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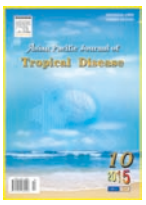

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Childhood tuberculosis in sub-Saharan Africa: A call to action

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ABSTRACT

Tuberculosis (TB) has remained a source of concern for the international community for several decades. Multi-drug-resistant TB and extensively drug-resistant TB have become impending emergencies. All these TB control challenges are magnified by HIV/TB co-morbidity. Although, there are recorded successes in the overall control of TB in adults, the level of success in children is uncertain. The high burden of TB in children is well recognised, but it is not well quantified in many endemic areas due to problems with definitive diagnosis. Childhood TB deserves special attention, because from the perspective of public health, any paediatric TB case is a sentinel event. It indicates recent infection from an adult who has the infection, and who could infect an average of 15 others in a year. It also indicates a possible severe disease and a possible future adult case. To the extent, childhood TB is prevalent, to that extent has TB control failed in the community where the childhood case came from. The objective of this review is to examine all aspects of childhood TB with a view to highlighting the management challenges and making recommendations.

1. Introduction

1.1. Burden of tuberculosis (TB)

TB, which has been known by the names of consumption/phthisis and white plague in the past, is a typically chronic granulomatous and highly infectious disease due to infection by members of the *Mycobacterium tuberculosis* (*M. tuberculosis*) complex (MTBC)[1]. It is one of the world's most widespread infections with a carriage rate of about 30% of the world's population[2], with a worldwide prevalence of close to 15 million. Close to 10 million new cases of TB per year occur worldwide, which translates to about 20 new cases per minute[2].

In 2012, 1.3 million deaths were notified worldwide–close to 3 800 deaths per day[3]. TB is, thus, the leading infectious cause of death worldwide, after HIV/AIDS[3,4], and it is the leading cause of death among the HIV-infected[4].

Data from the pre-chemotherapeutic era show that, without adequate treatment, TB kills about one-third of the patients within one year of diagnosis. The five-year mortality rate has been shown to be 65% among sputum-smear positive cases[5]. About 60% of the remainders undergo spontaneous remission while the other 40% will continue excreting bacteria[6]. Current studies show a 10-year case with fatality rate of 70% for sputum-smear positive cases and 20% for sputum-smear negative but culture-positive cases[7].

1.2. Social burden of TB

TB has been described as a social disease with medical aspects[7]. Just as the disease is fuelled by poverty, it is also known to perpetuate poverty, thereby creating a vicious circle[7]. This is consequent on the fact that 75% of the victims are in the economically productive age

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group[7,8]. The disability-adjusted life years from TB is very high and varies from country to country and is in accordance with age group and sex[9]. The worldwide TB disability-adjusted life years among females is 17 million[9]. The family cost of TB, in addition to loss of productive life, can involve sale of assets to offset treatment costs, family separation, cost of transport to health facilties and high burden of orphaned and neglected children[10]. In 2009 alone, 10 million children were orphaned as a result of parental deaths caused by TB[11].

1.3. Distribution and determinants of TB

TB results from infection by members of MTBC: *M. tuberculosis, Mycobacterium africanum, Mycobacterium bovis, Mycobacterium bovis* bacillus Calmette-Guerin (BCG), *Mycobacterium microti, Mycobacterium caprae, Mycobacterium canettii* and *Mycobacterium pinnipedii*. *M. tuberculosis* and *Mycobacterium africanum* have been found to be responsible for a vast majority of TB cases in the African environment[12]. Reservoirs of the infection are infected humans and cattle[13].

Ninety-eight percent of all cases of TB in children are acquired via the respiratory route[12], and the most important vehicle of transmission is the droplet nuclei which is the residue of solid material left after drying up of droplets generated by TB cases while talking, coughing and sneezing[3]. Patients remain infective until successfully treated. Smear-positive cases are most infective, though smear-negative cases are also infective[2-4]. Each case of active TB in an adult infects up to 15 persons in one year[2-4].

It follows that the major determinants of occurrence of childhood TB in endemic areas include the adult prevalence value, which is estimated at about 30% in Nigeria but can be up to 70% in some other endemic areas[14]. The smear-positive rate, which is reported to be about 56% in Nigeria, is another determinant[2-4]. Most infection transmission is by adults[1,2], though infection transmission by children is gaining significance[15,16]. Infectivity from any source has been shown to reduce by 90% following 48 h of effective antimicrobial therapy[7].

There are no definite seasonal variations in incidence and prevalence[8]. Males are generally more affected than females[10]. Most cases of TB in endemic areas occur in rural and semi-urban areas[7]. In the urban areas, cases are concentrated more in the slums[7].

