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Tuberculosis deaths are predictable and preventable: Comprehensive assessment and clinical care is the key

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ABSTRACT

The goal of reducing tuberculosis (TB) mortality in the END TB Strategy can be achieved if TB deaths are considered predictable and preventable. This will require programs to examine and address some key gaps in the understanding of the distribution and determinants of TB mortality and the current model of assessment and care in high burden countries.

Most deaths in high-burden countries occur in the first eight weeks of treatment and in those belonging to the age group of 15–49 years, living in poverty, with HIV infection and/or low body mass index (BMI). Deaths result from extensive disease, comorbidities like advanced HIV disease complicated with other infections (bacterial, fungal, bloodstream), and moderate-severe undernutrition. Most early deaths in patients with TB, even with TB-HIV co-infection, are due to TB itself.

Comprehensive assessment and clinical care are a prerequisite of patient-centered care. Simple independent predictors of death like unstable vital signs, BMI, mid-upper arm circumference, or inability to stand or walk unaided can be used by programs for risk assessment. Programs need to define criteria for referral for inpatient care, address the paucity of hospital beds and develop and implement guidelines for the clinical management of seriously ill patients with TB, advanced HIV disease and severe undernutrition as co-morbidities. Programs should also consider notification and audit of all TB deaths, similar to audit of maternal deaths, and address the issues in delays in diagnosis, treatment, and quality of care.

1. Introduction

Tuberculosis (TB) is one of the top ten causes of death globally. Since 2011, it is the leading cause of death due to a single infectious agent, (surpassing HIV) with an estimated 1.2 million estimated deaths in 2018 among the HIV negative people living with TB and another 0.25 million in HIV positive people with TB [1]. The END TB strategy aims to reduce TB incidence and mortality in 2035 (compared to 2015 figures) by 90%, and 95%, respectively [2]. A target of 75% reduction in TB mortality by 2025 is an ambitious milestone, as currently, TB mortality in HIV negative patients is declining by 3% per year [1]. Historically, cure rates in patients with TB of more than 95% were reached in developed countries with effective anti-tuberculosis drugs and assured adherence to therapy [3]. While the case fatality ratio (estimated mortality/estimated incidence) in high-income countries is 5%, it continues to be around 20% in high-burden countries [1]. The eight high TB burden countries that contribute to two thirds of the disease burden are India–27%, China–9%, Indonesia–8%, Philippines–6%, Pakistan–5%, Nigeria–4%, Bangladesh–4% and South Africa–3% [1]. An effort to reduce the disease burden and deaths due to TB in these countries, particularly India, is crucial in achieving these ambitious targets.

Mortality during TB treatment is not merely a function of the infection with M.Tuberculosis, but there are host, disease, and health system related factors that underlie and contribute to mortality. We believe that significant and even dramatic reduction of TB mortality in high burden countries is a goal achievable in the near future if we consider them predictable and preventable and recognize and address three crucial gaps. First, the epidemiological understanding of the distribution and determinants of TB mortality should inform and reflect in programmatic strategies and treatment guidelines. Second, there are significant gaps in the evaluation and management of patients with TB

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that are not addressed in the current operational model of patient-centered care. TB programs need to implement appropriate and comprehensive clinical care, as an essential pre-requisite of patient-centered care. Third, there are gaps in the health system preparedness leading to delays in diagnosis, difficulties in access, and lack of comprehensive clinical care to patients with severe disease. We use the WHO definition of TB mortality as mortality due to any cause in a patient who is on treatment for TB according to the international classification of diseases. We recognize there are methodological problems in estimating the mortality in high TB burden countries that lack universal health coverage, have poor vital registration system (VRS) and disease reporting system with poor information on burden of undiagnosed TB [4]. National TB programs may underestimate TB deaths as these do not account for deaths in undiagmosed patients, in those who default during treatment, in patients with recurrent disease or those due to sequel [5]. Several based studies have shown that diagnosis is often missed in patients with smear negative tuberculosis, disseminated and extrapulmonary TB [4–8]. On the other hand, some deaths that are recorded during treatment may not be due to TB [4,5,7,8]. This review outlines the gaps within the framework of epidemiology, clinical care, and health system readiness in reducing TB mortality

2. Addressing the programmatic gaps in the understanding of the distribution and determinants of TB mortality

2.1. The person distribution of deaths due to tuberculosis or who dies of tuberculosis?

There is a socio-demographic gradient to TB mortality. Globally, 95% of TB deaths occur in low and middle-income countries (LMIC) [1]. TB mortality disproportionately affects those living in poverty: as the indigenous populations, marginalized groups, homeless, [9,10] and those engaged in manual work [11]. In a hospital serving a predominantly poor population in Manila, the mortality rate among HIV negative adult patients with all forms of TB was 20.1–37.5% [12,13]. Living in an area of inequality was associated with a 5-fold higher risk of TB mortality [10]. Higher mortality in these groups could be related to delays in the diagnosis of tuberculosis and a lack of access to quality care.

