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Tracing the Children in Contact of Sputum Smear Negative Adults is the Need of the Hour to Achieve WHO "Stop TB Strategy"

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Tuberculosis has been a public health issue affecting a large number of population world wide. 1According to 2019 report, approximately 10 million of people fell ill by the disease around the globe. A considerable proportion of TB affected cases is constituted by paediatric patients solely. The WHO estimates that about 1 million children endure the disease each year of which a significant figure harbours the latent form of infection. Since, the accurate diagnostic test to confirm the tuberculosis in children has not been unrolled, a positive history of contact is regarded as the foremost feature for authenticating the diagnosis in children. A large proportion of children with tuberculosis lives under the same roof with sputum smear positive adults, tracing out the childhood TB cases in sputum smear negative contacts is equally important and needs to be diagnosed timely. This category of children left undiagnosed acts as a pool for further transmission of the disease from where new TB cases arise. Therefore, the early diagnosis of children of this group is the need of the hour and a challenge to "STOP TB Strategy".

Keywords: Adult; Contact; Tuberculosis; Tracing; Sputum negative.

Tuberculosis has tormented humanity since beginning and [2]contributes to be one of the top ten infectious causes of deaths worldwide [3]competing with HIV. [4]Tuberculosis puts to end the life of about 2 million people every year and is [1]considered to be the commonest cause of morbidity from a single infectious pathogen.

[2,5]According to the most recent survey done in 2018, the estimated deaths of tuberculosis are 1.2 million in HIV negative patients and 251000 in HIV positives. [6]As per WHO statistics 2011, India has the highest load of tuberculosis with incidence magnitude of 2.2 million cases out of a global incidence of 9.6 million. [7]Tuberculosis affects all geographical regions and all age groups, a considerable fraction of which is constituted by paediatric population. [2]In 2018, tuberculosis influenced about 1.1 million children globally with deaths of approximately 205000 children with HIV. Thus the affliction of the children living with tuberculous adults particularly those with positive sputum smear is the affair to be looked for. However, the number of infected and diseased children living with sputum smear negative contacts is not negligible. [4]This becomes more evident at young age (<3 years) with low socio-economic background and severe malnutrition.

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This article reviews the chances of children getting infected from the sputum smear negative adult TB contacts and the strategy for early diagnosis of these children with the help of conventional and pioneering aids.

Historical milestones

[8]The term "tuberculosis"has been coined by Johann Schonlein in 19th century. [4]Based on the trailblazing molecular biological measures, it has been approximated that this disease is not less than 15000 years old (Webb GB,1936). However, the *Mycobacterium tuberculosis* has been estimated to be in existence for more than 150 million years. [9]The disease is known by the term *King's evil* in France and England, [8]*Pthysis* in ancient Greece, *Tabes* in ancient Rome and *Schachepheth* in ancient Hebrew.

[4]A major twist in the grasp of the disease arrived when Robert Koch discovered its causing organism and delineated its staining characteristics. [10]By this time, tuberculosis had killed one out of every seven persons living in US and Europe. [11]Hence, the commencement in locating the cure was the discovery of the cause of tuberculosis by Robert Koch in 1882. Afterwards, the introduction of the sanatorium in Europe was the mainstay of the treatment which enhanced the awareness of the infected patients regarding the spreading nature of the disease and motivated the public health measures. Gradually, the drugs with anti-tuberculous action came into existence and ensured the cure to the disease if diagnosed timely.

[12]Tuberculosis had been viewed as a disease of adults by many physicians. However, it has been a paramount root of morbidity and mortality in young children in TB endemic areas. [4,13]The infected children serve as a pool for further transmission of the disease in community and generate new TB cases.

Epidemiology

Global scenario

[4]Tuberculosis has been a public health trouble despite of the presence of highly effectual medical therapy, approachability to the vaccine and discovery of *M.tb* years ago.