There are differences in the susceptibility of different age groups to disease following infection[16]. Close to 50% of infants will develop disease if infected while this chance reduces to about 25% in the 1–5 year age group[17]. Infected infants have an excessively high TB morbidity and mortality, and most cases of disseminated TB and central nervous system TB occur in this age group[16]. Considerable mortality and morbidity still occur at age 1–4 years[16]. While age 5–10 years is associated with the least morbidity, there is a sharp rise in morbidity and an ever-increasing incidence of adult-type disease as from age 10[16]. Incidence and prevalence of TB have been shown to be enhanced by immunocompromising co-morbidities, including HIV infection, cancers, malnutrition, tobacco smoking, steroid therapy, alcoholism, measles, and diabetes mellitus[7].

Most cases of TB are concentrated in 22 developing countries, where there is a strong association with poverty, inadequate environmental sanitation, illiteracy, malnutrition, overcrowding, terrorism, internal displacement, civil strife and other low socioeconomic factors[1,2]. Among these high burden countries, 13 of the 15 highest *per capita* incidence rates of TB are in the sub-Saharan African sub-region[14], and it is also in this sub-region that there are more than two-thirds of the world's HIV burden resides[14]. Furthermore, this sub-region carries up to 30% of the worldwide mortality burden of TB[3].

2. Special epidemiological indices of TB

2.1. Incidence and prevalence of childhood TB

Childhood TB can constitute up to 25% of the TB burden in many of the endemic countries[16]. In Africa specifically, 20%–40% of the TB case load is borne by children[14]. This situation is the result of two main factors: the broad-based pyramidal population structure which places a large number of children at risk of infection from a smear-positive adult[12], and the greater tendency of children to develop disease following exposure[16].

In addition to the high morbidity statistic, childhood TB deserves special attention, because from the perspective of public health, any TB case in a child is a sentinel event; since it indicates recent infection from a contact who, potentially, could infect an average of 15 others in a year[2,17]. It, thus, indicates on-going infection and transmission, which is mainly through the agency of the adults and adolescent children within the community[17,18]. The extent of epidemic control in the community is therefore mirrored in the incidence of childhood disease in the community[17,18].

Though the high burden of TB in children is well recognised, it is not well quantified in many endemic areas mainly due to problems with definitive diagnosis[12]. This statistical defect in endemic areas demands rectification.

2.2. Prevalence of HIV-TB co-infection

Sub-Saharan African children still constitute the vast majority of the current 3.4 million children living with HIV/AIDS worldwide[19]. The convergence of HIV and TB in sub-Saharan African sub-region has made the TB epidemic so devastating and out of control in these areas[20].

2.3. Prevalence of multi-drug resistance

Multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) have become impending emergencies because it tends to render TB untreatable and more fatal[12]. The World Health Organization (WHO) is therefore setting machineries for early detection of such cases, with a view to rapidly treating them and so to preventing their spread[11]. Poor treatment compliance and ineffective infection control measures form the background for the emergence of the MDR-TB epidemic[12].

Worldwide, 5% of all newly diagnosed TB cases are MDR-TB; an estimated 500 000 new cases occur *per annum* and a fraction of these MDR-TB cases are usually XDR-TB[21].

In children, MDR-TB more commonly, results from infection/re-infection with multi-drug resistant organisms, rather than resistance

mutation[21]. Therefore, the prevalence of multi-drug resistance in the adult population still translates to the prevalence in paediatric population via transmission[5].

3. Pathogenesis of childhood TB

3.1. General stages and timeline of childhood TB development

There are three basic stages of disease development–exposure, infection, and disease[20]. These three stages of disease development may not be so distinct in childhood TB diseases occurring in endemic areas, partly because of the high level of community-based transmission[22]. In all age groups, not every exposure to tubercle bacillus results in infection, and not every infection results in disease[22,23]. About 90% of immunocompetent adults who become infected by the tubercle bacillus do not develop the disease throughout their lifetimes; only about 10% do[17].

In children, the lifetime chance/risk of progression of infection to disease is generally higher but highly variable, depending on the age of the child when the infection occurred[18]. MTBC infections occurring in children under 2 years are usually followed by development of TB in close to 50% of the cases[20]. In all age groups, most of the life-time risk of progression to disease occurs in the first two years following infection[22]. Ninety-five percent of childhood infections that should progress to primary disease do so within the first 12 months post-infection[22]. Therefore, disease occurring later than 12-months post-infection is most likely to be post-primary TB, irrespective of the age of the patient[20].

In older childhood age groups, the tendency of progression to disease approaches the adult trends, as only 15% develop disease following infection; and the progression to extrapulmonary and complicated disease is slower, allowing reasonable time for diagnostic detection[20].

Following MTBC infection, the timeline for the development of TB and its complications in infants and children is fairly predictable[17]. Although massive lymphohematogenous dissemination leading to miliary or disseminated disease occurs in a small proportion (0.5% to 2.0%) of infected children, these severe forms of the disease occur quite early after the infection[20]. Thus, TB meningitis and disseminated TB occur within 3–6 months; TB lymphadenitis and endobronchial TB tend to develop within 3–9 months; clinically significant pleural effusion occurs in months to years; osteoarticular disease tends to occur within the next few years; and renal TB takes a few decades to develop[20].

