Editorial

Childhood tuberculosis

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Children less than 15 years of age in developing countries represent 1.3 million cases and 450,000 deaths annually from tuberculosis (TB)[1]. The incidence of TB in children indicates recent transmission of disease which is almost dependent on presence of sputum positive adult cases[2]. Resistant TB in children reflects resistant TB in adult contact. Development of secondary resistance in primary TB in children is extremely rare because of its paucibacillary nature[2]. Therefore prevention of multi-drug resistant TB in children involves proper control of adult TB[2],

Incidence rate is defined as "the number of new cases occurring in a defined population during a specified period of time"[3]. In Sri Lanka, TB incidence rate in the 0-14 age group has remained fairly constant from 1996-2000. It was 3.7, 4.3 and 3.7 cases per 100,000 population in 1996, 1998 and 2000 respectively[4].

The greatest impact on rising TB case rates in adults has been the HIV epidemic[5]. There have been very few paediatric cases of documented coexisting TB and HIV infection[6]. However, children with HIV infection are more likely to be in contact with HIV-infected adults with TB and are susceptible to tuberculous infection and disease.

Tuberculous infection without disease is the preclinical stage of infection with *M. tuberculosis*[7] Tuberculin test is positive but chest x-ray is normal and child is free of symptoms or signs. *Tuberculous disease* occurs when clinical manifestations of pulmonary or extrapulmonary TB become apparent, either by chest x-ray or clinical signs and symptoms[7]. The word *tuberculosis* usually refers to disease. Incubation period between asymptomatic infection and development of symptomatic disease can vary between 1 and 6 months in children[8]. Although in older children classic triad of fever, weight loss and night sweats can be seen, presentation in children under 5 years of age can vary from signs and symptoms of miliary TB and tuberculous meningitis, to a symptomatic hilar adenopathy found secondary to a contact investigation[9]. Extrapulmonary TB has a relatively high incidence in children, occurring in approximately 25% cases of TB in children under 4 years of age[8].

A positive tuberculin test is the hallmark of primary infection with *M. tuberculosis*. In most children, tuberculin reactivity becomes apparent in 3-6 weeks but may occasionally take up to 3 months after initial infection[8]. Tuberculin reactivity caused by infection with *M. tuberculosis* usually remains for the lifetime of the individual even after preventive chemo-therapy[10,11]. Previous BCG vaccination is not a contraindication to tuberculin skin testing. A reactive area greater than or equal to 10mm induration in a BCG- vaccinated child most likely indicates infection with *M. tuberculosise*. The BCG test is useful in tuberculin negative TB[12]. Its specificity has been established by Datta and Sep[13]. An induration of 15 mm or greater in a BCG vaccinated child indicates probable infection with *M. tuberculosis*[14].

Direct microscopic evaluation of sputum and other clinical specimens for acid-fast bacilli (AFB) with culture confirmation remains the gold standard for diagnosis of TB[7]. Traditional culture media for *M. tuberculosis* are egg-based (Lowenstein Jensen) and agar-based (Middlebrook) incubated in 5-10% CO_2 for 6-8 weeks[15]. Using radio-labelled components in liquid media, the BACTEC system detects growth of AFB radiometrically by measuring release of CO_2, This system reduces time to recover mycobacteria and a report can be obtained in 8-14 days[16]. The yield from cultures of early morning gastric aspirates from children with pulmonary TB is approximately 40%[15]. Broncho-alveolar lavage samples are no more likely to recover *tubercle bacilli* than cultures of gastric aspirates[17].

Many studies on successful detection of TB antigens by ELISA, latex-particle agglutination and radioimmunoassays have appeared[15]. Most tests appear to be rapid, sensitive and specific but validation in a large series of patients with culture proven disease remains to be done. Polymerase Chain Reaction (PCR) is a technique of DNA amplification that uses specific DNA sequences to serve as markers for presence of micro-organisms and is, in theory, capable of detecting a single organism in a biologic

specimen such as sputum, lavage fluid, CSF, pleural fluid and blood. Large studies from clinical laboratories have demonstrated specificity of PCR assays[18.19]. 2 studies using PCR specimens from children have been reported[20,21]. 2 PCR-based methods of finger- printing *M. tuberculosis* have been developed recently. They are called ampliprinting and mixed-linker PCR[22,23].

Two major. actions of anti-TB drugs include their bactericidal effect and prevention of emergence of resistance to other drugs. Isoniazid and rifampicin are bactericidal agents that kill tubercle bacilli in all environments and are effective in preventing emergence of resistance to other drugs[8]. Pyrazinamide is bactericidal but has little effect on preventing resistance. It exerts its maximum effect on organisms during first 2 months of therapy rather than throughout duration of treatment[8]. Streptomycin is bactericidal for multiplying organisms but is less effective in preventing resistance[8]. Ethambutol is not bactericidal but is effective in preventing emergence of resistance to other drugs[8].

Over past 2 decades a number of therapeutic trials have demonstrated that 6 month chemotherapy courses are effective in childhood TB. American Academy of Paediatrics has endorsed a standard therapy for pulmonary TB in children that includes 6-months of isoniazid and rifampicin supplemented during first 2 months with pyrazinamide. It is optimal to have medications administered daily for first 2 months, with remainder of the 6-month regimen administered twice weekly under direct observation of a health care provider (DOT)[24]. Controlled clinical trials for treatment of extrapulmonary TB in children are limited. American Academy of Paediatrics recommends 6-month chemotherapy for extrapulmonary TB except for disseminated disease, bone and joint infection and tuberculous meningitis where 12 month-therapy is recommended including isoniazid, rifampicin, pyrazinamide and streptomycin for 2 months followed by 10 months of isoniazid and rifampicin[24].

Optimal duration of isoniazid for preventive therapy in children is controversial. European trials in adults with tuberculous infection demonstrated that a total of 12 months duration of preventive therapy with isoniazid was more effective than a 6-month regimen. A comparable controlled trial in children has not been performed. American Academy of Paediatrics currently recommends a 9-month course of isoniazid preventive therapy in childrew[24].

It is proven beyond doubt that BCG provides protection against dissemination of TB[23]. However, inability of BCG to prevent primary infection necessitates research for a better vaccine which will not only prevent natural infection or exogenous forms of TB but also destroy dormant bacilli in various lesions to prevent their endogenous reactivation.

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