The risk of death due to TB is affected by age, gender, type of tuberculosis and drug susceptibility profile. Age as a predictor of mortality varies according to the countries. In developed countries like those in the European Union, Democratic Republic of Korea, Israel, advancing age is a predictor of mortality [14–16]. On the other hand, there is a higher burden of TB and TB mortality in younger age groups in the LMICs. In patients in the age group of 15–44 years in rural South India, the number of deaths due to TB was found to be 12 times higher than those expected in the general population [17]. In Brazil, age < 5 years and age > 60 years was associated with two-fold and ten-fold higher odds of mortality, respectively [18]. The number of cases in the younger age group is also more than older adults in LMIC. In a population-based survey from Bangladesh, TB was the second major cause of death in the age group of 15–49 years [19]. In the Global Burden of Disease (GBD) study, the largest proportion of TB deaths worldwide (37.4%) occurred in age group under 49 years, of which 84% was contributed by the 15–49 age group [20].

According to the results of the GBD study, the age-standardized mortality and incidence of TB in males is twice that in females [21]. The reason for this is not clear but may result from differential exposure to risk factors, effects of sex-specific factors on immunity and genetic factors. However in rural cohorts from India, the age at death in women was much lower (mean age at death of 32 years) [22] and the standardized mortality ratio in women was higher than in men [17]. Deaths occur predominantly in pulmonary TB (PTB); however, some forms of extra-pulmonary TB (EPTB) such as meningeal TB have a very high rate of mortality (27–60%) documented in reports from Africa [23], India [24,25], and Denmark [26]. While multi-drug resistance (MDR) is a risk factor, the majority of deaths in patients with TB occur in those with drug-susceptible tuberculosis (DSTB). According to the GBD study 2017 results, of the estimated 1.18 million TB deaths, 1.04 million (88%) occurred in patients with DSTB [27]. Thus deaths in patients with DSTB outnumber the estimated number of incident cases of MDR-TB. In India, in the year 2015, while the estimated number of TB deaths was 422,000 the total estimated incidence of MDR-TB was around 100,000 [28]; another indication that a large number of deaths occur in those with DSTB [29].

2.2. The place distribution of TB mortality or where are patients dying of tuberculosis?

In most of the high burden countries, there is no robust VRS, and/or the completeness and accuracy of the data is questionable [4]. In 2005, less than 10% of deaths in the world attributable to TB occurred in countries with a VRS; and in South-East Asia and Western Pacific, the figures were 0.1% and 2.6% respectively [5]. In India, 85% of TB deaths are not medically certified and possibly occur at home [30]. Some of this may have been patients with undiagnosed TB, while others might have been on medication for TB and were at risk of death, but were either not identified as such by the caregivers and treatment supporters; or experienced barriers in access to appropriate care. While the notification of TB cases has now been made mandatory in many high burden countries like India, there is a need to mandate notification of TB deaths. Standard 21 of the Standards of Care for Tuberculosis in India mentions that any TB death should be subjected to Death Audit by a competent authority, and this needs to be initiated as a process [31].

2.3. The time distribution of TB mortality or when do patients die due to tuberculosis?

There is a paucity of programmatic and community-based information regarding the timing of deaths due to TB and the available information is mostly from hospital-based studies, retrospective analysis or postmortem studies. Studies from both higher and lower burden TB and HIV settings suggest that a significant part of the mortality may occur in the first eight weeks of the intensive phase of treatment; and this period has been used to classify ‘early deaths due to tuberculosis’ [29,32]. In an autopsy based studyof TB among gold miners from Africa, deaths from TB occurred within the first two months of treatment in 90% and 85% of HIV negative and positive men respectively [33]. In India in a retrospective review of programmatic data, 65% of deaths occurred in the first two months of treatment [34]. Early deaths have been reported from Ethiopia, Sub-Saharan Africa and Brazil

Fig. 1. Delays leading to disability and death in patients with tuberculosis [85] Reproduced with permission for this figure.