3.2. Pathogenetic factors

Certain bacterial, environmental and host factors are known to determine the outcome of exposure to MTBC organisms[7].

3.2.1. Lipid, carbohydrates and protein contents in cell wall of tubercle bacilli

Many of the pathological attributes of MTBC can be explained by contents of the cell wall: lipids, polysacharides and proteins[24]. These lipids contribute to MTBC characteristics like poor uptake of aniline dyes, acid fastness, hydrophobicity, chemical and drought resistance, acid and alkaline resistance, immunogenicity, granuloma formation, cording and tuberculin sensitivity[24].

3.2.2. Host genetic factors

Polymorphisms in certain host genes, notably natural resistance-associated macrophage protein 1, histocompatibility leukocyte antigen, interferon (IFN)-γ, T cell growth factor, interleukin (IL)-10, mannose-binding protein, IFN-receptor, Toll-like receptor 2, vitamin D receptor, and IL-1, determine resistance/susceptibility to MTBC[24].

3.2.3. Bacterial genetic factors

Different MTBC strains, as characterized by IS*6110* restriction fragment length polymorphism, have been shown to possess various virulence properties as reflected in differences in transmissibility, ability to suppress Th1 response, tendency to preferentially evoke specific cytokines, including TNF-α, IL-10 and IL-6[24]. Variable expressions of specific microbial genes, including *KatG* and *rpoV*, have been found to play fundamental roles in determining MTBC survival[5].

4. Clinical features of childhood TB

The relevant combination of clinical features depends on the type and site of disease[22]. Involved sites may be pulmonary or extrapulmonary, although both sites are frequently involved[22].

4.1. Primary and post-primary pulmonary TB

Primary TB cases are asymptomatic in up to 50% of cases, but radiological features and tuberculin sensitivity are commonly present[22]. Symptoms are more likely to occur in infants and are least likely to occur in school age children[22]. In the symptomatic cases, generally, the initial presentation of primary TB is most commonly pulmonary, and includes non-productive cough and mild dyspnoea[22]. Specifically, in infants with primary pulmonary TB, pulmonary symptoms and signs are uncommon, although wheezing and decreased breath sounds may still accompany local bronchial obstruction[22].

Systemic symptoms and signs like fever, night sweats, weight loss, listlessness and anorexia are less common in children, although symptomatic infants tend to present with some of these[22]. However, initial presentation in all childhood age groups can also be with features of extrapulmonary involvement or those of disseminated disease[22].

Post-primary disease occurs more commonly among adults and adolescents[22]. It is uncommon among young children[24]. Incidence in children is usually from age seven[22]. In post-primary disease, the typical symptoms of TB are accentuated, and cough is more productive but physical signs may still not be pronounced or may be even absent even in the presence of large cavities[22].

4.2. Extrapulmonary TB

Generally, extrapulmonary TB occurs in about 30% of paediatric *M. tuberculosis* infections, compared to 15% of adult cases[22]. Many cases of extrapulmonary disease co-exist with pulmonary disease

and *vice versa*[22]. The coincidence rate depends on the type of extrapulmonary disease[22].

4.2.1. TB pleuritis

Pleural effusion occurs in 2%–38% of all cases of TB in children. The localized and small pleural effusion that commonly accompanies primary infection is asymptomatic and it resolves spontaneously[22]. Larger and more clinically significant pleural effusion do occur, though it is uncommon in young children[22]. This complication is usually unilateral but could also be bilateral[25]. TB pleuritis is more common in post-primary TB and in adolescent age group; and in this age group, the effusion is parapneumonic[26]. Pleural effusion presents with an acute onset of fever, transient chest pain that is worsened by deep inspiration and shortness of breath[22]. The signs of pleural effusion include tachypnea, decreased breath sounds, dullness to percussion, and sometimes, mediastinal shift[17]. Tuberculin skin test is usually positive in 70%–80% of cases[22].

4.2.2. TB lymphadenitis

The commonest extrapulmonary TB disease in HIV-seronegative children is lymphadenitis (also known as scrofula) and is usually unilateral[27]. The tonsillar, anterior cervical, posterior cervical, submandibular nodes and supraclavicular nodes are the usual sites; however, the posterior cervical and supraclavicular nodes are most commonly involved[22]. The involved nodes are enlarged, painless, non-tender, and usually discrete[22]. In late and severe cases, they could become matted and draining caseum in fistulous tracts could form[5]. HIV infection is a risk factor[5]. Systemic signs and symptoms other than a low-grade fever are usually absent, except in the HIV-infected patients[26]. The tuberculin skin test is usually reactive[27].

