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METHODS ARTICLE

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Better understanding extrapulmonary tuberculosis: A scoping review of public health impact in Pakistan, Afghanistan, India, and Bangladesh

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Abstract

Background and Aims: South Asian countries, including Pakistan, Afghanistan, India, and Bangladesh, have a high prevalence of pulmonary and extra-pulmonary tuberculosis (EPTB). This prevalence is influenced by various risk factors such as ethnicity, nutrition, socioeconomic disparities, high out-of-pocket healthcare expenses, and specific Mycobacterium Tuberculosis (TB) lineages. The COVID-19 pandemic has likely hindered access to healthcare and led to under-reporting of EPTB cases nationally and internationally. This rapid review aimed to summarize the literature on the prevalence and disease outcomes of EPTB in the mentioned countries, compare the situations across countries, and provide recommendations for future action.

Methods: The review utilized PubMed and Google Scholar databases to search for literature on EPTB in South Asian countries. The search string included keywords related to different forms of EPTB and the countries of interest while excluding pulmonary tuberculosis.

Results: The results showed that both TB, including drug-resistant TB, and EPTB are prevalent and burdensome in South Asia. In Pakistan, pleural TB was the most commonly reported form of EPTB, followed by lymph node TB, abdominal TB, osteoarticular TB, Central Nervous System TB, and miliary TB. In India, lymph node TB(LNTB) was more common among EPTB cases. Bangladesh reported a high prevalence of EPTB involving lymph node, pleura, and abdomen, while Afghanistan had a higher prevalence of forms such as LNTB and tuberculous meningitis.

Conclusion: In conclusion, the prevalence of EPTB in Pakistan, Afghanistan, India, and Bangladesh is alarmingly high and negatively impacts population health. Effective measures are needed for treatment and management of this condition,

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along with addressing current and future challenges. Strengthening the evidence base through surveillance and research is crucial to understand the patterns and significant factors related to EPTB, requiring investment in these areas.

KEYWORDS

extrapulmonary tuberculosis, LNTB, *Mycobacterium tuberculosis*, SARS-COV-2, South Asia, TBM

1 | INTRODUCTION

Mycobacteria tuberculosis is a rod-shaped aerobic bacillus that causes pulmonary (PTB) and extrapulmonary tuberculosis (EPTB).[1,2] EPTB is defined as Tuberculosis (TB) involving organs other than the lungs (e.g., meninges, lymph nodes, gastrointestinal tract, pleura, genitourinary tract, and bones). TB typically spreads through person-to-person contact via small airborne droplets after infected individuals cough, or sneeze.[2] However, there is emerging evidence around the role of asymptomatic transmission. For instance, a study of 188 patients with TB finds increased bioaerosol production in those with intrathoracic TB suggesting that TB spreads even during normal tidal breathing. This has implications for the infectivity of TB, especially during the course of treatment.[3,4]

EPTB represents 15% of all TB infections affecting the lymphatic system, and is particularly common in patients with immune system disorders such as Human Immunodeficiency Virus.[5] The pathophysiology and pathogenesis differ depending on the organ system affected, however, the proliferation of granulomas following reactivation, and hematogenous spread is shared among multiple forms of EPTB.[2,5] The clinical presentation of EPTB is diverse and challenging to diagnose.[6] Clinically, EPTB does not manifest in typical symptoms that would otherwise occur in a PTB patient. These include dyspnea, weight loss, cough, hemoptysis, and night sweats. Depending on the organ system affected, patients may present with abdominal pain, joint pain, headaches, diarrhea, or lymphadenopathy.[2,5] Moreover, patients may present with a normal chest radiograph, potentially misleading an important diagnosis. Hence, invasive diagnostic modalities are utilized to make a diagnosis of EPTB.[2]

In South Asia, Pakistan, Afghanistan, India, and Bangladesh all have high prevalence and incidence of TB. For instance, the incidence of TB occurs at 39% in the continent, with 3.4 million new cases that occur each year.[7] In conjunction with this, the prevalence of EPTB ranges from 19% to 23% in South Asia, predominantly affecting females.[8] Socioeconomic disparities, poor healthcare frameworks, high rates of illiteracy, and chronic funding issues create barriers to reducing the spread of EPTB in South Asia. Moreover, challenges in diagnosis and management make it difficult for physicians to assess and treat such patients quickly.[2] There is little information available on the overlapping effects of the COVID-19 pandemic on the surveillance and spread of EPTB in South Asia.[8] More importantly, coinfections of COVID-19 and EPTB can impose other challenges such as poorer prognosis, and a greater public health threat.[9] This state-of-the-art scoping review describes the necessity for reducing EPTB in these four South Asian countries with context-specific recommendations.

