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Editorial

Challenges and opportunities to improve tuberculosis care for Indonesian children

Stephen M. Graham[1,2,3], Bintari Dwihardiani[4], Felisia Felisia[4], Raspati Cundarani Koesoemadinata[5], Nina Dwi Putri[1,6], Bachti Alisjahbana[5], Trisasi Lestari[7], Finny Fitry Yani[8,9], Rina Triasih[4,10]

Tuberculosis (TB) is a common cause of hospitalisation and death in Indonesian adults and children, which also causes catastrophic costs to patients and their families. In 2023, the estimated annual incidence of TB in Indonesia was 387 cases per 100,000 population, with a case fatality ratio of 13%.[1] Following a marked drop in reported cases during the COVID-19 pandemic, there were 804,800 TB cases recorded by the *Indonesian National TB Program* in 2023, the highest number ever reported.[2] Indonesia is placed second to India on the *World Health Organization* (WHO) list of high-burden countries for TB and is one of just ten countries also listed by the WHO as high-burden for multidrug-resistant/rifampicin-resistant (MDR/RR) TB and for TB and human immunodeficiency virus (HIV) co-infection (TB/HIV).[1] The detection and treatment coverage of MDR/RR TB has increased sharply as access to molecular WHO-approved rapid diagnostics (mWRDs) has improved.[2] MDR/RR TB represents 2.2% of new and 25% of previously treated TB cases.

Tuberculosis (TB) notifications in children (<15 years) in Indonesia account for approximately 15% of the total caseload, with more cases reported in younger (<5 years) than older (5-14 years) children.[1,2] This age-related pattern is expected, as young children are a high-risk group for developing disease following infection.[3] High TB treatment success rates are achievable in children but are below the global average.[2] It is estimated that most TB-related deaths occur in children with TB who are untreated because they are undetected. The incidence of TB in children will reflect the prevalence of TB in the community, which is high overall in Indonesia, although varying between settings, with some of the variability thought to reflect differences in diagnostic practices.[4] An external review in 2022 reported that wide implementation gaps persist in Indonesia,

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From University of Melbourne Department of Paediatrics, Royal Children's Hospital[1] and The Burnet Institute[2], Melbourne, Australia; International Union Against Tuberculosis and Lung Disease (The Union), Paris, France[3]; Centre for Tropical Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Central Java[4]; Research Center for Care and Control of Infectious Disease, Universitas Padjadjaran, Bandung, West Java[5]; Universitas Indonesia[6] and Vital Strategies[7], Jakarta; Department of Maternal and Child Health, Dr. M. Djamil Hospital[8] and Department of Child Health, Faculty of Medicine, Universitas Andalas[9], Padang, West Sumatera; Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/ Dr. Sardjito Hospital, Yogyakarta, Central Java[10], Indonesia.

Corresponding author: Professor Stephen M. Graham. Melbourne Children's Global Health, University of Melbourne Department of Paediatrics, Royal Children's Hospital. Flemington Rd, Parkville, Victoria, Australia 3052. Email: steve.graham@rch.org.au.

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with insufficient detection and treatment of TB and MDR/RR-TB along with very low implementation of services for prevention such as contact investigation and TB preventive therapy (TPT) coverage.[2,5] Similar challenges are reported globally from other high-burden countries.[1] We aim to highlight ongoing clinical and programmatic challenges in Indonesia as well as opportunities informed by recent evidence and recommendations.

Strengthening detection - bacteriological confirmation

The detection and treatment gap in TB-endemic settings is particularly marked in young children.[1] Efforts to overcome the challenges of both bacteriological and clinical diagnosis in children are critical to closing the wide treatment coverage gaps for TB and MDR/RR-TB and to reducing TB-related morbidity and mortality. Despite the paucibacillary nature of TB in children, bacteriological confirmation tests should be performed whenever possible.[6] mWRDs such as *Xpert Ultra*® can be used on a variety of samples such as stool, nasopharyngeal aspirates, lymph node aspirates and cerebrospinal fluid in addition to sputum or gastric aspirate.[6,7] The mWRDs have higher sensitivity than smear microscopy in children, and two samples provide a higher yield than one.[8] WHO recommends that a symptomatic child with any level of detection by mWRDs should be initiated on treatment for TB and be reported as "bacteriologically confirmed".[7] Of positive *Xpert Ultra*® results, a "trace" result is very common in children and from extrapulmonary samples, but resistance cannot be determined from such a result.[9]

