

No.	Feature	TB	COVID-19
1	History of disease	Long history since 3000 years ago (19)	Short history. First case discovered since 9 months(20)
2	Nature of disease	Chronic communicable bacterial disease	Acute communicable viral disease.
3	Causative organism	Mycobacterium Tuberculosis(21)	SARS-CoV-2 RNA virus(22)
4	Route of entry in the body	Nose(inhalation)(21)	Respiratory, eyes, faeco-oral and body fluid routes(23)
5	Method of transmission	Respiratory droplets or fomites(21)	Airborne(24)
6	Incubation period	3 - 6 Weeks (21)	1-2 weeks (22)
7	Reservoir	Man, Cow (bovine TB)	Animal (bats, Pangolins)(21)
8	Total cases	24,28,314(Jan 1 2022-Jan 1 2023)(25)	6,37,597cases (Jan 3rd 2022-Jan 3rd 2023) 2020) (26)
9	Incidence rate	2022- 1734.5cases/million population	455.4cases/1 million

		(Jan 1st – Oct 9th2022)(27)	(Jan 1st -Oct 9th) 2020) (26)
10	Total deaths	Jan 1st 2022_– Oct 7th 2022 4,94,000(15)	4525 deaths(March 21st 2022) (28)
11	Mortality rate	352.9 deaths/million population -2021 (Jan-Oct 2019)(15)	3.23/10 million population (March 21st,2022)(29,30)
12	Case Fatality Rate- (*proportion of reported cases of a specified disease or condition which are fatal within a specified time).*	17% (2018) (31)	1% →WHO(2021 (28,32)
13	Reproduction Number (Measure of Transmission)	1.73(33)	1.04 (Jan 2023) (34)

Table 3: Comparing Clinical Features, Treatment of TB & COVID-19

No.	Feature	TB	COVID-19
1	Predisposing Factors	-Smoking, -Alcohol, -Social factors like poverty, -co-morbidities like diabetes, malnutrition. (17)(35)	-Presence of comorbidities like diabetes, hypertension, -immuno-suppressive disorders. (17,36,37),
2	Age Group Affected	all age groups. (21)	all age groups (people aged >60 years are more susceptible)(24)
3	Symptoms/Signs	When Tb is in lungs it begins with cough > 3 weeks with haemoptysis or sputum expectoration, followed by chest pain, fatigue, loss of appetite, weight loss. Other symptoms are chills, fever and night sweats(21,38)	Fever with chills, Cough, Dyspnoea, Fatigue Myalgia, Headache, anosmia, dysgeusia, Sore throat, congestion or runny nose Nausea, Diarrhoea, central cyanosis (37,39)
4	Organs Affected	Primary- lungs; Secondary- Heart, bone, intestine, brain, spine, larynx, urogenital tract (38)	Primary-lungs Secondary-side effects cause an impact on organs like CNS, heart, oesophagus, kidneys, bladder, and ileum (22)
5	Disease Association	associated with HIV. (17)	COPD is found to be associated.(39,40)
6	Samples For Diagnosis	Three consecutive sputum samples in 8-24 hr intervals (21)	Two samples from nasopharyngeal or oropharyngeal swab(39)
7	Diagnostic Tests	-Sputum microscopy - Culture, -X-ray, - CBNAAT(21)	-RT–PCR test, -serologic testing, -chest Xray, -antigen-antibody testing.(37)
8	Treatments	Anti Tb drugs-rifampicin, isoniazid, pyrazinamide, ethambutol(10,21)	Treatment guidelines for different age groups, disease severity have been decided and published.(37,41)
9	Complications	**Immediate** -Drug resistance pneumothorax, extensive pulmonary destruction, bronchiectasis, **Late** -heart and endothelial disorders, malignancy, chronic pulmonary aspergillosis, **Treatment complications**- like neurological complications, hepatitis, visual disturbance, renal failure.(21)	**Immediate** - cardiovascular complications, Disseminated intravascular coagulation, acute respiratory failure, GIT complications, Acute kidney injury, venous thromboembolism, liver injury **Late complications** - neurologic complications, long COVID, septic shock, cytokine release syndrome, paediatric inflammatory multisystem syndrome, pancreatic injury, autoimmune haemolytic anaemia, subacute thyroiditis(39,42,43)
10	Rehabilitation Needed	Breathing exercises to improve lung capacity, adequate lifestyle modification(17,44)	Improve immunity, proper rest needed, healthy food(41)