2 | MATERIALS AND METHODS

For this Scoping Review, the databases PubMed, and Google Scholar were used for searching literature on EPTB in South Asian countries. The collection of all literature was done using a search string with the following keywords, ("Extrapulmonary tuberculosis" OR "Abdominal tuberculosis" OR "Miliary tuberculosis" OR "Tuberculous meningitis" OR "Potts diseases" OR "skeletal tuberculosis" OR "genitourinary tuberculosis" OR scrofula OR "cervical tuberculosis lymphadenitis") AND ("South Asian countries" OR Pakistan OR Afghanistan OR India OR Bangladesh) NOT (pulmonary tuberculosis). The eligibility criteria consist of literature that is peer reviewed and indexed in the databases mentioned, published in English Language, available as open-access, study design being cross-sectional, original studies, case series, or reviews, published within the previous 12 years (2010–2022). The exclusion criteria comprise case reports (it is based on the clinical manifestations solely of one individual whereas case series accumulates multiple cases) or editorial letters/commentaries, studies not including South Asian countries, and duplicates. Further, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10] were used for carrying out the extraction of literature from the search. The extracted literature was filtered with dissimilarity in title, abstract, and full-text review. The records removed due to other reasons include those with inaccessible full-text, difference in language, insufficient data, and non-peer reviewed sources. The selection process is shown in the PRISMA flow diagram (Figure 1).

3 | THE BURDEN OF COVID-19 ON TB AND EXTRAPULMONARY TB

More recently, the transmission of TB was further exacerbated during the COVID-19 pandemic. A research assessed the relationship between SARS-CoV-2 host expression and the interactions of 26 SARS-CoV-2 proteins with 332 human proteins. It was observed that Mycobacterium TB shares most host protein interaction partners as

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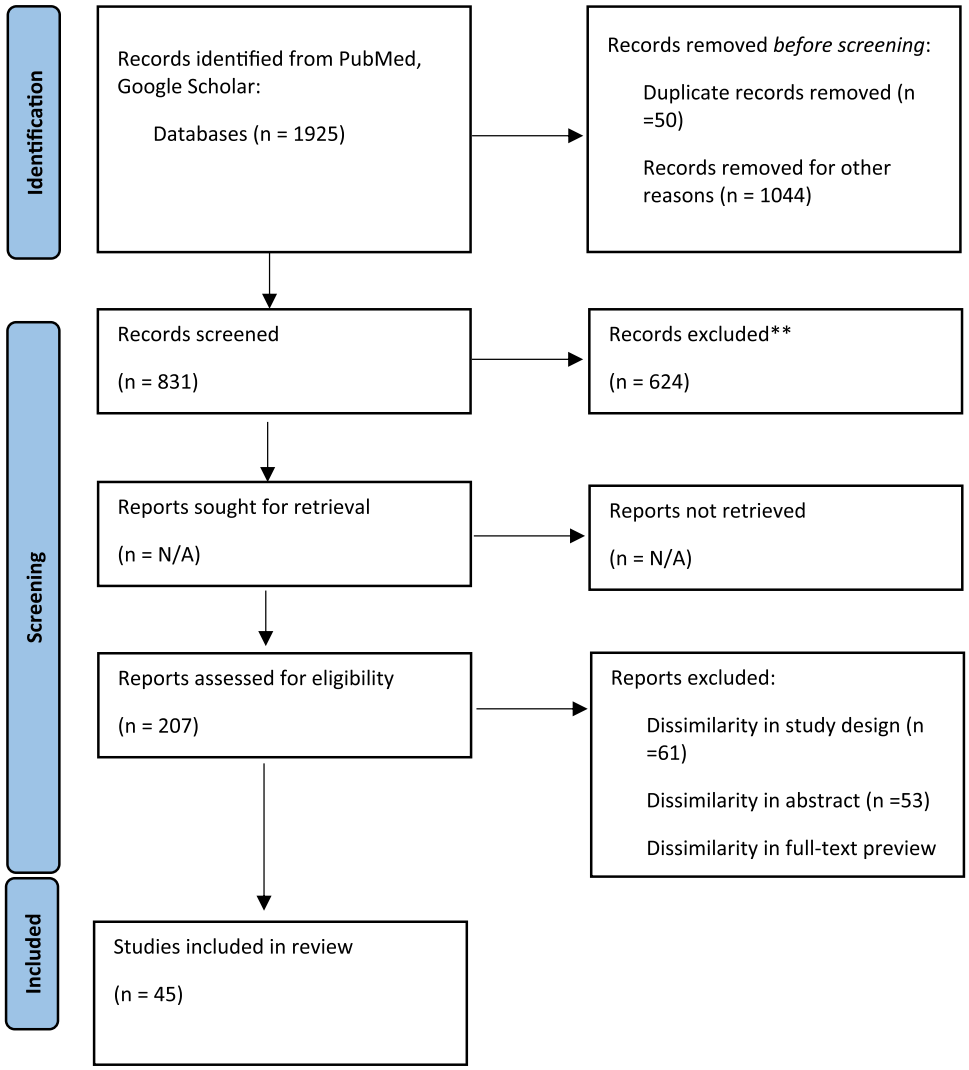