[14]According to the most recent report of WHO published on 14th October 2020, about 10 million people (range 8.9-11.0 million) had been estimated to become ill by tuberculosis globally in 2019. Approximately 1.2 million (range 1.1-1.3 million) subjects had lost their lives among HIV negative people in 2019 (a reduction from 1.7 million in 2000) and 208000 people (range 177000-242000) among HIV positives (a reduction from 678000 in 2000). About 56% of people developing TB in 2019 were men (>15 years of age) whereas 32% was constituted by women and 12% were children (<15 years of age). The South-East Asia, Africa and the Western Pacific were the zones where most of the people developed TB in 2019 accounting 44%, 25% and 18% respectively. Eight countries of the world had been viewed to carry two-third of the load of total TB cases and India was one among them with the magnitude of 26%.

Indian Scenario

[15] In India the mean prevalence of all embodiments of tuberculosis is approximated to be 5.05 per thousand. The prevalence of positive sputum smear cases is 2.27 per thousand. [16] It is noteworthy that 45% of TB epidemic in India is put up by sputum smear negative pulmonary and extra pulmonary tuberculosis of which around 15-20% is contributed by immunocompromised individuals.

Tuberculosis in children cohabiting with tuberculous adults (Sputum smear positive Vs negative)

[17] The WHO approximates that around 1 million children get infected by tuberculosis every year and around 2,30,000 children lose their lives. One-tenth of the estimated 10 million subjects world wide who developed TB in 2017 was contributed by children. [18]The WHO report 2014 divulged 1 million new victims of tuberculosis among children ensuing 136000 deaths of which 40,000 were HIV positive.

Tuberculosis is now regarded as an utmost cause of death in children below 5 years and among top ten causes of mortality globally in this age group. [19]A child with tuberculosis in a community constitutes non-fulfillment of the tuberculosis control program in that community. This may be due to the fact that authenticating diagnosis in children is challenging as the [18]diagnosis in children seldom rests on the bacteriologic confirmation. [3]Among the children enduring tuberculosis, it is often observed that the main offender of the transmission of the disease is positive adult who continues to lay out the infection to the children

dwelling in close contiguity and proves to be a single most important feature of diagnosis in children so far.

[3]Benjamin R et. al (2003) remarked that the occurrence of discrete forms of tuberculosis among children cohabiting with adult contacts was12.5% with contacts of positive sputum smear pulmonary disease, 7.7% with sputum smear negative pulmonary disease and 6.2% with extra-pulmonary disease

[20]In a study conducted in 2018 on 80 children cohabiting with sputum smear positive tuberculosis, 30.2% had +1 sputum positivity while 46.5% and 23.3% had +2 and +3 sputum positivity respectively. The active disease was established in 8.8% children contacts while 33.3% had latent disease. However, a huge proportion of children has been ignored to be evaluated who live with sputum smear negative contacts. This group is regarded to be more threatening as these children act as reservoir for latent TB infection from where fresh TB cases can arise.

[21]A systematic review regarding contact investigation of children exposed to tuberculosis in South East Asia disclosed that the infection among child contacts was higher (24.4-69.2%) in the age group of less than 15 years than active TB disease (3.3-5.5%). However, the disease was more accustomed among children less than 5 years of age whereas TB infection was more prevalent in older children.

[22]A study conducted by Israr et. al on children <12 years of age for tracing out the contacts of TB infected children. Among 129 children studied, 60 (46.51%) children were in household contacts of 23 sputum smear negative and 69 (53.49%) children were in household contacts of 25 sputum smear positive adults with pulmonary tuberculosis. Among 30 (23%) diseased children, one-fourth were in contacts of negative sputum smear cases and the remaining belonged to the smear positive adults. 40 children among them were Montoux positive (31%) of which one-third were in close contiguity with sputum smear negative adults and 22.58% cohabiting with sputum smear negative adults were discovered to be infected ($p < 0.05$).