[31,35,36]. Early deaths during TB treatment have also been reported in a series from England [37], Israel [16] and recently from Korea [15, 38]. In a region with a high prevalence of HIV, the risk was higher in the first week of treatment [39] and the first month of treatment [35]. It is clear from these limited studies that patients diagnosed with TB require close monitoring and effective clinical care in the first weeks of treatment in the clinic and programmatic settings if the risk of mortality is to be addressed@@. (Fig. 1)

2.4. The determinants of TB related death or why do patients die of tuberculosis?

The determinants of TB related death may vary according to the epidemiological setting with respect to the burden of TB, HIV, undernutrition, and resources within the health systems. The risk factors which have been identified in a review of 33 studies of TB mortality broadly differ according to the epidemiologic setting. [40]. It was found that in high-TB incidence and high HIV prevalence settings, age > 35 years, smear-negative disease, HIV infection and malnutrition are the major risk factors. In low TB incidence and HIV prevalence settings, the risk factors were age > 50 years, smear positive disease, non-infective comorbidities, alcoholism, homelessness and injection abuse [40]. The above conditions lead to a higher risk of mortality by either contributing to extensive TB disease and/or contributing to a serious co-morbidity. HIV co-infection increases the risk of mortality 3–8 fold [40], therefore assessment of HIV status has become a routine in all newly diagnosed patients with TB and early initiation of antiretroviral therapy is now recommended by the WHO. However, the most prevalent comorbidity in high TB burden but lower HIV prevalence countries like India is undernutrition [22,41]. Studies in India have shown that undernutrition is nearly universal in Indian patients, severe, potentially fatal (with BMI of as low as 10 kg/m^2 recorded), increasing the risk of TB by 2–4 folds [22]. It is consistent risk factor for TB mortality in all regions of the world, irrespective of HIV and drug susceptibility status [40]. Studies across regions have also shown that under-nutrition poses a significant risk for early death [15,36,42–44]. In a cohort study of patients with HIV infection, the incidence of mortality was nearly two fold higher in underweight patients (BMI < 18.5 kg/m^2) compared to those with normal BMI, after adjusting for antiretroviral therapy and CD4 count [45]. Body weight < 35 kg was a major risk factor for death in patients treated under DOTS in India and in Africa [34,35,46].

The WHO has recommended that nutritional assessment should be an integral aspect of TB care and moderate to severe undernutrition in patients with TB should be addressed [47]. Anemia as a result of micronutrient undernutrition (e.g. iron deficiency) or inflammation (anemia of inflammation) or both, is common in patients with TB [48], and is often severe. In the rural cohort from India, anemia was present in 75% of patients with PTB and was severe in a quarter [22]. Anemia could contribute to morbidity due to TB and also to TB mortality [49]. Hemoglobin measurement is not a part of the routine diagnostic workup in most national TB programs of LMICs and should be made a part of routine evaluation.

Apart from the risk factors which predict death, it is also important to understand the direct cause of death in patients with tuberculosis. There have been few autopsy studies of the direct causes of death in patients with TB, and these have been predominantly in HIV infected individuals [50,51]. The proximal causes of death have been examined in a few studies based on autopsies [33,35,52]. It emerges from these studies that the causes of early deaths may differ from those occurring later. Most of the early deaths in patients with TB with/without HIV infection are attributable to TB. Opportunistic infections like cryptococcosis, pneumocystis pneumonia contribute to death in those with HIV coinfection but occurred after two months in the majority of cases (in 89% in one such study [33]. These studies have reported the causes of death as the effects of extensive TB including acute respiratory failure and disseminated TB, bacterial co-infections, and other opportunistic infections (e.g. cytomegalovirus). Bacterial pneumonia and severe bacterial infections can coexist with active TB [51] and can contribute to mortality in both the early and later phases, and in both without/with HIV infection [33,35,52]. In a recent autopsy based study, nearly half of patients with TB had coexisting bacterial disease [51]. In a study from Malawi, the frequency of bacterial infections leading to acute deterioration in patients with PTB was equal in both HIV positive and negative individuals [29]. In a study on HIV negative patients with PTB from the Philippines, bacterial co-infections were associated with a 1.7 fold higher risk of early mortality [53]. The non-TB respiratory pathogens identified in this study where a significant number of patients had coexisting lung disease were H.Influenzae, S.Pneumoniae, and M.Catarrhalis. It is also relevant to note that a sepsis syndrome may occur in patients with active TB, which may result from co-existing bacterial infection or due to TB itself which has been described as M. Tuberculosis septic shock [54]. This sepsis syndrome is associated with increased lactate levels, features of bacterial translocation and features of multi-organ dysfunction [55]. Taken together, the clinical implication of these findings is that seriously ill hospitalized patients with PTB may benefit from the addition of broad-spectrum antimicrobial therapy to reduce mortality [40,51,53].