FIGURE 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

SARS-CoV-2. This is of vital relevance since both diseases have significant affinity for lung tissue.[11] Since inflammations of the lungs occur in both diseases, it is reasonable to speculate that COVID-19 may induce a hyperinflammatory environment that accelerates the progression of TB disease. Furthermore, profound lymphopenia and hyperinflammation associated with COVID-19 may facilitate M. TB reactivation.[12] On the other hand, a person infected with TB is also more prone to developing an active disease like COVID-19 which can further then further infect 10–15 people a year.[13] According to the Centers for Disease Control and Prevention, patients having respiratory problems as a result of their TB infection are more likely to contract a severe COVID-19 infection.[11] The simultaneous occurrence of TB and SARS-COV-2 also contributes to the development of EPTB manifestations. In a study held in a public hospital in Buenos Aires, 10,809 cases of COVID-19, 106 of TB, and 20 of TB-COVID-19 coinfection were identified. A total of 5 (25% of these 20) presented with EPTB involvement. Of these, 3 cases presented exclusively as extrapulmonary involvement of the central nervous system (CNS), whereas the pulmonary and pericardial systems in conjunction were involved in 2 of the cases.[12]

The transmission of TB has likely been further exacerbated during the Covid-19 pandemic. Research has identified that *Mycobacterium tuberculosis* shares most host protein interaction partners as SARS-CoV-2, meaning that both diseases have significant affinity for lung tissue.[11] Since inflammations of the lungs occur in both diseases, it is possible that COVID-19 may induce a hyperinflammatory environment that accelerates the progression of TB disease. Furthermore, profound lymphopenia and hyperinflammation associated with COVID-19 may facilitate M. TB reactivation.[12] On the other hand, a person infected with TB is also more prone to developing an active disease like COVID-19 which can further then further infect 10–15 people a yearc.[13] According to the USA Centers for Disease Control and Prevention, patients having respiratory problems from their TB infection are more likely to contract a severe COVID-19 infection.[11] The simultaneous occurrence of TB and SARS-COV-2 also contributes to the

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development of EPTB manifestations. An Argentinean study reported on 106 cases of TB, of which 20 of TB-Covid-19 coinfection were identified. Within the 20 cases, 5 (25%) presented with EPTB involvement. Of these, 3 cases presented exclusively as extrapulmonary involvement of the CNS, and the pulmonary and pericardial systems in conjunction were involved in 2 of the cases.[12] The burden of TB and EPTB is much higher in South Asia than in Argentina.

4 | SUSCEPTIBILITY OF EXTRAPULMONARY TB IN SOUTH ASIANS

Host-ethnicity-related characteristics are very important in determining the clinical phenotype of TB. A data set of 902 extrapulmonary *Mycobacterium tuberculosis* complex (MTBC) isolates from Saudi Arabia revealed that South Asian ethnicities were more strongly associated with EPTB.[14] In another retrospective study conducted in 31 hospitals in Tuscany for the incidence of TB, it was determined that South Asian-born patients were at increased risk of EPTB.[15] Another study of 37 patients diagnosed with the genitourinary TB in an East London Hospital reported that 65% of patients were born in the South Asian region.[16] There is also some evidence that ethnicity-related characteristics, such as polymorphisms and haplotypes, significantly influence how the host immune system responds to MTBC infectionsg.[14]

Another factor that may make South Asians more prone to developing TB is their waning immunity, which increases likelihood of extrapulmonary illness manifestation and distant organ dissemination In addition, changes in nutrition or adverse socioeconomic factors may further cause a loss in immunity, which may contribute higher TB risks.[17]

Additionally, TB multidrug resistance is highly-prevalent throughout South Asia. As of 2015, Afghanistan had the second-highest TB burden in the World Health Organization's (WHO) Eastern Mediterranean Region, despite not being a high-burden country. Pakistan, India, and Bangladesh also have a high burden of multidrug-resistant TB.[8]

TB patients in these regions are primarily infected by the East African Indian (EAI) and Central Asian (CAS) lineages of MBTC. Pakistan had the highest percentage of CAS (64.4% of strains), followed by North India (34.7%). Conversely, South India (22.9%) and Bangladesh (47.9%) had high EAI proportions. When compared to the EAI group, the CAS group had considerably more multidrug resistance and extensively drug resistance TB (30.6% and 1.0%, respectively) than the EAI group (12.1% and 0.3%, respectively; $p = 0.0001$). Additionally, compared to the CAS lineage (57.1%), the proportion of pan-susceptible strains was greater among the EAI lineage (69.8%).[18]

We summarize, study characteristics and epidemiological trend of EPTB prevalence up to 2022–23, in four South Asian Countries that is, Pakistan, India, Bangladesh, and Afghanistan in Table 1.

4.1 | Pakistan

According to reports by the National Institute of Health, Pakistan ranks fifth amongst the countries which come under a high TB burden, with prevalence, incidence, and mortality, of 348, 276, and 34 per 100,000 population per year, respectively.[38] In 2016, around 54,000 TB cases were recorded in Pakistan, of which 29.2% were EPTB cases.[19] Compared to the percentage of EPTB among reported TB cases in 2011 (17.4%), the prevalence steadily increased to reach 20% in 2016, which is mainly due to negligence of the management of EPTB in Pakistan.[19]