Table 4: Comparing Preventive Strategies and Control Measures of Tb And Covid-19 In India

No.	Feature	Tuberculosis	COVID-19
1	Methods of Prevention	• Masks-N95(not mandatorily used) • BCG vaccine, • drugs for treatment, • isolation • no social distancing(10,45)	• Protective suits and mask usage stressed, • Vaccination-3 doses of Covaxin and Covishield. • Social distancing &quarantine • Other measures-lockdown, sanitization drives, awareness on hygiene and social distancing(35,46)
2	Economic Benefit	Incentive of Rs 500/- to every patient on getting notified, completion of IP phase of treatment and at the completion of treatment. (47)	• Financial support was provided to poor. • salaries in advance were given • meals provided to homeless, • cost of test reduced, • incentives provided for quarantine(46,48,49)
3	Data System	Nikshay portal for notification(27)	Dashboards for recording of cases, ICMR site all test data are uploaded(26)

4	Dots Supporters	Mostly health care workers or family members are designated as DOTS supporters. To improve patient adherence to treatment along-with its monitoring(8)	The health workers play the same role of providing treatment, monitoring patients except improving patient adherence to treatment(39,43)
5	Treatment Categorization	According to types-Tb only, HIV-Tb coinfection, MDR-Tb, XDR-Tb(8,38)	According to severity-asymptomatic, mild, moderate and severe(39)

Table 5: Comparing Recovery & Discharge Plan on TB & COVID-19

No.	Feature	TB	COVID -19
1	Follow Up	Tb patients are followed up for • 6 months in case of normal treatment regimen. • 2 years for resistant category of treatment (44)	• The first follow up visit (Physical/telephonic) should be within 7 days after discharge, and • subsequent follow up visits till a period of 1.5 to 3 months are done as per case (18)
2	Recovery	It depends on adherence of treatment by the patient. Recovery may range from 6-9 Months depending on treatment category.(44,45)	In case of COVID-19, people mostly recover within 7-10 days. Patients are monitored to check for long-covid symptoms.(16,22,37)

Table 6: TB and COVID-19 Interaction (9,18)

Impact specific to TB	General Effects (Pertaining to country)	Impact specific to COVID-19
Increase In House Hold Contacts		
Increase In Testing and Treatment Delays		
	Decrease in Community and Hospital Infections (During Covid-19 Intervention Phase)	
Increase in Mask Wearing		
Decrease In BCG Vaccination Coverage		Decrease In Covid-19 Vaccine Coverage/Delay in Getting Vaccinated
Tb resistance Increase in AMR		
Increase In Stockouts		
Decrease In Tb Notifications		
Increasing Severity of Diseases Leading to high fatalities		
Increase in poverty and migration trends leading to increase in causation of diseases		
Increase in treatment costs		

6. Discussion

Overall, the review presents comparative evidence on both diseases from 65 sources-about 54 articles on Tb, on COVID-19 on their Tb-CoV-19 Coinfection and describing both simultaneously. Some books, reports, dashboards and websites are also included in these sources.

6.1 Origin

Both the diseases Tb and COVID-19 differ according to the form of the organism, with one being bacteria and the other being viruses. Tb originates from humans (common form), cows (bovine Tb) rather than bats, palm civet cats, camels, or pangolins(20) An article by(50) provided similar evidence that the genomic sequence of SARS-CoV-2 is 75–80% identical to that of SARS-CoV but is even more closely related to that of several bat coronaviruses. Phylogenetic analyses of SARS-CoV-2 genomes have identified bats as the primary reservoir of SARS-like coronavirus. Mycobacterium. Bovis, another causative agent for TB, is a potential cause of bovine Tb in humans and is transmitted by infected milk products(51).