Indonesian children with presumptive TB presenting to primary care (community health center/*puskesmas*), as well as some private healthcare facilities, often have poor access or utilization of laboratory diagnostics compared to chest X-ray (CXR).[10,11] Access to mWRDs in Indonesia is improving, as large numbers of *GeneXpert* machines have been installed for TB diagnosis in facilities across Indonesia, including many at the puskesmas level.[2] Collection of sputum in young children remains a challenge. Sputum induction and gastric lavage have been introduced with training provided to healthcare workers; however, these are rarely performed in healthcare facilities. The combined use of stool and respiratory samples will achieve the highest diagnostic yield in young children, and is also likely to be cost-effective.[8,12,13] However, only one sample is usually tested although two samples are recommended by the national programme.[2] A study that includes children as well as adults with presumptive TB is underway in Bandung, West Java; the study evaluates both novel diagnostics and sampling approaches at puskesmas facilities while measuring the accessibility, cost, and impact on case reporting.[14]

Strengthening detection - clinical diagnosis

Most children with TB, including those with MDR/RR-TB, require a clinical diagnosis as bacteriological confirmation with molecular diagnostics is not achievable in the majority, even in optimal, tertiary settings.[8] Therefore, treatment decision approaches using algorithms and/or scoring systems have been developed to guide clinical decision on the basis of symptoms, contact history, risk of disease and CXR.[15,16] A scoring system developed by the *Indonesian Pediatric Society* (IPS) has been used for decades, one of many such scoring systems developed globally. As with all such approaches, there are challenges with accuracy and implementation.[17,18] TB is very common in children with severe malnutrition and a separate treatment decision approach has recently been validated for this high-risk group.[19]

The treatment decision approach included in the *WHO 2022 Operational Handbook for Children* (<10 years) with presumptive pulmonary TB includes two scoring options, one when CXR is available and the other when not available.[7] Developed using data from over 4000 children with TB, the cut-off score was deliberately chosen to prioritize sensitivity over specificity, therefore minimising missed cases while accepting overtreatment.[16] *The IPS TB Working Group* recently used clinical data from Indonesian children with presumptive TB to retrospectively evaluate this new IPS algorithm, the treatment decision approach with scoring system published by WHO and the diagnosis made by attending doctors in ten hospitals in five cities in Indonesia.[20] There was moderate agreement between the IPS algorithm and the WHO treatment decision approach. However, there were some limitations in interpretation and accuracy. The IPS scoring system is still commonly used without the algorithm. It is challenging to develop a universal

algorithm or scoring system applicable across all patient conditions and resources. In addition, the skill levels and clinical judgment of the healthcare provider evaluating the sick child remains important.[20]

Strengthening health systems for children with TB is a priority for resource-limited settings.[21] Tools are available to support the diagnosis and care of TB in children at all levels of care. Most children who require care or prevention for TB, including MDR TB, present initially to primary care. Because of this, it is important that the general practitioner in a Puskesmas or private healthcare facility has the competence to first consider TB as a possible cause of the child's illness, and subsequently to perform clinical evaluation with appropriate use of laboratory and clinical tools. Assessment for TB-related symptoms, malnutrition, and a positive contact history can be performed at all levels of care, as can identification of clinical indicators of MDR TB in children, such as contact with an index case with MDR TB or failure to respond to first-line TB treatment. Indeed, there needs to be improved engagement between pediatric healthcare providers and TB services at all levels of care, including secondary and tertiary care, whether in public or private healthcare facilities.

The CXR has a number of important roles for clinical care and prevention: to diagnose intrathoracic TB and determine the severity of disease; to identify alternative diagnoses; and to exclude active TB in contacts to determine eligibility for TPT. In reality, most children with presumptive TB in Indonesia are referred to a secondary healthcare facility for CXR examination, TB infection test, and sputum induction if necessary. Although CXR is often not available in the Puskesmas, a physician in a primary health facility should be able to interpret the CXR image of a child as a diagnostic aid but also to minimise overdiagnosis by CXR. *The International Union Against Tuberculosis and Lung Disease* (The Union) has developed training tools to support healthcare workers at all levels of care in CXR reading for child TB diagnosis that are freely available - and this includes a diagnostic atlas translated into Indonesian.[22-25] Mobile or portable CXR with computer-assisted artificial intelligence is being used for community-based screening and active TB case detection in adolescents and adults, such as in Yogyakarta, but this tool requires adaptation, evaluation, and validation to support diagnosis in children.[26,27]

A test for TB infection, such as a skin test or IGRA, is often used to support a diagnosis, but availability of and access to such tests are variable. IGRA in particular is expensive and requires laboratory support limited to higher level facilities or the private sector. A positive test for infection is particularly helpful in a child with presumptive TB when contact history is negative or in making the decision to provide TPT in high-risk children without TB disease.[3] Following IPS recommendations, tuberculin solution is often available at the puskesmas and hospital facilities, but training on test administration and interpretation are required.