Results from a nationwide multicenter retrospective study showed that EPTB was more common among females than males (30.5% and 27.9%, respectively).[19] The most common form of EPTB was pleural TB with prevalence of 29.6%, followed by lymph node TB (LNTB) (22.7%), abdominal TB (21.0%), osteoarticular (9.4%), CNS (4.6%), other (3.7%), and miliary TB (0.6%).[19] Even though females had a higher overall prevalence of EPTB, pleural TB specifically was more common among males (34.5% vs. 25.1%, $p < 0.001$). The most common form of EPTB among females was LNTB (26.6% vs. 18.4%, $p < 0.001$).[19] Findings also suggested that pleural TB was found more in adults (34.2%) and abdominal TB (38.4) was more prevalent among children. Moreover, with the increase in age a rise in the risk for pleural and osteoarticular TB was noticed in this study.[19] Treatment of the majority of the forms of EPTB, including pleural, lymphatic, and abdominal TB, had a 90% success rate, with the exception of TBM, which had a significantly lower success rate of 74.3% ($p < 0.001$).[19]

Compared to the previous study, a similar trend of prevalence of different type of EPTB was presented by Atif et al., that is, pleural TB (33.4%) being most prevalent followed by LNTB (26.1%), abdominal TB (12.3%), bone/joint/spinal TB (3.5%), TB meningitis (TBM) (5.8%), and skin (0.9%).[20] The treatment success rates in this study were also similar to those of the previous study as the TBM success rate was low compared to other forms of EPTB.[20]

EPTB manifestations are observed in children in Pakistan. High rates of acute and chronic malnutrition among children in Pakistan are a contributing factor to the country's high TB loads and further complications. Younger ages and developing immunity all contribute to the heightened illness risk in children, who are more likely to present with EPTB than adults. The following frequency of EPTB disease by site was discovered in a descriptive analysis carried out in Pakistan among 3607 children (age 0–14 years) with TB registered nationwide in 2016: abdominal TB (38.4%), LNTB (22.4%), pleural TB (14.0%), CNS (CNS; 6.0%), osteoarticular (3.9%), and site not specified (12.1%). According to a study done in 2022 by Dubois et al., abdominal TB and LNTB were the two most often reported sites of EPTB for children across all demographics.[21]

TBM is the most severe form of EPTB and can be 100% fatal if left untreated.[21–23] The most common symptom of TBM in Pakistan was found to be fever followed by other symptoms such as headache, neck stiffness, seizures, vomiting, altered consciousness, and a few even reported cranial nerve lesions in some patients.[22–24] The association of gender as a risk factor for TBM in Pakistan is

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TABLE 1 Study characteristics and epidemiological trend of EPTB prevalence on basis of site involvement up to 2022–23, in Pakistan, India, Bangladesh, and Afghanistan included in the study.

Study	EPTB cases (*n*)	Average age (years)	Female (%)	Pleural (%)	Abdominal TB (%)	Osteoarticular (%)	LNTB (%)	TBM (%)	Skin (%)	CNS (%)	Disseminated/ miliary TB (%)
Pakistan											
Tahseen et al.[19]	15,790	24	30.5	**29.6**[a]	21	9.4	22.7	N/A	N/A	4.6	0.6
Atif et al.[20]	651	33.7	48.7	**33.3**[a]	12.3	3.5	26.1	5.8	0.9	N/A	N/A
Dubois et al.[21]	157	<14	46.5	N/A	**72.4**[a]	N/A	19.9	N/A	N/A	N/A	N/A
Salekeen et al.[22]	52[b]	36.29	50		3.8[b]	1.9[b]	1.9[b]	**100**[a]	N/A	9.6[b]	9.6[b]
Wasay et al.[23]	559[b]	47.8	40.3	N/A	N/A	N/A	N/A	**100**[a]	N/A	N/A	N/A
Anjum et al.[24]	40[b]	4.24	37.5	N/A	N/A	N/A	N/A	**100**[a]	N/A	N/A	N/A
Shore et al.[25]	50[b]	43	40	N/A	N/A	N/A	N/A	**100**[a]	N/A	N/A	N/A
Afridi et al.[26]	100	30	55	N/A	**100**[a]	N/A	N/A	N/A	N/A	N/A	N/A
Noor et al.[27]	40	32.3	47.6	N/A	N/A	N/A	N/A	**100**[a]	N/A	N/A	N/A
Wahid et al.[28]	101	32.56	62.37	N/A	N/A	N/A	**100**[a]	N/A	N/A	N/A	N/A
India											
Prakasha et al.[29]	528	<14 to >65	48.48	**28.1**[a]	9.7	12.3	24.8	N/A	N/A	12.5	N/A
Shamseeda et al.[30]	406	41.6	57.6	**30.3**[a]	22.27	8.7	22.7	4.9	N/A	N/A	0.2
Bangladesh											
Yang et al.[31]	85	<24 to ≥80	16.9	5.9–10.6	5.9–10.6	**27.1**[a]	17.1	5.9–10.6	5.9–10.6	5.9–10.6	15
Khanum et al.[32]	27	10–60+	8.47	12	12	**28**[a]	**28**[a]	N/A	N/A	N/A	N/A
Afroz et al.[33]	152	25–34	57.2	29.6	21	19.7	N/A	**43.6**[a]	N/A	N/A	N/A
Quddus et al.[34]	200	35.67	60	15	N/A	N/A	50	N/A	N/A	N/A	N/A
Afghanistan											
Fader et al.[35]	118	31.5	79.1	8.5	6.8	11.9	**37.3**[a]	N/A	N/A	20.3	1.7
Rahimi et al.[36]	818[b]	4.8	60.9	N/A	N/A	N/A	N/A	**100**[a]	N/A	N/A	N/A
Shah et al.[37]	90[b]	49	26.7	N/A	N/A	N/A	N/A	**100**[a]	N/A	N/A	N/A

Abbreviations: CNS, central nervous system; EPTB, extrapulmonary tuberculosis; LNTB, lymph-node TB; TB, tuberculosis; TBM, TB meningitis.