3. Integrated patient-centered care in tuberculosis: the blind spots in the current framework of clinical care of patients with TB

Tuberculosis is caused by an infection (often drug-resistant) which causes a disease that may be life-threatening and associated with serious infective and non-infective comorbidities, in persons who may face significant barriers in access to diagnosis, treatment and prevention. TB care in the past has been largely focused on treatment of the infection, gradually evolved over time, and now the recent guidelines emphasize

Table 1
Evolution of models of care in tuberculosis: Elements and challenges.

	Infection centered model	Disease centered care	Patient centered or person centered
Elements	Anti TB treatment by effective chemotherapy	Anti TB treatment with management of TB related morbidity (severe disease, complications) and management of TB related comorbidities (HIV, diabetes, undernutrition and substance misuse)	Anti TB treatment with management of TB morbidity, co-morbidities along with responsiveness to the needs and preferences of patient
Challenges	Drug sensitivity testing and availability of drugs for drug resistant TB	Inadequate clinical evaluation, inadequate clinical care. Treatment guidelines still do not address all comorbidities	Lack of support services, Community groups of persons with TB are still in infancy

TB—tuberculosis; HIV—Human immunodeficiency virus.

a patient centered approach. Table 1 discusses the evolution of TB care to illustrate the elements and challenges in each of these models that evolved, some of which persist even in the 'patient or patient-centered care'.

3.1. Infection centered model of care

An infection-centered model of care existed till the 1980s where patients were regarded as "cases" and treatment was self-administered "chemotherapy"[3]. There were gaps in this infection-centered model, as DRTB was either not recognized promptly, or not adequately addressed.

3.2. Disease centered model of care

Since the 1990s with the onset of the HIV epidemic, the coinfection was recognized as a risk factor for TB morbidity and mortality, and later diabetes and under-nutrition were added to this list. The clinical care model thus expanded to incorporate the treatment of selected co-morbidities. In this disease-centered model, the provision of HIV treatment took many years to become a reality but there are gaps in the management of coexisting diabetes, undernutrition and tobacco-related comorbidities which is a work in progress for most programs [56–58].

3.2 Patient-centered model of care

Finally in the END TB strategy, patient-centered care entered the lexicon of TB care [59]. It has been defined as "providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions" and in the context of the END TB strategy as "tuberculosis care and support that is sensitive and responsive to patients' educational, emotional, and material needs" [59]. A recent Lancet Commission report recommended high-quality services that are "person-centered" which was defined as "holistic, individualized, empowering and respectful, encouraging informed decision making and self-determination" [60]. However, these terms are more aspirational than operational in most national programs of high TB burden settings. In operational terms, patient-centered care has been defined as care that incorporates one or more treatment adherence interventions (patient education, communication, material support including food support, and psychological support) in conjunction with treatment administration options suitable for the patient [61].

In a disease that claims millions of young lives every year, one would expect a more comprehensive model of care to emerge, addressing the care of patients who are predominantly poor, undernourished and in distress. However, the current model of care is a fragmented one with the foundation of chemotherapy at its base to which has been added the management of selected co-morbidities (chiefly HIV and diabetes) and some treatment adherence interventions. Others like undernutrition and substance misuse remain largely inadequately addressed. The result is that this current model of TB care does not offer comprehensive clinical care which addresses the infection, the disease, all comorbidities and the personal needs of the patient that would be essential to reduce TB morbidity and mortality.

4. Components of comprehensive clinical care

This requires effective chemotherapy, management of TB morbidities (including management of severe disease and complications), and management of co-morbidities (infective, nutritional and non-infective).