[23]Another study conducted by Singh on 200 adult patients, 100 sputum smear positive and 100 sputum negative with total 281 children in contact. 30 out of 95 tuberculin skin test positive children belonged to the sputum smear negative adults. The chest radiograph was congruous to the positive tuberculin outcome in 9 children, 7 of whom were in close proximity with the sputum smear positive adults and the rest two with the sputum negative ones. However, of the 95 tuberculosis afflicted children, 23 children were cohabiting with adults who were sputum smear negative.

[24]In a systematic review held in Netherland for 8 years (1996-2004) in 392 groups with a sum of 1285 patients, 12.6% of the secondary cases were transmitted from a patient with sputum smear negative. The fraction of the transmission rate among patients with sputum negative tuberculosis in comparison to sputum positive was 0.24 (at 95% confidence interval, 0.20-0.30). The contact tracking delineated that 26 (6.2%) of the 47 sources as identified by the Municipal Health Services had sputum smear negative tuberculosis.

[25]The mortality rate is higher in TB patients with concurrent HIV infection than non HIV cases, particularly those with sputum smear negative pulmonary and extra pulmonary tuberculosis owing to the delay in diagnosis of sputum negative subjects. As a consequence, a delay in initiation of treatment will expose the cohabiting children for longer duration to get afflicted.

It is noteworthy that tracking down the adult contacts in childhood tuberculosis is the primary line-up. The overhead exemplars demonstrate that drawing attention to just the sputum smear positive contacts does not suffice the need to check the transmission of disease among children as a remarkable figure of children is getting afflicted by *M.tb* by sputum smear negative cases. Therefore, neglecting out this group underdiagnosed may lead to the failure of the WHO 'STOP TB Strategy'.

Diagnosis

[26]The childhood tuberculosis is usually paucibacillary in nature, hence the treatment of children with tuberculosis is not regarded a priority by Tuberculosis Control Programmes. A vast TB burden lies on the heads of paediatric population solely. The extent of the childhood TB load is well conceded but not well mensurated in many TB endemic areas. In countries like Sub-Saharan

Africa and India, the TB endemic is fueled by wide spread immune compromised conditions, low socio-economic status and malnutrition. Undoubtedly, recent advances in technology have upgraded our knowledge in diagnostic fields, however, establishing the diagnosis of latent and active TB in children is yet challenging and relies on clinical and radiological basis supported by positive H/o contact and tuberculin skin test. [27,28]The mimicry of the disease with other common childhood conditions (like generalised viral and bacterial infections, pneumonia, malnutrition and HIV), inability of children to dispel out sputum, [29,30,26,31]vague clinical presentation and lower bacterial load (smear negative) contribute to difficulty in diagnosis of TB in children by conventional techniques particularly in smear negative cases. Therefore, the new diagnostic methods have been evolved which play an important role and provide an ease in diagnosis.

Polymerase Chain Reaction

[32]PCR being an in vitro technique, amplifies the specific DNA sequences and detects the disease in samples with negative microscopy and culture. The diagnostic rate of PCR is 100% for culture positive specimen and 76.7% for negative smear samples. However, [30]the accuracy of the laboratories, cost factor, need for the advanced equipments limit the use of PCR in many developing countries.

In-House Nucleic Acid Amplification Assay

It has been proved by some reports that this technique can diagnose the TB in children with positive clinical signs but negative culture by way of DNA extraction and amplification. But the inference of its performance in children population is confounded by dearth of specific and sensitive reference standards.

Adenosine Deaminase

It is a non microbiological technique that provides a novel tool for the diagnosis of TB. The sensitivity of this method is 100% for pulmonary tuberculosis in pediatric population with specificity of 90.7%. However, it differs broadly in case of extra pulmonary TB and is less useful than the multiplex PCR .

Serology

[32]It has a little role in diagnosis of tuberculosis in children. The specificity is high with poor sensitivity as results can be altered by a number of factors like age, BCG vaccination and exposure to atypical mycobacteria.