[a]Most prevalent form of EPTB.

[b]With history of TBM.

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uncertain,[23,24] and another study stated that female gender had a higher risk of developing TBM. One study by Shone et al. showed that Type 2 diabetes mellitus was the major comorbidity that led to a higher incidence of TBM.[25] Hydrocephalus was found to be one of the common complications in TBM patients, however, the rates varied significantly.[22–24] A ventriculoperitoneal shunt was placed in these patients as management. TBM patients from Salekeen et al. and Anjum et al.'s studies also had cranial nerve involvement with roughly similar prevalence, 26.9% and 23.5%, respectively.[22–24] According to Salakeen et al.'s study conducted in Pakistan, abducens nerve palsy (25%) was the most common form of cranial nerve palsy in TBM patients, followed by oculomotor nerve (17.3%), facial nerve (9.6%), and vestibulocochlear nerve palsy (1.9%).[22] A retrospective study by Wasay et al. determined the predictors of cerebral infarctions in TBM cases, which was found to be present in 25.8% of their participants.[23] The findings of their multivariable logistic regression showed that age over 40, hypertension, dyslipidemia, and diabetes mellitus were independent predictors of cerebral infarcts in patients with TBM. All the studies discussed here had a high mortality rate in patients with TBM, which explains why TBM has been deemed the most severe form of EPTB.

Abdominal TB can present clinically via a range of otherwise-common symptoms and is thus difficult to diagnose. For example, a cross-sectional study in Karachi, Pakistan, showed that abdominal pain (72%), weight loss (62%), low-grade fever (38%), and ascites (42%) were the common symptoms.[26] Other common symptoms included pallor, malaise, anorexia, constipation, vomiting, and diarrhea.[27] The most common form of abdominal TB involved tuberculous peritonitis.[26,27] Other forms include intestinal obstruction (abdominal TB is the most common cause in Pakistan), ileocecal mass, enterocutaneous fistula, and subacute intestinal obstruction.[26,27] The prevalence of different forms of abdominal TB differs greatly between different patient groups. Most patients with abdominal TB in Pakistan present to emergency with acute complications, in contrast to the developed world where abdominal TB is rarely associated with acute emergencies.[27] Afridi et al.'s study showed that surgery had an 82% success rate among 100 patients, in addition, Noor et al.'s study also concluded that surgical interventions for abdominal TB had a good survival rate.[26,27] Morbidity and mortality were found to be associated with a late presentation with sepsis, fecal peritonitis, or intestinal obstruction.[26]

The WHO has classified Pakistan as the eighth highest incidence country globally, and first in the eastern Mediterranean region, for tuberculous lymphadenitis, which is quite common in Asian nations. A study conducted by Iqbal et al in Pakistan deduced that TB was the most frequent finding in 220 patients with enlarged neck lymph nodes. According to another study in 2013 by Fazal-i-Wahid et al. in Pakistan, 75.2% of cervical lymphadenopathy cases had EPTB as the primary diagnosis. The results of these studies are in concordance with another study held in Pakistan which elucidated that 66.4% of cases of cervical lymphadenopathy had EPTB.[28]

The out-of-pocket healthcare expenditure can be significant for TB taking into consideration factors such as the need to sometimes buy the antibiotics and the long duration of treatment. A study by Razzaq et al. estimated the pre- and post-diagnosis cost of TB which came out to be 63.8 USD pre-diagnosis, 24 USD after diagnosis, 10.5 USD for treatment, and 349 USD for hospitalization.[39] Moreover, according to a cross-sectional survey in 2020, the median cost of TB in Pakistan was found to be approximately 360 USD and around 67% of patient's households were affected by the catastrophic costs, especially if the patient is the sole bread earner of the house as the treatment led to unpaid sick leaves and even loss of job.[40] Due to the recent spike in inflation in Pakistan, and multiple areas affected by catastrophic floods in 2022, around 5.8–9 million Pakistanis have been pushed below the poverty line.[41] This implies that a majority of the population affected by TB might not be able to afford the treatment. The mass migration due to flood destruction might have additional consequences, such as further overcrowding in the cities, increasing both the risk of TB and multi-drug resistant TB (MDR-TB) transmission in different parts of Pakistan.

4.2 | India

TB is one of the greatest health challenges that India currently faces. The WHO indicates that India reported 2.4 million cases of TB in 2019, the greatest number of any country and accounting for more than one-quarter of global cases.[42] Following the COVID-19 pandemic's interruption of TB tracking and reporting, notifications of TB cases in India decreased, with just over 1.6 million cases being recorded in 2020, indicating the majority of cases went unreported.[42] Furthermore, because of limited access to TB care facilities, the number of persons treated for drug-resistant TB declined by 15%.[43] Additionally, one-fifth of all cases in India are due to EPTB.