6.2 Incidence of Cases & Disease Spread

Tb has been known to be an ancient disease for more than 3000 years since its control efforts started in 1993(45). Currently, the number of Tb cases is 24,28,314 (jan 1 2022--jan 1 2023), whereas the number of COVID-19 cases is 6,37,597 (jan 3rd 2022--jan 3rd 2023) (6,29)

6.3 Transmission

The measure of transmission is Ro. The reproduction number estimates are greater for Tb than for COVID-19. Once exposed to an index Tb, a patient is liable to become infected within a range of 1–5 years of exposure. The method of transmission for COVID-19 is airborne through respiration, whereas that for Tb involves inhalation of respiratory droplets. The reservoirs for Tb include humans, bisons, etc, whereas those for COVID-19 include bats, pangolins, etc. Tb has a longer incubation period than COVID-19 does. (23,33)

6.4 Clinical Features, Predisposing Factors

Age and comorbidities increase the susceptibility of any person to any disease. The case fatality rate of patients without basic disorders was as low as 0.9%, while the case

fatality rates of patients with cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer were 10.5%, 7.3%, 6.3%, 6.0%, and 5.6%, respectively. In one large series reporting 526 patients with COVID-19, HIV and TB at a single centre, the case fatality rate was 8.9% higher than that reported in historical controls. The contributions of 16 variables (including risk factors, health system settings and pandemic duration) to COVID-19 case fatality death were estimated in 34 countries.(11,32) TB incidence had one of the highest impacts: each unit increase in TB incidence per 1,000 inhabitants increased COVID-19 fatality rates by 3.2% (1.09–5.22; P=0.004). An overview of 36 case reports and case series related to COVID-19-TB coinfection revealed that the percentages of deaths and severity in cases of COVID-TB coinfection were 5.7% and 51.4%, respectively, whereas the percentages were 3.2% and 28%, respectively, in non-Tb patients. (52,53)Other evidence even suggests that people with COVID-TB are 2.21 and 2.27 times more likely to die or develop severe disease, respectively, than are COVID-19 patients. Increased latitude may also be associated with an increased risk of cases and deaths in some countries. A positive correlation has been found between lower death rates and a country's proximity to the equator, suggesting a correlation between sunlight exposure (and vitamin D levels) and reduced mortality. (54). Gradually, with time, habits, economic conditions, and living conditions were also included as role players. There is consistent evidence that people in prisons, migrants having increased impacts from diseases such as Tb, COVID-19 and their coinfection as one of the vulnerabilities to such diseases are poverty and unhygienic lifestyles(55)(56). In terms of clinical features, both diseases similarly affect the lungs, except that the effect of COVID-19 is more extensive, causing a loss of smell and taste. Tears act as the route of transmission to other organs of the human body through the nasolacrimal system.(50)The viral load is highest in the upper respiratory tract (nasopharynx and oropharynx) early in the course of infection and then increases in the lower respiratory tract (sputum) before rapidly decreasing after symptom onset. (54)Both diseases affect children. In children, immune maturation is a major determinant of risk in infants (<2 years of age) for disease development and potential dissemination (57) In the case of COVID-19, children (<1 year) have chances of being affected by their caregivers, showing mild symptoms, no symptoms and, in some rare cases, severe cases.(24)

6.5 Treatment and Complications

Drugs for Tb became available approximately around 1950--1967 and were given in 2 phases: intensive (4 months) and continuous (2 months). The dosage of drug, treatment, and recovery depend on the patient's severity, age, bacterial/viral load, allergies, resistance, etc. There may be a cure, a death, a recurrence, and a treatment change in a person undergoing any of the treatments.(2)The patient is followed at home or in a hospital setting by an experienced clinician until the disappearance of symptoms and normal pathological tests.(16,58) The decreased efficacy, side effects, misuse of drugs, and resistance to treatment require the discovery of new drugs with better efficacy for specific categories of patients (59). Few new Tb drugs, such as bedaquiline and Delamanid, have been discovered for the treatment of resistant Tb. Few Tb patients are lost to follow-up due to the side effects of drugs, such as coloured urine, neuropathic effects, hepatitis, arthralgia, colour vision, auditory nerve damage, renal failure, proteinuria, nephrotoxicity and other effects. Few studies suggest that the BCG vaccine prevents COVID-19 (54), but further research is needed to confirm this finding. A new form of treatment known as convalescent plasma therapy (CPT), which has shown good response over the last two decades against SARS, MERS, and H1N1 infection, is still in trials. There are chances of vitamin D supplementation causing improvement in patients with COVID-19, but no such evidence has been confirmed in patients with Tb.(41)