4.2.3. Disseminated TB

Lympho-haematogenous seeding of MTBC organisms from primary foci is usually asymptomatic and may be the first presenting form of TB, especially in infants and the severely immunocompromised[27].

However, some cases of release of organisms into the bloodstream are accompanied by fever, hepatosplenomegaly, and lymphadenopathy, as well as features of involvement of many other organs[22]. Some of the other organs include the brain, bone marrow, bones, joints, kidneys and skin (as papulonecrotic tuberculid lesions)[27]. Disseminated TB if untreated is associated with high mortality[28].

4.2.4. Central nervous system disease

TB meningitis is the presenting form of TB in 5%–10% of children under 2 years, and the frequency of this form of TB drops to less than 1% after age 2[22]. It is also the presenting form in up to 40% of cases of disseminated TB[28]. Onset of disease is insidious[27]. Clinical features in children include low-grade persistent fever, malaise, anorexia, weight loss, headache, weakness, hepatomegaly, splenomegaly and generalized lymphadenopathy[22]. This stage with non-specific features has been referred to as the first stage[29]. Stage two is characterized by neck stiffness, altered deep tendon reflexes, demonstration of choroid tubercles by fundoscopy, and cranial palsies[22].

Altered consciousness, seizures and focal neurological signs characterize the third stage[22]. Corroboratory findings include a moderate lymphocytic pleocytosis, low glucose level, an elevated protein concentration, abnormal chest radiographs in 50% of cases and tuberculin reactivity in about 50% of cases[22].

4.2.5. TB pericarditis

TB pericarditis occurs only in 0.5%–4.0% of TB cases in children and arises either by direct invasion or through lymphatic drainage from subcarinal lymph nodes[22]. It usually presents with non-specific symptoms, including low-grade fever, malaise, night sweats and weight loss[30]. However, pericardial friction rub, distant heart sounds and pulsus paradoxus may be present while chest pain is unusual[22]. The pericardial fluid is typically serofibrinous or hemorrhagic and rarely Ziehl-Neelsen positive. Pericardial fluid culture could be positive in 30%–70% of cases[27]. The bacteriologic yield from pericardial biopsy is higher than that from pericardial fluid[22].

4.2.6. Cutaneous TB

Cutaneous TB constitutes 1%–2% TB cases[22], and presents as either hypersensitivity skin lesions and/or as lesions caused by direct effect of the pathogens[31]. True cutaneous TB infections include lupus vulgaris, TB verrucosa cutis, cutaneous miliary TB, cutaneous primary TB, TB cutis orificialis[32]. The hypersensitivity lesions, referred to as tuberculids, are papulonecrotic tuberculids, lichen scrofulosorum, erythema induratum[32]. Involvement of the skin in lymph node or osteo-arthritic TB is referred to as scrofuloderma[32].

4.2.7. TB of the gastrointestinal tract

Included in this group are TB enteritis, and the rare painless tuberculous ulcers on the mucosa, palate, or tonsils that are associated with enlargement of the regional lymph nodes[5]. TB oesophagus, usually due to high inoculum ingestion of MTBC or tracheo-oesophageal fistula in a pulmonary tuberculosis patient, is also rare, along with TB parotitis[5].

TB enteritis, also acquired by swallowing MTBC-laden material or by the haematogenous route, presents as chronic abdominal complaints like diarrhoea, constipation, pains, low grade fever, in association with weight loss and a positive tuberculin skin sensitivity test[22]. In this disease, shallow ulcers form in the Peyer's patches of the terminal ileum and around the appendix[33]. There are usually associated features of mesenteric adenitis which may be complicated by intestinal obstruction and peritonitis[22].

Peritonitis could also result directly from haematogenous spread, in which case, it will be generalized, rather than localized[22]. Sometimes, a non-tender mass lesion could result from matting of the nodes, the omentum and the peritoneum[22].

4.2.8. Genitourinary TB

Disease usually starts silently with only haematuria and sterile pyuria[22]. Dysuria and/or flank abdominal pain are associated with prolonged disease[22]. Intravenous pyelogram often shows unilateral mass lesions within the renal parenchyma, multiple filling defects, along with features of possible complications like hydronephrosis, dilated ureters and ureteral stricture[22].

4.2.9. Congenital TB

Congenital TB used to be a rare form of TB but the incidence in TB endemic areas has increased, mirroring the HIV-TB epidemic[12,34]. The transmission may be transplacental or perinatal following aspiration of the pathogen from infected amniotic fluid of a mother who has TB[35,36]. If transmission is transplacental, the primary complex is located in the liver and porta hepatis while aspiration-based disease has the primary complex in the lungs[37]. They usually present before three months with lymphadenopathy, hepatosplenomegaly, ascites, tachypnoea, feeding problems and lack of weight gain[27,37]. The index of suspicion is raised by active maternal TB during the pregnancy and poor response of the neonate to treatment[16,37]. Confirmation can be effected by histopathological examination of the placenta[37]. Fatality is common and occurs within two months, because the disease progresses rapidly and disseminates early[35]. However, with early detection and institution of six months of combination therapy, response is good[37].