Amongst the clinical manifestations of EPTB in India, body organs affected other than the lungs mainly include; lymphatics (35%), pleural cavity (20%), spinal (10%), and genitourinary (9%). Other sites known to be affected include the gastrointestinal system, joints, skin, and other organs, constituting (26%) of cases.[29,44] People who have HIV/AIDS or other immunocompromised states, such as diabetes mellitus and malnutrition, are significantly more likely to get EPTB as a common opportunistic infection.[44] According to a report, 15%–20% of patients with TB had additional immunocompromised diseases, and 50% of reported TB cases involved HIV-positive people.[44]

A record-based study in India, which included 476 people with PTB and 406 with EPTB, found that EPTB was more common in female patients (57.6%) and patients with ages between 21 and 40 years (33.7%), whereas PTB alone was reported to be more common in male patients and older ages.[30] Shirvastava et al. investigated the demographics, clinical characteristics, and risk factors for EPTB in central India in a related retrospective study. They discovered that the ratio of TB to EPTB is 1:3.6, with LNTB being the most prevalent. Ages between 20 and 39 and diabetes mellitus [MH1] are the risk variables involved.[45]

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The most prevalent form of EPTB in India, LNTB, is one of the far less serious manifestation. The majority of the superficial lymph nodes affected by it are those in the suprascapular fossae or the posterior and anterior cervical chains, but it can also affect the submandibular, periauricular, inguinal, and axillary groups.[29] It is frequently encountered in females and young children.[46] The lymphadenopathy is usually noncontiguous and bilateral. Between 5% and 62% of cases had concomitant pulmonary involvement. The treatment of LNTB is frequently met with significant challenges. However, surgical intervention is rarely necessary and the majority of cases can be treated conservatively.[46] Besides this, Pleural TB accounting for the second most prevalent form of EPTB can also prove to be deadly. A study by Chakraborty et al. selected a total of 75 patients with tuberculous pleural effusion and found that 57 patients were males, showing male predominance. Associated symptoms include cough, chest pain, dyspnea, and fever, while none of them presented with hemoptysis.[47] In addition, the prevalence of MDR-TB among EPTB is a significant health concern in India. A prospective study conducted by Kant et al. assessed the 13.4% increase in MDR-TB cases among EPTB patients in Northern India, which is a rising trend. If unattended, this could escalate to increased and diversified resistance toward higher line therapeutic agents, potentially causing a steep increase in morbidity and mortality.[48]

4.3 | Bangladesh

Bangladesh, the eighth most populous country in the world located in South Asia, has been majorly impacted due to infectious and communicable diseases. Poor economic status, and unsanitary living conditions, along with unaffordability and inaccessibility to health services, have exacerbated the substandard health concerns in the country.[49] Pertaining to infectious diseases, TB is one of the primary culprits negatively impacting Bangladesh in terms of its health and well-being. With over 434 people in every 100,000 people affected with TB, it is considered as the seventh most TB burden country in the world.[50,51] According to the report of 2020, around 360,000 people developed TB, out of which 44,000 that is, (14%) succumbed to the disease, making TB the third most common cause of death in Bangladesh.[52] Besides this, Bangladesh is considered to have a high-MDR-TB burden, with an estimated prevalence of multidrug resistance amongst 1.6% of new cases and around 29% in previously treated cases.[53]

In Bangladesh, EPTB accounts for 15%–19% of all TB cases. According to the Annual TB Report 2020 from the National TB Control Program (NTP), a total of 1819 EPTB deaths were reported in Bangladesh. A study carried out among 330 TB patients evaluated the prevalence of pulmonary TB was 74.5% while EPTB was 25%.[32] Among EPTB, TB involving the lymph nodes, pleura, and abdomen is the most common in Bangladesh. A cross-sectional study conducted in rural Bangladesh that included 152 EPTB patients found that the disease was more common in females in the age group between 25 and 34 years. They also reported the distribution of sites of EPTB infection, which includes pleural (29.6%), glands (24.3%), abdominal (21%), spinal (19.7%), brain (4.6%), and cardiac (0.7%).[33] A similar retrospective study of 200 EPTB cases discovered that EPTB was more common between the ages of 16 and 45 and among females (60%). While lymph nodes were the most common site involved (50%), the second most common involvement was tubercular pleural effusion (15%).[34]

4.4 | Afghanistan

Afghanistan, a low-income country suffering from multiple humanitarian crises and a struggling healthcare system, does not hold the potential to deal with the rising burden of TB. According to WHO, 47,406 TB cases were recorded in Afghanistan in 2017, of which 12,329 (26%) comprised EPTB.[54] In 2020, more people likely died in Afghanistan from TB than COVID, with 73,000 Afghans being newly-infected by TB in 2020 (a steep increase from 2017) and only 50,000 cases being identified, indicating major lacunae in effective screening and surveillance.[55]

According to a retrospective study comprising 118 participants, EPTB was more common in females than in males, with a ratio of 2.03:1.[35] Moreover, the most common extrapulmonary manifestation of TB in Afghanistan was LNTB, $n = 44$ (37.3%), which most commonly involved cervical lymph nodes.[35] Symptoms of LNTB included swelling in the affected area, fever, and weight loss.[35] According to the same study, the second most common system involved in EPTB was CNS, and TBM, with 24 cases (20.3%) of the 118 participants.[35] The most common symptoms involved headache, fever, and vomiting.[35] Neck stiffness was also reported in 26.1% of the participants and 1 participant was found to have an intracranial hematoma.[35]