6.6 Prevention & Control

Tb has a control program, the RNTCP, which is an umbrella program with labs, benefit schemes, notification portals, treatment therapy, associated medical colleges and hospitals, and staff designated as treatment supporters (60). Control measures for COVID-19 include social distancing and quarantine with the use of specific personal protective equipment. Screening is performed at entry points, along with house-to-house surveillance, in some states, such as Andhra Pradesh and Tamil Nadu.(35,61) Almost all people from the lowest cadre to the highest cadre, from sweepers to doctors and ministers, were involved (48).Since the emergence of the new pandemic, infection control, sanitation, and hygiene have become increasingly important. Healthcare workers are at potential risk of exposure to COVID-19. A study suggested that viral RNA can be detected on nearly all surfaces tested (handles, light switches, bed and handrails, interior doors and windows, a toilet bowl, and a sink basin) in the airborne infection isolation room of a patient with symptomatic mild COVID-19 prior to routine cleaning. Therefore, environmental infection control procedures should be implemented to reduce the spread of the COVID-19 virus(62) (54). Both TB patients and COVID-19 patients, when under treatment, become depressed, poverty stricken, stigmatized, etc., which affects their recovery. During these times of struggle, they need the support and empathy of family and counsellors to help them fight the disease. The practice of yoga and breathing exercises may also help in combating the psychological stress caused by both individually and as a coinfection. Even when individuals are affected by either COVID-19 or TB, they fear further infection and do not test for the other, although the same is suggested. (63)

6.7 Clinical effects of TB-COVID-19 coinfection

An overview of 36 case reports accounting for 89 patients with Tb-covid coinfection was provided. The chances of death increased with increasing age, the presence of comorbidities, delay in diagnosis, etc.(42)

A total of 56.41% of COVID-19-TB patients have comorbidities, the most common of which is diabetes, followed by hypertension, HIV infection, hepatitis, epilepsy, chronic kidney disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, or cancer.(18)

The 10 most common symptoms of COVID-19 at admission were fever, cough, dyspnoea, weight loss, fatigue, expectoration, chest pain, headache, myalgia and vomiting.

The non survivors had a greater percentage of patients with dyspnoea than did the survivors (72.73% vs. 30%) (p= 0.014).

In addition, with respect to radiographic abnormalities, non survivors were more likely than survivors to have bilateral lesions, infiltrates or tree-in-bud features.(43,49)

Elevated laboratory findings in COVID-19-TB patients included neutrophil count, D-dimer, C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), the procalcitonin ferroprotein (FER), aspartate transaminase, lactate dehydrogenase (LDH) and creatinine. The reduced laboratory indicators included the lymphocyte count and haemoglobin level(42)

There were no significant differences between the survivors and non survivors regarding the laboratory test indicators except for the leucocyte count. There are numerous reports in different countries where COVID-19 patients who are receiving treatment, die due to delayed diagnosis of Tb coinfection, which is later confirmed at postmortem.(53)

6.8 Pathogenesis of coinfection

A case report suggested that a reduction in cd4 cells caused the progression of latent infection to active Tb, similar to HIV. A retrospective study by (64)reported that the number of T cells significantly decreased in patients requiring intensive care unit (ICU) care. The counts of CD4+ T cells and T cells are negatively correlated with survival and the concentration of serum interleukins. The production of cytokine storms upon exposure to Tb infection leads to ARDS. Like in several cancers, including Tb, exhaustion of T cells occurs when T cells are involved in viral clearance. The pathogenesis of each of the causative agents needs to be understood to prevent the promotion and worsening of coinfection.(52)

A study by (65)revealed that acute SARS-CoV-2 infection causes a reduction in mycobacterium-specific CD4+ T cells in COVID-19 patients. This decline in specific CD4+ T cells reduce the immunity of the individual, as an intact T-cell response is crucial in maintaining the Mycobacterium granuloma. The loss of granuloma structure in latent infection due to a cytokine storm and T-cell exhaustion is part of the pathogenesis of coinfection and the activation of latent infection as a result of SARS-CoV-2.