5. Diagnosis of childhood TB

5.1. Diagnostic approaches

In sub-Saharan Africa, TB diagnoses have been based on certain validated traditional criteria for decades. These could be grouped into clinical, bacteriological, immunological and radiological criteria[38]. More recently, molecular techniques have been validated for diagnosis of drug-sensitive and drug-resistant cases[11].

5.1.1. Clinical features-based diagnostic approach

In the absence of laboratory facilities, as is frequently the case in endemic areas, diagnosis of childhood TB could still be made with reasonable certainty, followed by commencement of full course of anti-TB therapy, if the presenting patterns in the communities are carefully studied[38]. The cases diagnosed this way are classified as "case of TB", as opposed to "case of definite TB"[12].

The clinical features included in the criteria include cough, history of contact, fever, lymphadenopathy and weight loss[38]. Clinical follow-up is also a valuable diagnostic tool that further improves diagnostic accuracy[16].

The challenges of clinical criteria include the fact that up to 50% of primary TB cases show no presenting symptoms[22]. However, for symptomatic cases, sensitivity is high though specificity is low[12,39].

5.1.2. Bacteriological approach

Bacteriological approach is the oldest and most specific diagnostic method, and includes acid-fast smear microscopy and mycobacterial culture of a wide range of specimens[16]. The commonest specimens include sputum, gastric aspirates, pleural aspirate/biopsies, cerebrospinal fluid, *etc*.[29]. Direct sputum smear microscopy is the most widely used test for the detection of pulmonary TB cases[40].

Sputum samples may be collected by expectoration or by ultrasonic nebulization (induced sputum)[40]. Three early morning specimens have been proven to be of great value because of the high concentration in the mornings and the intermittent release of exudates into the airways[41]. In order to ensure compliance and shorten the time to diagnosis, however, the Nigerian TB control programme uses the "spot-morning spot" sputum collection protocol to collect three specimens[42].

Yet, serial double sputum specimen examination on the same day of clinic visit ("front loading") is currently recommended by WHO for HIV-TB co-endemic areas, where TB burden is fast over stretching the healthcare system[40]. Although, smear microscopy is usually the only available test in endemic areas, the sensitivity is very low (10%–15%) in children[22,43]. Though culture is more sensitive, the value is still limited (30%–40%)[22,43].

5.1.3. Immunological methods

Included are tuberculin tests, several serological tests, IFN-γ release assays, BCG and several skin patch tests[44-47].

In 2011, WHO generated and meta-analyzed a wide range of evidences, based on WHO statements that emphasized the unreliability of serological diagnostic tests and their unsuitability for application in the national TB control programme algorithms[11].

5.1.4. Radiological methods

Radiological findings have always occupied an important place in the diagnostic assessment of pulmonary TB in children, because even when clinical features are minimal, radiological features tend to be prominent[48,49]. The relevant features, suggestive of pulmonary TB, include hilar lymph node shadows, para-tracheal shadows, pulmonary infiltrations, pulmonary consolidations, fibrocystic/cavitary changes, calcifications, nodules (tuberculomas), hyperinflation, atelectasis, and pleural effusion[50].

5.1.5. Molecular techniques

Nucleic acid amplification techniques of various formats have been validated for diagnosis of TB from specimens and this seems to be recommendable for paucibacillary cases, as in children[51]. Two nested real-time PCR assays have been endorsed by WHO for programmatic application, and are capable of distinguishing between drug-sensitive and drug-resistant TB[52,53]. Line probe assays are deployed at central laboratory level; while Gene Xpert MTB/RIF are for application at peripheral laboratories[52,53].

5.2. Case classification of childhood TB

While the details of the diagnostic methods are beyond the scope of this review, the unreliable nature of each method in affecting a definite diagnosis of paediatric TB is well known[16]. Consequently, TB case classification systems, based on combination of findings from each of the methods, have been developed by WHO[11].

There are three broad case classification systems that are recommended by WHO; two are for diagnostic purposes while one is for directly observed treatment strategy (DOTS) registration/treatment monitoring purposes[11].

In the commonest system used by national TB control programmes, every case being assessed for TB could be grouped into one of three categories: suspected TB, probable TB, and confirmed or definite TB[12]. The three TB case categories are based on the diagnostic

criteria used[11,42]. Suspected TB is based on history of contact, cough, and non-response to antibiotics[11,42]. A case of "probable TB" satisfies the criteria for suspected TB and also has positive tuberculin skin test result or suggestive chest radiograph, histopathological report or favourable response to specific antituberculous therapy[11,16], whereas an impression of "confirmed TB" is bacteriological[11,16,42]. It is recommended that every effort be made to achieve confirmed TB diagnosis[38].