Decentralisation of services can improve access for TB care in children and adults.[28,29] Resources are increasingly available to support policy translation to optimize care at all levels by providing training for individual or group participants, without the need for costly face-to-face workshops. In 2023-2024, the WHO developed two short e-learning courses for child and adolescent TB.[30,31] One aims to inform healthcare workers on how to diagnose, treat, and prevent tuberculosis while emphasizing the importance of locally relevant evidence-based guidelines.[30] The other aims to support programmatic implementers and trainers including stressing procurement needs of diagnostics and child-friendly treatments.[31] In 2025, The Union has launched a comprehensive and interactive online training that has been field tested and uses adult learning principles.[32]

Tuberculosis and malnutrition

Undernutrition is a leading risk factor for TB globally and in Indonesia, with a population attributable fraction of 15%, compared to 7.6% for HIV and 3.1% for diabetes.[1,2] *The 2022 Indonesia Nutrition Status Survey* showed that 21.6% of young children were stunted, 17.1% were underweight, and 7.7% were wasted.[32] The prevalence of TB is high (around 20%) in young children with severe acute malnutrition in TB-endemic countries.[19,34] Individuals who are undernourished also have greater severity of TB and increased likelihood of unfavourable treatment outcomes, including mortality or relapse.[35-37] In a study involving adult MDR TB patients in Indonesia, severe underweight was associated with a longer time to achieve initial sputum culture conversion.[38]

There are recent compelling data from India of the protective effect of nutritional support to prevent TB disease and TB-related mortality.[39,40] Policies aimed at reducing the burden of undernutrition are critical components of efforts to improve TB outcome and thereby decreasing TB mortality. All children with malnutrition in Indonesia should be considered as presumptive TB and undergo further evaluation for TB and HIV.

Improving treatment outcomes

TB treatment success rates in Indonesia are below the global target of 90% and fell during the COVID-19 pandemic.[2] In children treated for TB, overall treatment outcomes are usually better than in adults, and there is less drug toxicity. However, adherence is critical for optimal outcomes. Adolescents commonly require particular attention and support to achieve cure or treatment completion. Barriers include TB drug stock-outs, limited transportation to drug access, low education levels, loss to follow-up when the patient transitions from the hospital to the Puskesmas, and lack of health insurance coverage for the costs of outpatient treatment.

Treatment regimens now recommended by the WHO are becoming shorter, such as for non-severe pulmonary or lymph node TB, for TB meningitis and much shorter and less toxic than previously for MDR/RR-TB.[6,7] These shorter regimens are currently in an evaluation phase of implementation in Indonesia or are a future target of operational research by the *IPS Working Group*. The recommended use with evidence of safety of second-line drugs such as bedaquiline and delamanid for all ages has been critically important so that children with MDR/RR-TB no longer require injectable aminoglycosides that cause life-long disability in the form of hearing loss. Treatment is supported by the availability of child-friendly formulations of first- and second-line drugs with weight-based dosage guidelines.[7,15]

Early detection and treatment are critical in reducing long-term consequences in addition to prevention. Post-TB lung disease is well-recognized and common in adults and recent data suggest that pulmonary TB in children and adolescents also has a negative long-term impact on lung function and quality of life even after successful treatment of disease.[41-43] Permanent neurological disability due to TB meningitis is common and data from clinical trials evaluating novel regimens with higher than currently recommended dosages of rifampicin are eagerly awaited.[44,45] It would be extremely helpful to have a TB meningitis registry in Indonesia to monitor caseloads and outcomes.[44] Prevention strategies are key to reducing the burden of TB-related disability.[46,47]