6.9 Recovery & Discharge

Recoveries have occurred more often in the case of COVID-19 than in the case of Tb because of increased efforts in both healthcare and administrative functioning towards COVID-19. (57) There is evidence that recovery in patients with COVID-19 begins in the 2nd or 3rd week, whereas discharge occurs after 2–3 days of afebrile conditions and negative culture reports.(16,58) The course of Tb treatment continues for 4–6 months, and tests are then performed in the 4th month to check for negativity. There is even evidence that a follow-up of a minimum of 1 year should be performed after treatment. There are other hindrances in Tb, which are resistance to treatment with one or more drugs, which would require a change in regimen, or the patient can be susceptible to HIV, requiring ART to be given along with Tb treatment. (38)

The term "long COVID" is divided into phases: one is ‘post covid’ syndrome (beyond 12 weeks), and the other is ongoing symptomatic COVID-19 (4--12 weeks). has been used to describe post-acute COVID-19 symptoms.(16,51) Evidence shows the occurrence of fungal infections (mucorrmycosis) as one of the sequelae post-COVID-19 (22,43).

Among those aged 18 to 34 years with no underlying chronic medical conditions, 20% had not returned to their usual state of health, potentially because of factors such as sex, older age, glucocorticoid therapy, high-baseline SARS-CoV-2 load, variable genotypes, or reinfection or secondary bacterial or viral infection. (42)Similarly, Tb disease has an intermediate latent stage of infection that progresses to active Tb disease. Currently, COVID-19 treatment outcomes range from cure to death to complications ranging from shock, oedema, and multiorgan failure. Common long-term symptoms include cough, low-grade fever, fatigue, dyspnoea, chest pain, myalgia, headaches, rashes, gastrointestinal symptoms, neurocognitive difficulties, and mental health conditions. In the case of Tb only, the patients are checked for reports before discharge or are designated cured patients. (58)

6.10 Strengths & Limitations

The strengths of the study are that COVID-19 has been compared with the age-related disease tuberculosis with respect to a geographic region to give provide a context-specific view of the interactions of both diseases. There are few or no articles on the interaction of both, so this review is one of the few.

The limitations of this study are that less information might be available on Tb than on COVID-19, as COVID-19 has received more attention in this shorter span than the former. In addition, most data on Tb are available until 2021, with the exception of the case incidence data available to date, whereas incidence and mortality data on COVID-19 are available in real time. Another limitation might be that it is a single-country contextual review that may not be similar to others, so the conclusions may not be appropriate yet relevant.

6.11 Recommendations

The response to both tuberculosis and COVID-19 needs to be comprehensive and not just focused on COVID-19. The COVID-19 pandemic provides a picture of the capabilities of our health care system.(18)

The recommendations are mostly learned from the lessons of the COVID-19 pandemic. Improved data reporting platforms, improved diagnostic tools, increased availability of Tb testing services (mostly vulnerable groups), development of Tb-covid19 integrative services, increased investment in capacity building on Tb as a disease, and research on new vaccines, point of care tests and new treatment plans are recommended. (53)Healthcare with consistent diagnoses should be followed at every nick and corner of the country to screen high-risk groups.

There is a need for continued information, advocacy for stigma and its abolishment, and the empowerment of family and community to influence the government to control both TB and COVID-19 as priorities.

7. Conclusions

COVID-19 has spread worldwide with a massive impact and is more transmissible than is tuberculosis, with a span of 5–6 months. More effort has been put into COVID-19 than Tb, at least in India, which is quick, technology driven, resourced, and learning from other countries. Currently, the disease has shown the opposite trend due to increasing Tb cases and their severity. COVID-19 was already a double-edged pandemic with a toll on both mental health and economic well-being. With reports of coinfection with Tb, it has become more difficult than before, as it has increased the chances of missed diagnosis, under treatment, and increased the severity and fatality of cases.

In conclusion, the interaction between COVID-19 and tuberculosis presents significant challenges for public health in India. This review highlights the importance of integrated disease management approaches, early diagnosis, and effective treatment strategies to mitigate the impact of coinfections. Future research should focus on exploring new diagnostic tools, vaccines, and treatment regimens to improve patient outcomes and reduce the dual burden of these diseases. Even, understanding the importance of microbiome relationships between the environment, humans, and animals also opens up the potential for innovative and integrated approaches to the diagnosis and treatment of diseases in animals and humans(53,61)
(5200words)

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