Cases diagnosed using the score chart (adapted from the WHO guidelines by the Nigerian Health Ministry to enhance diagnostic recovery of childhood TB) are also probable TB[42]. WHO recommends that the scoring system be used as a screening tool only and not for making a firm diagnosis[38].

Another case classification for diagnostic purposes is based on smear microscopy result[11]. In this format, a diagnosed TB case should be classified as smear-positive pulmonary TB, smear-negative pulmonary TB, or extrapulmonary TB[54,55]. A smear-positive case is defined as one in which at least 2 sputum smears are acid-fast bacilli positive while in smear-negative TB, criterion for smear-positive case is not satisfied but culture is positive or the diagnostic score is significant[42,54]. This definition has been recently revised by WHO, in that one positive smear is now acceptable for defining a smear-positive case in endemic areas[56]. Extrapulmonary TB is defined as a TB case which involves organs other than the lungs[54].

By category of DOTS registration on diagnosis and for treatment monitoring purposes, cases should be classified into new cases, treatment failure cases, cured cases, treatment completed cases, return-after-default cases, and relapse cases[11,42].

There are other case classification systems in use. Cases may also be classified into drug-susceptible or MDR-TB[11]. For treatment monitoring purposes, the MDR-TB cases can also be categorized into cured, completed treatment, treatment failure and others as in drug-susceptible cases[11]. However, consultations are still on-going with a view to achieving consensus[11].

5.3. An overview of the issues of TB diagnosis in sub-Saharan Africa and most endemic areas

Generally, there is yet no satisfactory diagnostic reference or diagnostic standard for childhood TB diagnosis[16]. While bacteriological diagnosis has been known to be very specific, the sensitivity in children is low, usually less than 50% at best[22,43]. This is due to poor specimen quality and the paucibacillary nature of TB in this age group[22,43]. The low bacteriological yield of specimens from childhood TB cases is always compounded by TB/HIV co-morbidity[57]. The high specificity of bacteriologic diagnosis (smear microscopy or mycobacterial culture or both) is, however, of importance, because a positive result from most specimens is adequate for definitive diagnosis and initiation of treatment. The search for reference standard continues[11].

With the exception of bacteriological criteria, none of the listed validated traditional diagnostic approaches can achieve a definite diagnosis of childhood TB; and this is because of their low specificities[16]. The diagnostic challenge is compounded in TB-endemic areas (including sub-Saharan Africa). The challenges specific to endemic areas stem from: community-based rather than individual-based TB transmissibility, the high prevalence of childhood diseases that are radiologically similar to TB, and the high non-tuberculous mycobacteria prevalence[17,58]. These challenges lead to a relative failure of previously validated diagnostic criteria (which respectively include positive history of exposure, suggestive chest-X-ray findings, and positive Mantoux test) for accurate detection of childhood TB disease in endemic areas[16,17,58]. Diagnostic criteria in endemic areas require redefinition.

In the national TB control programmes, there is much emphasis on demonstration of smear-positivity (as a marker of infectiousness). Smear-positivity is difficult to demonstrate infectiousness in children[22,43]. Thus, though the millennium development goals-target of detecting 70% of the estimated smear-positive cases has been met, the proportion of childhood cases in this success is uncertain[4,11,39]. Moreover, the belief that children do not contribute significantly to disease transmission is getting obsolete, at least, in endemic areas[15]. Targets of control programme require redefinition, along with diagnostic criteria.

Currently, paediatric TB diagnoses in most centres in Nigeria rely on a clinical scoring system, which is associated with significant false positivity, and according to WHO, yields diagnoses of "probable TB" at best[11,16,38]. The program does not prescribe the utilization of any other specimen other than sputum[42]. In fact, a cursory observation of activities in most centres show that little effort is being made in achieving bacteriologic diagnosis in these centres. Even, culture that has a better sensitivity than microscopy is being mystified as a preserve of National Reference Laboratories. This is unnecessary because while culture is skilled-labor-intensive, it is not capital-intensive. Pathogens causing TB in children also require isolation and specific characterization.

While effort should be made to enhance bacteriological diagnoses not just for diagnostic purposes but also for research purposes, molecular diagnoses should be available to every child at peripheral laboratory levels. Currently, in the few centres where GeneXpert MTB/RIF is available, children under 5 years are systematically excluded because of the exclusion of gastric aspirates (and specimens other than sputum) from the standard operative procedures. The administrative focus of Xpert MTB/RIF on HIV/TB co-infection ensures that only sputum specimens from HIV-infected children are readily accepted. National guidelines need to be revised to address this issue in clear terms.

6. Treatment, control and prevention of TB

6.1. General principles of TB control

Since 1995, treatment strategies have been programmatic and the programme packages have been combinations of environmental control, diagnostic, therapeutic and preventive measures[11,16].