4.1. Effective chemotherapy

Effective chemotherapy is the one that is appropriate to the drug susceptibility profile of the infecting organism. This has been a huge challenge for TB programs in past, as they have struggled to establish drug susceptibility testing facilities. Surveillance data on drug resistance is now available with 37 of the 40 high TB burden countries [1]. Drug susceptibility testing for rifampicin has expanded, but while 80% of the diagnosed patients had access to second-line drugs, only 25% of the estimated 558,000 patients with MDR-TB globally, had access to treatment which indicates a large global gap [1].

4.2. Appropriate management of TB morbidity

This primarily includes assessment of the severity of disease and complications and its management in patients with PTB and EPTB. In any potentially fatal disease, one of the primary decisions to be made by the care providers is whether the patient is seriously ill and requires referral to an appropriate level of care. This assessment of the severity of the illness and appropriate triage is essential to prevent mortality and may include tools based on clinical evaluation of vital signs, assessment of specific organ dysfunction with laboratory (or radiological) evaluation. Some of the examples of such tools are the quick Serial Organ Failure Assessment (qSOFA) score for triage of sepsis, the CURB-65 score triage of community-acquired pneumonia. However, the current international treatment guidelines for tuberculosis or the international standards of tuberculosis care lack any recommendation on the assessment of the severity of the illness and predictors of TB mortality [62,63]. As a result, in many high TB burden countries, a patient with pneumonia may receive a clinical evaluation and an X-ray, while the evaluation of a patient with TB may be limited to sputum based tests, without a mandated clinical evaluation or an X-ray which would reveal the extent of disease.

There have been attempts to develop and validate clinical prediction rules to predict mortality risk in TB in both high and low-income countries. In countries with better access to health care and lower TB incidence, the Tuberculosis Risk Assessment Tool (TReAT) [64], a TB prognosis score for in-patients [65], and a predictive fatality score [66] have been developed with reasonable predictive ability. However, these tools are not appropriate for LMICs with limited resources as they require estimation of arterial oxygen, albumin, and X-Rays. Moreover, they have been developed in admitted patients and intensive care unit (ICU) settings, which may not be generalizable to other situations.

In the LMICs, there has been a paucity of attempts to develop clinical prediction rules and severity assessment tools for patients with active TB. These have included variables like symptoms, vital signs, nutritional indicators like the BMI, mid-upper arm circumference (MUAC), anemia and the ability to perform activities of daily living. A TB-score based on five symptoms and six clinical signs was validated and was found to be useful in predicting unsuccessful treatment outcomes [67]. It included variables such as cough, chest pain, respiratory distress, night sweats, hemoptysis, anemia, BMI, MUAC, positive chest auscultation findings, pulse-rate, and temperature. Some of these may be difficult for a frontline healthcare worker to perform. A recent improvisation on this was TBscore II which included only the cough, dyspnea, chest pain, anemia and poor BMI or MUAC[68]. Serial values of the TB score II assessed in 2 LMICs, predicted treatment failure but did not predict death consistently[68]. A simple prognosis score has been proposed recently for validation, which includes 'Clinical form of TB, Age, BMI and HIV infection' (CABI) [69]. A triage tool proposed by the national TB program in India includes one or more of the following: (BMI $\leq$ 14 kg/m^2 or BMI $\leq$ 16 kg/m^2 with pedal edema, or MUAC $\leq$ 19 cm, signs of respiratory insufficiency (assessed clinically by

breathlessness or respiratory rate > 24/min or an oxygen saturation on pulse oximetry < 94%), and an inability to stand as features which indicate high risk and a need for admission [70]. This has not been validated independently although the inability to walk unaided, and a low BMI were independent predictors of mortality in a cohort of seriously ill HIV infected patients with suspected TB [71]. Tachycardia, tachypnea and inability to walk unaided are also danger signs suggested by WHO to identify seriously ill patients with HIV disease [72].

