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Editorial

Childhood Tuberculosis – a new era

Recently there has been renewed interest in childhood tuberculosis (TB) with it acknowledged as constituting a substantial burden of the global TB caseload. Childhood TB contributes approximately 15 to 20% of all cases, increasing to up to 40% in some high TB burden countries. [1,2] Moreover, it is increasingly appreciated that the epidemiology of childhood TB reflects the success or failure of TB control programmes, as paediatric TB is usually acquired from an infectious adult contact. While the global TB control strategy has focused predominantly on smear positive cases (and therefore not on paediatric TB which is usually paucibacillary and smear negative), the World Health Organization (WHO) has instituted a policy of reporting childhood TB cases for 2 age groups, those 0-4 years and 5-14 years. [3] In addition, global guidelines on the management of TB in children and also in HIV-infected children have recently been published, including a revision of recommended drug dosages of the first-line TB drugs for children.[4]

The wealth of scientific research has provided a more accessible and robust knowledge base for evidence-based TB diagnosis and management, with establishment of free web based resources for TB (www.tbevidence.org, for example).[5] Renewed interest in prevention of childhood TB has focused on the development of improved vaccines, and on specific preventative strategies in HIV-infected children including early use of antiretroviral therapy and isoniazid prophylaxis. Increased global funding for research especially in the areas of diagnosis, management, and vaccine development has further enabled advances in childhood TB. Recognizing these advances, the Stop TB Partnership's New Diagnostics Working Group and the DOTS Expansion Working Groups have both created special childhood TB subgroups to advance the field.

It is therefore appropriate that this edition of the journal provide an update on childhood TB. Infants, young children and HIV –infected children of all ages have an increased risk of developing disease following infection with *M tuberculosis* and a higher risk of disseminated or severe disease. Delineating the immunological responses to infection are key to understanding such susceptibility to infection or disease, to developing measures that correlate with protection and appropriate immunodiagnostic tests and to evaluating the efficacy of new vaccines. In the first paper, Jones *et al.* review the many factors involved in containment of infection and the age related differences in responses, highlighting the need for further research in this area [6].

TB in children may be difficult to definitively diagnose due to non-specific clinical and radiological signs, paucibacillary disease, and lack of capacity for microbiologic diagnosis. Increasingly, TB has been recognised as a cause of *acute* pneumonia in children that is difficult to clinically or radiologically distinguish from other pathogens. In addition, childhood pneumonia is often caused by multiple pathogens; co-infection with *M tuberculosis* and other organisms may further complicate diagnosis. Diagnostic uncertainty has been compounded by the HIV epidemic in which chronic lung disease, anergy and non-specific clinical and radiological signs make definitive diagnosis even more challenging. Ling and Pai review immune based diagnostic tests for childhood TB [7]. Currently available serological tests should not be routinely used for diagnosis of childhood TB as there is insufficient evidence to support their use in children; adult studies have found wide variability in the reliability of current assays, and the WHO is considering a negative policy recommendation to curb the abuse of these serodiagnostics in many developing countries. Furthermore, interferon-gamma release assays (IGRA) do not seem to offer substantial improvements over the tuberculin skin test (TST) for the diagnosis of latent or active TB infection in low and middle income countries except possibly in HIV-infected, very young or malnourished children. Both tests appear to have only modest predictive value for progression to TB disease, and this means the search for novel predictive biomarkers has to continue. [8] However, a positive TST or IGRA in a young child contact of an adult case must be taken seriously and preventive therapy must be initiated if the child has no evidence of TB disease.

Definitive microbiologic diagnosis and antimicrobial susceptibility has become increasingly important in children given the issues of pill burden, adherence and the emergence of drug resistant isolates. The article by Nicol and Zar addresses advances in microbiological diagnosis in children [9]. Sputum induction has increasingly been shown to be useful and safe and provides a good specimen for microbiologic confirmation even in infants.[10] Recent data suggest that sputum induction may be feasible in primary care settings. Development of capacity for microbiologic diagnosis in children at all levels of health care systems is needed. The use of new, rapid molecular based diagnostic tests on suitable specimens offer further promise. [8] However, a reliable, affordable point of care test for childhood TB still remains elusive.

Recent revisions of treatment guidelines have highlighted the need to use higher doses of TB drugs. Graham reviews changes in treatment guidelines [11]; widespread implementation of these will be important. Higher drug dosages are now recommended for treatment of childhood TB, based on pharmacokinetic evidence. [4] Providing appropriate therapy including fixed drug combinations that contain such higher TB drug doses remains a challenge. The paediatric incidence of multidrug resistant (MDR) disease, in which *M tuberculosis* is resistant to both INH and rifampicin, is unclear due to lack of microbiologic data, but worldwide the incidence of MDR cases is approximately 3 to 4% of the TB caseload.[12] Schaaf and Marais address the challenges of treating

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drug resistant TB in children, and provide practical management recommendations [13].

The resurgence in TB incidence has been driven by the HIV epidemic, with dual epidemics occurring in a number of low or middle income countries. [1] Marais *et al.* address the issues of TB and HIV co-infection in children, including prevention and treatment [14]. HIV-infected children have a much higher risk for developing TB compared to immunocompetent children[15]; the risk may be reduced by use of INH prophylaxis and by HAART[16,17]. Conversely, TB accelerates the progression of HIV. Dual treatment of TB and HIV remains difficult due to pill burden, potential for side effects, adherence issues and drug interactions. The use of HAART is now advocated early as soon as a child is diagnosed with HIV, but adjustments in antiretroviral therapy may be needed with concomitant TB treatment especially when rifampicin is used, as this reduces levels of protease inhibitors and some NNRTIs. [4] Immune reconstitution inflammatory syndrome (IRIS) occurring in the context of unrecognized TB infection or during TB treatment remains a particular challenge in HIV-infected children who commence antiretroviral therapy, as this must be distinguished from drug resistant TB and from other infections.[18]

Hawkridge and Mahomed discuss the prospects for a safer, more effective TB vaccine [19]. While Bacillus Calmette-Guérin (BCG) vaccination is widely used and effective for preventing disseminated disease, it offers variable and incomplete protection against pulmonary disease and is contra-indicated in HIV-infected children due to the risk of severe, disseminated BCG. [20] These authors discuss progress in the development of new candidate vaccines, which may offer the best hope for TB control, in combination with better diagnostics and shorter treatment regimens.

Development of better diagnostic, treatment and preventative strategies for childhood TB still remains a great challenge. However, there is much to be optimistic about, as suggested by recent advances that are highlighted in this edition of the journal, and by increased funding for research in these areas. Political will and commitment to strengthening of national programs for childhood and adult TB and to HIV services will be crucial for global progress in managing this epidemic. As the knowledge base and evidence for improved diagnostic and management strategies for paediatric TB increases, so implementation of these will be crucial. Clinicians have a key role to play in implementing newer policies and technologies, not only to provide improved care of their patients, but also to control TB at a global level.

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