Other studies have also reported cases of TBM which they define as the most severe form of TB.[6,7] A prospective cohort observational study by Rahimi et al., states that TBM is associated with a high mortality rate of 15%–30%, despite receiving treatment, which is attributed to the delay in diagnosis of TBM due to limited diagnostic tools and resources.[36] This study comprised 818 children with TBM from Kandahar, Afghanistan.[36] Of these participants 96% had fever, 82.1% had a headache, and 38.4% had some form of cranial nerve palsy.[36] As this study comprised of children less than 18 years of age, one of the significant risk factors for death by TBM was not being vaccinated for BCG; followed by not receiving dexamethasone, male sex, recent weight loss, and stage of TBM.[56] A retrospective study conducted in Pakistan among 90 Afghan immigrants also showed that fever ($n = 79$, 87.8%) was the most common clinical manifestation among the participants who had TBM.[36] Cranial nerve involvement was also significant with 60 out of 90 participants exhibiting the manifestation in their study, with the most common cranial nerve to be involved was the hypoglossal nerve ($n = 22$).[37] Furthermore, they also reported that hydrocephalus was more common in males (30%) than females (11.1%).[37]

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Apart from TBM, EPTB can also present as spinal cord injury due to CNS involvement. As illustrated by Michael and Roth, the second most common cause of spinal cord injury in Afghanistan is TB, comprising 16.3% of the total cases.[57] Spinal cord injury can prove to be deadly, especially if the cervical spine gets involved, and thus it is of great concern in Afghanistan as there is very minimal knowledge about spinal cord injury among the Afghan medical society.[57]

In addition to LNTB and TBM, EPTB also presents as skeletal TB. A retrospective review by Fader et al. reported that 11.9% of their participants had skeletal TB, more frequently involving the spine, elbow, knee, and forearm.[35] Most common symptoms included fever, progressive paraplegia, and back pain. In addition to skeletal TB, 8.5% of their total participants presented with pleural TB, with symptoms of shortness of breath and cough.[35] A minority of their participants had abdominal, cutaneous, genitourinary, pericardial, military, or breast TB.[35]

In Afghanistan, somewhat data is available on the CNS manifestation of EPTB, however, the literature on different types of EPTB is extremely scarce, which signifies the lack of surveillance among the population, limiting the ability to identify, and manage these cases effectively.

5 | PUBLIC HEALTH RESPONSE EFFORTS

5.1 | Pakistan

Pakistan have set up the National TB Control Program which aim to increase the coverage of notified TB cases, to keep the treatment success rate of 91% stable, reduce the incidence of MDR-TB among those patients who have never received any TB treatment, and improve public sector support for TB control.[19] NTB is also working to reduce TB prevalence in the population of Pakistan by 50% by 2025 in comparison to 2012 by making quality care easily accessible.[38] Although steps are being taken to improve the TB situation in Pakistan, the fact that Pakistan ranks fifth among the high TB burden countries is alarming.

5.2 | India

The case fatality ratio of TB in India must be lowered globally to less than 5%, according to the WHO End TB Strategy. To cope with the alarming conditions, India started the National TB Elimination Program in 2017 to achieve the aim of ending the TB pandemic by 2025.[56] Interventions under this program include significant financial support for healthcare, provision of additional nutrition, organization of a national epidemiological census for TB, and a national campaign to link the often-fragmented Indian government and private health infrastructure. Although India's case fatality ratio for treatment are in line with WHO guidelines, the bulk of cases is still undetected, which lowers the level of optimal care available nationwide.[58]

5.3 | Bangladesh

Ongoing efforts by the Bangladesh National TB Program and numerous NGO organizations have significantly reduced the disease's spread. For example, the NTP recently created a National Strategic Plan for TB control from 2021 to 2025. This plan emphasizes coordinated, patient-centered prevention, strong policies, and helpful systems, as well as increased research and innovation. NTP previously adopted DOTS (Directly Observed Treatment, Short-course) that showed a 78% cure rate in 1993, along with a phase-based treatment plan in 67 million rural areas in 1996. Since its inception, the NTP has achieved a 90% success rate in treating patients. The FAST initiative is one of the additional measures being taken to fight the disease (Find cases Actively, Separate safely and Treat effectively). The program aims to stop the spread of the disease in healthcare facilities by identifying active TB cases. The NTP and other NGOs have made some progress since the 1990s, but the program's objectives continue to be seriously hampered by considerable delays in care-seeking and treatment beginning.[59,60]

5.4 | Afghanistan

As EPTB has nonspecific clinical manifestations, it often goes undiagnosed which can prove to be a threat to Afghanistan's public health. Due to the 2021 regime change, the healthcare system in Afghanistan has suffered a huge shortage of funding and resources as donors, such as the World Bank, USAID, and the European Commission, withdrew their donations and funding. This has severely affected the Sehatmandi program, the backbone of Afghanistan's health system, which includes 2331 health facilities providing care to millions of Afghans.[61] Due to a lack of funding, many healthcare workers have not been paid salaries which might progress to a shortage of professional healthcare staff and thus lead to an increased number of EPTB cases going undiagnosed and untreated.[61]