Interferon Gamma Release Assay

[33]This immune-based test has substituted the tuberculin skin test for diagnosis of latent TB infection, being more specific to the M.TB than purified protein derivative. The commercial tests in this method are Quantiferon TB-gold (QFT-G) and enzymed linked immunospot assay (ELISPOT). QFT-G is found to be more specific then TST even in children who are malnourished. [34]Studies suggest that the development of the active TB disease can be predicted by IGRA thus illustrating the role in preventive therapy to some contacts.

Gas Sensor Array Electronic Nose

This innovative approach uses electronic smell sensors by detecting the change in each sensor's electrical characteristics when exposed to particular odour (sputum with mycobacterium). However, the significance of this test in diagnosis of chilhood TB is yet to be explored and substantiated by further studies.

DISCUSSION

Tuberculosis has put to end the lives of millions of children worldwide especially those dwelling in close contiguity to the TB affected adults. [4]Young age, low socioeconomic status and severe malnutrition have powerful coalition with infection and active TB disease. Malnourished children are precarious of developing the disease owing to their enfeeble immunity. Infection itself upshots the failure to thrive ushering the child to malnourished state which further sets up the infection leading to the fully established disease. [21]Screening children living in close contacts of tuberculosis cases is invariably advocated but seldom implemented in TB endemic areas. The early diagnosis and commencement of preventive therapy will check the progression from infection to active disease. Despite of the advancement in the investigative techniques, the diagnosis of childhood TB is yet challenging in many developing countries owing to the limited resources and inaffordable cost needed for these tests and therefore [35]banks on the meticulous and rigorous guaging of all the relevant aspects derived from a conscientious history and clinical examination. The systematized approaches need to be assimilated into existing guidelines and

plan of action developed by National Tuberculosis Control Programmes. Bringing down the burden of tuberculosis in children requires commuting and ameliorating many existing exercises such as those related to contact investigations. [4]In antecedent studies,the prevalence of childhood tuberculosis was represented by lower number of cases owing to the inclusion of only sputum smear positive adult contacts and disregarding the sputum negative cases. However, it is presumed that sputum smear negative cases harbour the infection and relay it to healthy persons although the spreading tendency is infrequent.

The aforementioned article scrutinizes the significance of sputum smear negative adult contacts in context to the childhood tuberculosis. It was remarkably noticed that the figure of infected and diseased children exposed to the sputum smear negative tuberculous adults is not trifling, hence, neglecting this category of children is erroneous. This discards and refutes the preceding concept that only open cases can pass the infection.

[36]Tackling tuberculosis in paediatric population requires to address all the risk factors that make the child vulnerable to infection by *M. tb* including those with sputum negative adult contacts which is often overlooked. [37]Spotting diagnosis and managing tuberculosis in children effectually will not only bring down the child's ailment and death but can also have a pronounced effect on TB epidemic in the community.So, in order to deal a child as TB suspect, unearthing the contacts must be the utmost target be it sputum smear positive or negative.

CONCLUSION

[38]This article deduces that despite of the availability of highly efficacious treatment, up to the minute diagnostic techniques and various ongoing National Tuberculosis Control Programmes, childhood tuberculosis remains a paramount global health concern in developing countries. This is imputed to the ignorance of tracing the contacts who are sputum smear negative and only the sputum positive subjects are taken into reflection and managed. However, it is evident from the aforementioned article that a large paediatric population harbours the infection living in contact with sputum smear negative adults but remains underdiagnosed and further becomes the source of new TB cases. Therefore, as a paediatrician, it is our concern to realise the dire need to hold out the bottom of the ice-berg i.e. the children's reservoir of tuberculosis lying in the kins of family. Once its top is attained as index case, the endeavours to control the morbidity and mortality will be made. Only then the goal of 'Stop TB Strategy' will be achieved and accomplished successfully.

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