The rationale for the inclusion of the above parameters is that they can be assessed by the community-based health worker using simple skills and equipment. The BMI indicates the severity of under-nutrition, which is an independent risk factor for death. When the BMI falls below 13 kg/m^2 in males and below 11 kg/m^2 in females, it can be incompatible with life [73]. The degree of wasting revealed by the BMI is also a surrogate for the extent of the disease, as it correlates well with the severity of TB disease [74,75]. MUAC < 20 cm was associated with a mortality rate ratio of 3.61 (95%CI: 2.38, 5,47) in a study from Africa [76]. MUAC measurements that were sex-specific (females: 18.5 cm; males: 20.5 cm) predicted mortality in patients with TB in Philippines [12]. The physical activity performance status assessed by a modified Eastern Cooperative Oncology Group scale (0–4) has the potential to be a simple and reliable predictor of early death in patients with TB in the community as well as inpatient settings [65,76]. Scores of 3 (capability for limited self-care, spends >50% of time in chair/bed) and 4 (totally confined to chair/bed) on the performance scale were associated with a mortality of 33% and 51% and hazard ratios of 4.1 (95%CI: 1.4, 12.1) and 9.1 (95%CI: 3.7, 22.3) in a cohort from Africa [77]. Even a single point increase in physical activity performance status score was associated with a 2.3 fold (95%CI: 1.8, 3.0) increase in the hazard ratio of death [78].

Patients who show signs of severe disease need to be hospitalized and programmatic guidelines to outline indications for admission for patients with severe disease will be an important step in reducing TB mortality. At present, the number of beds available for patients with TB is low even in high TB burden countries like India, often citing the lack of facilities with appropriate infection control measures. According to estimates, India has approximately 50,000 beds for tuberculosis patients, i.e. 4 beds /100,000 population while annually there are about 187 new cases/100,000 and about 39 deaths/100,000 population [79].

4.3. Appropriate management of severe disease and complications

The complications of TB include respiratory failure, pneumothorax, massive hemoptysis, pleural effusion and empyema, sepsis syndrome and multi-organ dysfunction, and rarely adrenal insufficiency. In the presence of HIV co-infection, there could be other opportunistic infections including bloodstream infections. All these complications require admission into an inpatient facility with the ability to provide skilled care for severe disease and complications.

An additional factor of relevance in the treatment of the critically ill patient with TB is the altered pharmacokinetics of anti-TB drugs given as fixed-dose combination drugs (FDCs) through the enteral route. Subtherapeutic levels of rifampicin were found in more than half of 10 patients in ICU in a study from South Africa [80]. Moreover, there are alterations in pathophysiology during ICU admission with regard to the volume of drug distribution, increased metabolism due to higher hepatic and renal blood flow and low serum proteins. This leads to subtherapeutic drug levels when injectable drugs may be preferable [81].

Reports have indicated high levels of mortality in admitted patients with severe forms of TB, with figures ranging from 28% − 53% [82,83]. Many forms of EPTB are associated with life-threatening manifestations and/or complications. Abdominal tuberculosis (perforation, obstruction, bleeding), meningeal tuberculosis (hydrocephalus, stroke, seizures, altered mental state), pleural tuberculosis (pleural effusion, empyema, pneumothorax), tuberculosis of joints (joint effusion, cold abscess, ankylosis), tubercular pericarditis (pericardial constriction) require advanced investigations and skilled surgical care. If the number of hospital beds available for TB patients is sparse, ICU facilities and specialized surgical expertise is at a premium, the care available to such patients is likely to be compromised leading to increase mortality.

4.4. Appropriate management of comorbidities

HIV co-infection and diabetes are important co-morbidities and patients with TB undergo screening for both these co-morbidities. The collaborative framework between TB and HIV is in place in most high burden countries. TB in any clinical form is a WHO clinical stage 3 or 4 event which places the patient in the category of advanced HIV disease. Therefore, all such patients with HIV-TB co-infection should receive the care package as per the recent WHO guidelines [72]. This package includes screening and preventive interventions, rapid initiation of antiretroviral therapy and adherence support. However as mentioned earlier, the most prevalent, easy to assess and reversible co-morbidity is that of undernutrition and needs to be listed among comorbidities in the International Standards of Tuberculosis Care, which should be assessed and addressed [62]. Severe undernutrition in the patient with TB needs to be managed with a standardized protocol in a similar line of severe acute malnutrition (SAM) in children, with attention to cautious feeding, hydration, supplementation of electrolytes, and vitamins.

Although food support is mentioned in the current treatment guidelines of the WHO, it is not mentioned in the context of a co-morbidity that needs nutritional therapy but as an intervention which might improve adherence [47]. This is not appropriate in countries like India, where the median weights of adult males and females with TB are as low as 42 kg and 38 kg respectively, and median BMIs are as 16 kg/m^2 and 15 kg/m^2 respectively [22]. Patients with these levels of undernutrition are all eligible for nutritional support which should be considered an essential rather than optional part of treatment. The Government of India has announced a direct benefit transfer of INR 500 ($7.50) per month to enable purchase of nutritious food but the allocation is insufficient and is beset with operational challenges [84].

