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A research agenda for childhood tuberculosis

Improving the management of childhood tuberculosis within national tuberculosis programmes:

research priorities based on a literature review

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Improving the management of childhood tuberculosis within national tuberculosis programmes: research priorities based on a literature review.

This review was produced by the Stop TB Department and the Department of Child and Adolescent Health and Development of the World Health Organization

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[1] Organized under the auspices of the DOTS Expansion Working Group (one of the seven working groups of the Global Partnership to Stop TB). Its goal is to reduce the global burden of mortality and morbidity caused by TB in children.

Contents

Abbreviations

AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ARTI	annual risk of tuberculous infection
BCG	Bacille Calmette-Guérin
CXR	chest X-ray
DOTS	"brand name" of the international TB control strategy
EMB	ethambutol
HIV	human immunodeficiency virus
INH	isoniazid
NTP	national tuberculosis programme
PAS	para-aminosalicylic acid
PCR	polymerase chain reaction
PPD	purified protein derivative
PZA	pyrazinamide
RMP	rifampicin
RTT	response to treatment
SM	streptomycin
TB	tuberculosis
TU	tuberculin unit
WHO	World Health Organization

Preface

"…a joint meeting of the Tuberculosis Association and the British Paediatric Association was held, and, in spite of the friendly spirit evident, it was clear that each party viewed the problem in an entirely different light. The Tuberculosis Association members quoted figures from their official returns, both of morbidity and mortality, which were at total variance with the clinical experience of the paediatricians, and in the main their conclusion was that "childhood tuberculosis is not of great importance to the public health services", and their plea was for the paediatricians to preserve a sense of proportion!"
Gaisford, 1946

"Physicians dealing with adults, either as individuals or in populations, knowing how great is the reservoir of infection in any given country and the implications of this for children, will want to spend as much of their resources as possible on problems relating to adults. But paediatricians are faced with the need to treat children and naturally wish to protect them from infection and so cannot avoid being concerned with these urgent human problems. Each must understand the other's position."

Miller, 1973

The new WHO Stop TB Strategy reflects the importance of the need to improve care for children with TB: the aim of the Strategy is to "ensure equitable access to care of international standards for all TB patients – infectious and non-infectious, adults and children, with and without HIV, with and without drug-resistant TB" (WHO, 2006a). The new Strategy also highlights the importance of research in the global campaign to Stop TB. The launch of the Stop TB Strategy therefore provides a timely opportunity to promote a prioritized research agenda for improving the management of childhood TB within national TB programmes (NTPs).

Summary

Childhood TB is a neglected aspect of the TB epidemic, despite constituting 20% or more of the TB case-load in many countries with high TB incidence. This "orphan disease" exists in the shadow of adult TB and is a significant child health problem, but is neglected because it is usually smear-negative and is thus considered to make a relatively minor contribution to the spread of TB. In order to redress this neglect and integrate childhood TB into the mainstream of TB control activities, research priorities are identified that will assist in improving the prevention and management of childhood TB as a part of national TB programmes (NTPs). The proposed research agenda seeks to better define childhood TB, to optimize the treatment of childhood TB and to identify the best management practices by which childhood TB can be accurately documented and recorded, and efficiently managed within NTPs.

At the outset it should also be recognized that HIV/AIDS is not only responsible for the exacerbation of the TB epidemic in many developing countries, but has also added another element of difficulty to the diagnosis and management of TB in young children.

The main elements of the proposed research agenda (*Fig. 1*) are:

1. Carry out a prospective evaluation of the incidence and burden of childhood TB in different communities, making use of the diagnostic criteria (as defined in line with WHO policy) for suspecting and diagnosing childhood TB. Evaluate trends in case detection of childhood TB making use of data already available within some NTPs. Study the annual risk of tuberculous infection (ARTI) in young children.

2. Evaluate new methodologies to aid the diagnosis of *Mycobacterium tuberculosis* infection and TB disease in children. Evaluate the Mantoux skin-test response in HIV-infected and non-infected children. Determine the proportion of children dying of suspected TB who do actually have TB, e.g. through postmortem studies.

3. Review existing published studies of the treatment of TB and the pharmacokinetics of antituberculosis agents in childhood. Evaluate the pharmacokinetics of the "first-line" and "second-line" antituberculosis agents under different conditions of nutrition across a range of ages, accompanied by studies of drug-drug interactions and drug toxicity, particularly in HIV-infected children who are receiving antiretroviral treatment. Evaluate rates of adherence, treatment failure, recurrence and relapse in children with and without HIV; and evaluate 3- and 4-month regimens of treatment in paucibacillary forms of childhood TB, and the necessity for longer treatment in HIV-infected children. Determine the most effective treatment of disease caused by resistant bacilli. Assess how best to promote compliance with treatment and the role of family members.

4. Determine the numbers of HIV-infected and non-infected children in contact with both sputum smear-positive and smear-negative adults, both HIV-infected and non-infected, that might qualify for chemoprophylaxis in different communities; and the value of conventional chemoprophylaxis with isoniazid compared to shorter, multidrug chemoprophylaxis in both HIV-infected and non-HIV-infected children. Explore different methodologies to ensure compliance with recommendations for chemoprophylaxis. Determine the use of chemoprophylaxis

for the close childhood contacts of adults with both sputum smear-positive and smear-negative drug-resistant TB. Evaluate TB chemoprophylaxis in sexually active adolescent with TB and HIV co-infection.

5. Evaluate the needs for and availability of qualified staff and different diagnostic investigations at the various levels of care under different circumstances. Evaluate the quality of routine NTP data and its value in documenting the community burden of childhood TB. Determine how best to promote the process of recording and reporting childhood TB and the integration of the data into the national reporting systems. Evaluate the accuracy of classification of individual cases. Evaluate the role of the private sector in the management of childhood TB. Evaluate family-centred services and clinics for the management of TB and the management of children with TB within a family-oriented approach.

6. Document the complications of BCG immunization in children and evaluate the most appropriate means of managing these complications. NTPs play a key role in the preparation of vaccine trial sites for the evaluation of new TB vaccines.

The value of these studies would be maximized if carried out at a number of centres throughout the world under a variety of different epidemiological conditions.