Such strategic packages include the directly observed therapy, short course (DOTS), stop TB strategy, International Standards for TB Care (2nd edition), patients's charter for tuberculosis care, and practical approach to lung health[11,16,55]. All these packages and more, are operational to various extents in all TB-endemic areas; and they

are designed to control TB at the four levels of prevention, namely, primordial, primary, secondary and tertiary levels[7].

6.2. Summary of TB control issues at each level of prevention

6.2.1. Primordial level: Creating an anti-TB environment

At the primordial level of prevention, the general population and the environment are the targets, and the overall goal is to create a TB-deterrent physical, human and social environment[59]. Good people-oriented governance should be put in place to eliminate poverty, enable empowerment of the people to take charge of their health care and to effect adequate budgeting for health including TB control programmes[59]. In Nigeria and many other endemic areas, there is zero social security expenditure on health[60].

Only 5.4% of the GDP is spent on health, and a larger proportion of this is actually from non-governmental sources, and the proportion of external resources for health is rapidly dwindling[60]. With escalating national security challenges, the statistics are not likely to change for the better, unless definite steps are taken.

6.2.2. Primary level: Protecting the individual from MTBC-infection and disease

6.2.2.1. General measures

At primary level, the target population is the healthy people and the goal is to prevent incidence of TB. Prevention at this level involves both general measures and specific measures; and health education and immunization are key activities[59]. As part of primary health care, behaviour change communication should address avoidance of overcrowding, ensure adequate ventilation, better personal habits with regard to spitting and coughing, and good nutrition[7,13].

6.2.2.2. Specific measures: Vaccines and immunization

Immunization of infants using BCG vaccine is part of the national programme on immunization[61]. This vaccine is currently the only WHO-approved one and it does not have full protective effect[62]. It, however, can protect from severe disease; and this accounts for its continued routine use in endemic areas[62]. However, HIV-infected patients should not be given BCG, since they are prone to disseminated BCG disease[63].

The apparent unreliability of BCG vaccine has prompted the search for other vaccines[64]. The public-private partnership formed by stop TB Department of WHO and dedicated to the development of new TB vaccines is called "Aeras" which was set up in 2002[11]. Since then, up to 9 prospective vaccines have been developed and are at various stages of clinical trials[11]. Some of them are modified BCG, while others are entirely new[64]. Out of all the candidate vaccines, modified vaccinia Ankara DNA vaccine has completed phase I clinical trials[64]. It is also doing well in phase II, along with a few others[64]. One or two of these is expected to enter phase III in the next two or three years with a prospect of becoming an approved vaccine by 2020[4,11].

6.2.2.3. Specific measures: Chemoprophylaxis

For patients, like children under 2 years and HIV-infected patients who are at risk of developing active disease, if infected, isoniazid preventive therapy is administered as soon as it is confirmed that they have been infected with MTBC[65]. It is essential that TB is ruled out in these patients before commencing isoniazid preventive therapy[65]. Duration of treatment stipulated by Nigerian TB control programme is 6 months, although other authorities state that it should not be less than 9 months[42,66].

The practice, in endemic areas, of treating only patients who have the disease or those who are at increased risk of developing it, is attributed to resource limitations[23]. In developed countries, patients with MTBC infection are treated, even though they might not have developed TB[23,38]. This practice should be implemented worldwide, so that the fight against TB will be won. Care is needed, in all instances/settings, to differentiate between infection and disease. This further underscores the need to strengthen bacteriologic diagnosis in all approved treatment centres.

6.2.3. Secondary level: Early case detection and treatment

Secondary prevention is the most fundamental aspect of TB control[40]. Although it is directed at the individual patient, it is the most important step towards breaking the transmission chain[38].

6.2.3.1. Early case detection

In addition to usual case-finding strategies, a strategy known as FAST is currently being implemented with a view to finding suspect cases actively and separating them for diagnosis and treatment[67]. In order to forestall an epidemic of MDR-TB and XDR-TB, the WHO now endorses detection of drug-resistant TB (by Xpert MTB/RIF) at the time of initial evaluation of the patient[4,11]. The WHO also recommends that bacteriological confirmation should be achieved as much as possible, followed by drug susceptibility testing[38]. Furthermore, surveillance studies to assess the prevalence of MDR-TB and XDR-TB have been made essential for every country, community and institution, before treatment programmes are designed[68].

6.2.3.1.1. Early case treatment: Approach to drug-sensitive TB

Diagnosed cases are channelled to DOTS[42]. Every case is classified as new case, relapse, treatment failure or return-after-default, and treatment regimes are adapted to the case class[42].

Among Nigerian children, treatment-naive cases are treated with 2HRZ/4HR regime: 2 months of initiation therapy using isoniazid, rifampicin and pyrazinamide, and 4 months of continuation phase therapy using isoniazid and rifampicin[42]. Direct observation, community-based TB care and other necessary methods are employed in ensuring adherence to treatment schedules[42]. One notable step is the production of formulations specific for childhood TB therapy[11]. The Green Light Committee of the WHO sees to it that high quality drugs are available in order to prevent programmatic failure[11,55].