Closing the prevention gap

Potential public health strategies for TB prevention include vaccination, TPT for high-risk populations such as household contacts, and infection prevention control in health facilities. The emergence of effective, safe and shorter TPT regimens using child-friendly formulations have the potential to close the current prevention gap.[46] The protective benefit of newborn BCG immunization against severe TB in young children is well recognized.[47] BCG coverage in Indonesia fell during the COVID-19 pandemic along with coverage of other childhood vaccines48 which, along with a fall in detection of infectious TB cases and likely increased transmission in the community,[2] may have impacted the risk and burden of TB in children. There have been some promising developments in TB vaccines[49] that aim to reduce disease in adolescents and adults, and thereby reduce transmission and risk to children; efficacy is now being evaluated in two sites in Indonesia as part of a multinational phase III trial that includes seven countries.[50]

Contact investigation as per national guidelines has a great potential impact through active case-finding, early treatment of disease, and prevention, but there is a wide implementation gap in Indonesia.[2] Recent developments provide important opportunities to reduce TB disease burden in Indonesian children and adolescents through prevention. There are safe and effective recommended TPT options for recent contacts of people with TB, including for contacts of MDR/RR TB that is fluoroquinolone-susceptible.[46,51] The recommended use of TPT has expanded beyond young child (<5 years) contacts and people living with HIV to include HIV-uninfected older children and adolescent contacts without TB disease. A recent meta-analysis which includes data from Indonesian children presents the protective efficacy of TPT across age groups.[52]

Despite the benefits and availability of shorter TPT regimens, the uptake of TPT among household contacts in Indonesia is low.[2] Implementation and

coverage can potentially be improved by decentralizing services from a passive, health facility-based approach to a more proactive, community-based approach with evidence of higher coverage of contact screening, TPT initiation and completion.[53,54] A multinational study that included Indonesia reported an increase in the proportion of household contacts initiating TPT after an intervention in the healthcare system.[55] A recent study reported excellent results of implementation of TPT by a dedicated nurse within a community-based active case-finding initiative in Yogyakarta.[56]

Active case-finding for prevention

The potential of active case finding and treatment of infectious TB cases in the community, including those who do not report symptoms, is commonly overlooked. Most children who develop TB have been infected through transmission from an adult or adolescent with bacteriologically confirmed pulmonary TB. Therefore, reducing the prevalence of TB in adults will reduce infection in young children, and therefore reduce the risk of disease. A reduction in TB prevalence in districts in Southern Vietnam achieved through active case finding was associated with a similar reduction of infection prevalence in young children in the same communities compared to non-intervention districts.[57] There is a consistently high yield of active case-finding in children through contact investigation due to high risk in this age group.[58,59] Improving case-finding in children will reduce TB-related morbidity and mortality but is unlikely to impact transmission, especially as the yield of bacteriologically positive child TB cases will be low. Strengthening TB services at the Puskesmas has improved case-finding in Indonesia.[29] Community-based active case-finding to detect and treat TB disease is now integrating the detection and treatment of infection and provision of TPT.[60,61]

Summary

There is much to improve in the detection, treatment and prevention of TB in Indonesian children. The evidence base has greatly expanded in recent years including from research being conducted in Indonesia. With the development of new tools and policy updates, the opportunities for implementation have never been greater, but important challenges remain to close the wide policy-practice gaps, to strengthen services to further decentralize levels of care that will greatly improve access to care and prevention, and to evaluate models of care with high quality implementation research. Recommendations to close policy-practice gaps are listed in **Table 1**.

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Table 1. General recommendations to facilitate progress in overcoming current challenges to improve TB care for Indonesian children

1. Develop a roadmap for maternal, child and adolescent TB activities in Indonesia for 2026-2035 with leadership by the Indonesian Child TB Working Group in collaboration with the national TB program.
2. Strengthen the integration of management between pediatric and TB services at all levels of care, including strengthening of integrated TB services at Puskesmas and community levels for early detection and prevention.
3. Ensure that all children with malnutrition be considered as having presumptive TB and be further evaluated for TB and HIV.
4. Develop local and national child and adolescent TB champions to improve advocacy, education and community engagement.
5. Identify and support dedicated healthcare workers to provide TB services to the community including for detection, treatment support, and prevention activities for child TB.
6. Strengthen recording and reporting so that all children treated for TB disease are reported to the national TB program, including those treated in private healthcare facilities.
7. Implement routine reporting of coverage of contact investigation along with uptake and completion of TPT in eligible contacts of all ages.
8. Identify priorities and funding for operational research with involvement of national stakeholders and academic institutions while providing opportunity to develop capacity and professional careers in TB research.

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