5. Addressing gaps in the health system to reduce TB mortality

Each death due to TB is a preventable tragedy. The health-seeking behavior of patients, compounded by deficiencies of the health systems and low-quality care are involved in the chain of causation leading to death of poor and young patients with TB in LMIC. This is illustrated in the following figure:

It has been suggested that a TB death should be accompanied by a mortality audit comprising of community-based death review (CBDR) as well as a facility-based medical audit (FBMA) in case the patient was admitted or discharged from a hospital [85]. While CBDR gives the perspectives of the family and identifies factors along the tuberculosis care cascade which may have contributed to the death, the FBMA probes the clinical care that the patient received in the hospital. Such a mortality audit helped health facilities in Malawi reduce their death rate from about 16% to about 3% [85]. TB deaths should be accorded the same importance as maternal deaths and should be accompanied by a mortality audit, which should address the delays in health care seeking, diagnosis, treatment and quality of care.

The health system in high TB burden settings needs to be configured to achieve reductions of TB mortality. A large proportion of TB mortality occurs in those who have not been diagnosed, and universal health coverage and the availability of point-of-care diagnostics in high burden settings are important interventions that can reduce TB mortality [1]. National TB programs should provide a comprehensive risk assessment at diagnosis, identify patients for intensified follow-up and provide clear criteria for admission and referral services to enable such care. Health facilities will require tools, guidelines and skills in the management of comorbidities like severe undernutrition, and availability of intensive medical and surgical care for a limited number of patients who require such interventions.

Box 1 describes the essential and desirable diagnostic tools and therapeutic modalities, which should be available at health facilities to deal with patients with tuberculosis who require admission for management.

Box 1
Essential and desirable diagnostic and therapeutic requirements for tuberculosis

Essential Diagnostics
- Chest radiography
- Anthropometric equipment: Weighing machine, stadiometer/ staturemeter, Mid-upper arm
- Pulse oximetry
- Complete blood count
- HIV testing and Blood sugar
- Renal function tests, Liver function tests
- Blood grouping

Essential Therapeutics
- Oxygen
- Broad spectrum antibiotics, including intravenous drugs
- Non-invasive ventilation for co-existing acute type 1 respiratory failure, chronic obstructive pulmonary disease exacerbations
- Hydrocortisone, vasopressor drugs
- Multivitamins and iron supplements
- Surgical expertise: Chest tube insertion for pneumothorax and empyema
- Blood transfusion facility
- Management of severe acute malnutrition:
- Oral potassium, oral rehydration solution including rehydration solution for malnutrition, enteral feeding with F-75 and F-100 formula feeds (can be made with milk or milk powder, sugar,vegetable oil)

Desirable Diagnostics
- Blood culture
- CB-NAAT
- Serum Cortisol
- Computed Tomography

Desirable therapeutics
- Facilities for invasive ventilation
- Surgical expertise: laparotomy, ventriculo-peritoneal shunt, spinal decompression, decortications surgery
- Bronchial artery embolism for control of massive hemoptysis

6. Conclusion

TB deaths are predictable and preventable. In the era of END TB strategy, comprehensive assessment and clinical care for patients should be implemented as a key component of patient-centered care and an important intervention for the reduction of TB mortality. In countries with a high burden of TB, the poor, the young, those with extensive pulmonary disease or serious forms of the disease, and with comorbidities like HIV and undernutrition are at higher risks of deaths due to TB. It should be closely supervised in the initial eight weeks of treatment when the majority of deaths due to TB occur. Assessment for predictors of death like BMI, MUAC, performance status and vital signs should become part of the routine evaluation of patients with TB and those with critical values should be admitted for inpatient care. Referrals for patients requiring inpatient care should be strengthened and paucity of hospital beds for TB patients should be addressed. Health facilities and the staff will need to be equipped with tools and skills to deliver comprehensive clinical care for patients with severe and complicated disease, and manage comorbidities with the recommended package of care for advanced HIV, diabetes, and severe undernutrition. There is also a need for research to develop and validate simple prognostic scores that can be used by field staff, and on developing comprehensive care packages for patients with TB and comorbidities.

Author statement

AB conceptualized the manuscript structure. Both AB and MB did the review of literature and generated the first draft, worked on the revising and editing the manuscript to give it a final shape.

Declaration of Competing Interest

None.

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