Even though the current situation of TB in Afghanistan is alarming, it is not going unnoticed, as efforts have been made by the Government of Japan and WHO in gathering funding which provided 7 million USD to make anti-TB medications and molecular advanced diagnostic kits for TB available throughout the country. Moreover, new health facilities have been developed to provide effective TB diagnosis and treatment.[61] Despite these efforts, various factors such as drug susceptibility and drug-resistant TB cases going undiagnosed, and the banning of women from positions in public health and healthcare, are hindering progress[62,63]

6 | DISCUSSION

Both TB (including drug-resistant TB) and EPTB are high-burden diseases throughout South Asia. As of 2015, Afghanistan had the second-highest TB load in the WHO Eastern Mediterranean Region

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with more than 45,000 TB cases being recorded in Afghanistan in 2017, of which around one-fourth comprised EPTB (54), despite not being a high-burden country. Pakistan, India, and Bangladesh are among the countries in South Asia with a high burden of multidrug-resistant TB.[8]

The most common forms of EPTB reported in Pakistan, were pleural TB, followed by LNTB, abdominal TB, osteoarticular, CNS, site not-specified, and miliary TB.[19–28] The LNTB form of EPTB is more common in India. Amongst the clinical manifestations of EPTB in India, body organs affected other than the lungs mainly include; lymphatics, pleural cavity, spinal, and genitourinary. While, gastro-intestinal, joints, skin, and other organs constitute remainder.[29,30] Among EPTB, TB involving the lymph nodes, pleura, and abdomen is the most common in Bangladesh.[31–34] In contrast, forms of EPTB that is, LNTB and TBM dominates in Afghanistan.[35–37]

6.1 | Limitations and strengths

This study was associated with certain limitations. As this study discusses a broader perspective of the topic, it was difficult to gather all the literature relevant to this study. Moreover, some South Asian countries had limited literature on this topic therefore, so a precise comparison could not be established between all the South Asian countries. There are insufficient studies providing data on distribution of EPTB based on site involvement, in Pakistan, India, Bangladesh, and Afghanistan. Hence, the review illustrates a general picture of epidemiological trend of EPTB cases across South-Asian countries, based on site involvement up to 2022–23. Further observational studies would allow for more in-depth data around the burden of disease and any associated temporal changes. The strength of this research is the thorough and extensive quality of the search strategy to gather available evidence.

7 | RECOMMENDATIONS

As one of the initial protocols to combat EPTB, modern and efficient screening methods should be introduced that are accessible to vulnerable and high-risk populations across Pakistan, Bangladesh, India, and Afghanistan. This applies in particular to the ones with preexisting respiratory issues. Low immunity is a major concern when it comes to the progress of EBTB disease and thus higher quality information needs to be available around the prevalence of risk factors such as nutrition. Governments, healthcare institutes, and other stakeholders can provide health promotion about the spread of EBTB and the precautions to be taken. This can for example be done by launching national awareness programs through social and mainstream news media and other modes. It is also essential to identify key reasons around any stigma or lack of education that can result in later attendance at health facilities.

Further observational studies would allow for more in depth data around the burden of disease and any associated temporal changes. We need to know more about the prevalence of EPTB in males and females—the evidence base at the moment appears to indicate females are more greatly affected albeit with variation across the different clinical presentations. Priority-setting exercises, led by in-country stakeholders and supported by international organizations such as the WHO, can define a patient-led research agenda.

Alongside improved data infrastructure and research priority-setting, Governments of high-risk countries should invest in exclusive specialist health facilities with molecular advanced diagnostic kits and anti-TB medications at the district level readily available to meet the demand of increasing prevalence as well as designated and qualified human resources. Policies allowing the provision of antibiotics over-the-counter at pharmacies should be revised, as a means to control multi-drug resistance and thus to reduce the impact of EPTB. A new generation of anti-TB medicines and vaccines are much needed. Training according to the guidelines of WHO should be made essential for healthcare workers in all settings to enhance the quality of service provided in TB management.

8 | CONCLUSION

The prevalence of EPTB Pakistan, Afghanistan, India, and Bangladesh is very high, with significant negative population health impact. Measures are required to treat the condition as well as cope with current and future situations. A stronger evidence base is required to understand the pattern and significant variables of EPTB, and that requires investment in surveillance and research.

AUTHOR CONTRIBUTIONS

Areesha Jawed: Project administration; Writing—original draft; Writing—review and editing. **Zoaib Habib Tharwani**: Writing—original draft. **Amna Siddiqui**: Writing—original draft. **Waniyah Masood**: Writing—original draft. **Khulud Qamar**: Methodology. **Zarmina Islam**: Writing—original draft. **Aleeza Jawed**: Writing—original draft. **Muzhgan Shah**: Writing—original draft. **Alishba Adnan**: Writing—original draft. **Mohammad Yasir Essar**: Conceptualization; Writing—review and editing. **Sudhan Rackimuthu**: Writing—review and editing. **Michael G. Head**: Writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available in the manuscript.

TRANSPARENCY STATEMENT

The lead author Mohammad Yasir Essar affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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