6.2.3.1.2. Treatment approach to drug-resistant TB

The approach recommended in the last review of the Nigerian guidelines is: initiation phase treatment of 3 months of isoniazid, rifampicin, and pyrazinamide, and 2 months of streptomycin; and the continuation phase treatment consists of 5 months of isoniazid and rifampicin[42]. Other authorities have recommended treatment durations of up to 2 years, on a patient-to-patient basis[66,68]. This approach is being replaced by use of regimen consisting mainly of second-line drugs, which are selected from Groups 2 to 4, with adequate consideration of their susceptibility test results, costs, and

the side effects[66,68]. To this end, the WHO has classified drugs used in the treatment of TB into five groups. Group 1 are the first-line drugs of proven efficacy and low toxicity, and are coded as HRZE (H for isoniazid; R for rifampicin; Z for pyrazinamide, and E for ethambutol)[66,68]. Group 2 anti-TB drugs include the aminoglycosides (streptomycin, amikacin, and kanamycin) and capreomycin, a polypeptide antibiotic[66,68]. Group 3 agents include the fluoroquinolones, *viz.* moxifloxacin, gatifloxacin, levofloxacin and ofloxacin[66,68]. Ciprofloxacin has been removed as an agent for TB treatment[66,68]. Group 4 agents include ethionamide, prothionamide, cycloserine, terizidone and para-aminosalicylic acid[66,68]. In Group 5, thiacetazone and high-dose isoniazid are included[66,68].

However, susceptibility test results of pyrazinamide and ethambutol have not been found to be reliable, and the clinical efficacy should be the basis of assessment[66,68]. In its use for MDR-TB treatment, doses of ethambutol could be raised to 25 mg/kg, in order to harness the bactericidal effect[25].

Generally, in the treatment of drug-resistant TB, "the Union" recommends that treatment should be in line with susceptibility test results and should continue for a minimum of 12 months after the last positive culture[25].

6.2.3.1.3. Treatment approach in special situations: HIV-TB co-morbidity and complicated cases

According to the national TB control programme, drugs used in the management of children with severe cases like disseminated TB and miliary TB should include streptomycin[42,65]. Such cases should be monitored clinically, as fever usually responds in 2–3 weeks[42,65].

Among HIV patients with confirmed active disease, the same treatment regimens are used although there is a need for closer follow-up because of the increased risk of adverse reactions, intolerance and drug interactions[69]. Therapeutic drug monitoring has been advocated, in order to make up for the sluggish pharmacokinetics in the HIV-infected[69]. In newly diagnosed HIV and TB cases, anti-TB treatment is always indicated, but the commencement of anti-retroviral therapy (ART) depends on the CD4 count[42,65].

The Nigerian TB control programme advocates the use of rifampicin throughout the treatment[65]. In the design of the ART regimen for patients with HIV-TB co-morbidity, severely interacting ART drugs, such as the protease inhibitors, should be avoided; and there should be a replacement of nevirapine with efavirenz[65]. Nevirapine and protease inhibitors are associated with virologic failure if used together with rifampicin while efavirenz is not[2,13]. Furthermore, according to the global plan to stop TB 2011–2015, cotrimoxazole preventive therapy should be instituted on any diagnosed HIV-TB cases[65]. The treatment regimen may have to be modified for those with other co-morbidities, including renal and hepatic diseases[65].

Adjunct steroid therapy could be indicated in meningeal TB, in order to prevent the development of an internal hydrocephalus; in severely ill miliary TB cases, in order to provide symptomatic relief; and in TB pericarditis cases, in order to reduce the risk of constrictive pericarditis and the need for subsequent surgery[65,69].

7. Summary of recommendations

Efforts should be committed to achieving precise, accurate and prompt diagnosis of childhood TB in endemic areas. Improved diagnosis will lead to generation of more reliable disease statistics and better epidemiological characterization, with a view to effecting better control in the paediatric age group and ultimately in the general population.

Since incidence of childhood TB is an indicator of open TB in the adult contacts, TB in children can be used to monitor the efficacy of national TB control programmes in the communities.

National guidelines need to address the regular use of Xpert MTB/RIF on all children with suspected TB; and standard operative procedures should be developed to accommodate paediatric specimens other than sputum, especially gastric aspirates and cerebrospinal fluid.

The focus on MTBC disease control, rather than MTBC infection control, in endemic areas has been on for too long. Such an approach is at best a stop-gap measure and is obsolete. TB including MDR-TB should be addressed as a public health crisis, and control policies should tend to be more wholistic. Every infection should be treated, whether it is causing disease or not.

The subjects for clinical trials in the course of the search for new drugs and vaccines should include children under 5 years.

Conflict of interest statement

We declare that we have no conflict of interest.

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