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The Evolving Research Agenda for Paediatric Tuberculosis Infection

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ABSTRACT

There are unique challenges facing the diagnosis and management of tuberculosis infection in children. Following exposure to an infectious tuberculosis case and subsequent infection, children frequently progress to tuberculosis disease more rapidly than adults. Increasingly, investigators recognize the concept of sub-clinical disease, an entity referring to early asymptomatic disease. Our understanding of the pathogenesis of tuberculosis in children remains limited but could be improved through animal models, laboratory studies evaluating the responses of blood or respiratory samples to mycobacteria in vitro, as well as evaluating immune responses in children exposed to tuberculosis. Identifying children with sub-clinical disease, at high risk of progression to clinically apparent disease, through biomarker discovery, would mean that treatment could be targeted to those most likely to benefit. These studies could be embedded in large observational or interventional cohorts. The optimization and discovery of novel treatments for tuberculosis infection in children need to account for mechanisms of action of tuberculosis drugs as well as child-specific factors including pharmacokinetics and appropriate formulations. In this article we present the result of discussions at a large international meeting and the series of research priorities that were developed.
BACKGROUND

Current Situation

The conventional conceptual framework when considering the pathogenesis of tuberculosis in children is linear and unidirectional, with two distinct dichotomous clinical states: tuberculosis infection and tuberculosis disease. Children are exposed to *Mycobacterium tuberculosis* via aerosolized droplets. Some develop tuberculosis infection, defined as immunological evidence of sensitization to *M. tuberculosis*, and from this state, some progress to tuberculosis disease, defined as the presence of symptoms and signs of tuberculosis, usually together with radiological, and sometimes microbiological, evidence of disease. Young children are at particularly high risk of progressing from infection to disease and are also more likely than adults to develop severe, debilitating forms, such as tuberculous meningitis. Worldwide nearly seventy million children currently have tuberculosis infection, and each year about one million children progress to tuberculosis disease. A quarter of them die, representing one of the top ten causes of under-five mortality.

Treating Tuberculosis Infection

In order to prevent this mortality, it is increasingly recognized that it will be necessary to identify and treat children with tuberculosis infection in addition to children with tuberculosis disease. The World Health Organization, and almost every national tuberculosis guideline, has for many years, advocated the provision of isoniazid preventive therapy to young children, following exposure to an infectious case of tuberculosis. In spite of these recommendations, however, tuberculosis infection treatment is rarely implemented in high tuberculosis-burden settings.

Developing A Research Agenda

Failures in implementation of preventive therapy can result from the perception that a large numbers of well children require treatment to prevent each case, and that treatment is long. It is hoped that in the future biomarkers will be discovered that can predict progression to tuberculosis disease. It is also anticipated that research will lead to improvements the management of tuberculosis infection in children. A better framework of feasible and achievable research in paediatric tuberculosis infection would provide direction to researchers and funders and allow for the rational development of a research agenda. On 27-28 September 2017, 165 global participants attended a two-day workshop in Dubai with the aim of arriving at consensus on the priorities required to better understand, diagnose and treat tuberculosis infection. The meeting was supported by the Division of AIDS, National Institute of Allergy and
Infectious Diseases and hosted at the Harvard Medical School Center for Global Health Delivery–Dubai. A session focused on children, and presentations were given with subsequent discussion from all attending participants. Themes were then taken forward amongst several paediatric investigators after the meeting, and over the course of multiple conference calls and cycles of written feedback consensus was arrived at for research priorities that are described in this manuscript and in Table 1.

**PATHOPHYSIOLOGY**

*Evolving Concepts in Childhood Tuberculosis*

An improved understanding of the natural history, pathophysiology and immune responses associated with paediatric tuberculosis would enhance our current ability to identify those children most likely to benefit from treatment of infection. It is increasingly clear that the concept of latent infection versus active disease is too simplistic, given the dynamic spectrum from exposure to disease, with children potentially moving in both directions (Figure 1). The concept of sub-clinical and incipient disease has gained prominence in recent years referring to early disease in asymptomatic persons, which is either evident radiologically (sub-clinical) or not (incipient). Although most investigation into these early clinical states has been in adults, this concept in not novel in children. Children progress more rapidly than adults from exposure to infection to clinically apparent disease, and hence represent a unique cohort in which to study the pathophysiology of sub-clinical disease and associated host responses. In the interest of clarity, we use the term sub-clinical to refer to both sub-clinical and incipient states for the remainder of this review.

The distinction between sub-clinical and clinically apparent disease is likely to be due to a quantitative difference in bacterial load, rather than a change in the replication state of the mycobacteria. This has implications for novel diagnostics as the host immunological and metabolic responses may be measurable in sub-clinical disease and similar to those in clinically apparent disease. A current research priority is to identify children with sub-clinical disease who are thought to be at highest risk of developing clinically apparent disease in the future. As is discussed later, this has been undertaken in adolescent and adults but not in younger children.

Following exposure to *M. tuberculosis*, several outcomes are possible. Organisms can: 1) be cleared by immune responses, 2) progress to clinically apparent disease, or 3) reach an equilibrium in which the organism is not cleared, but is contained by the host in a dynamic state
that may fluctuate over time. The pathogen may later be cleared, or it may overcome the host defenses and clinical symptoms and signs of disease develop (Figure 2). In high tuberculosis-burden settings, the force of infection is so great that frequent re-infection is also common, following either clearance or containment of the organism. In the absence of large-scale longitudinal studies, including repeated sampling of the same individuals, it is therefore difficult to ascertain whether progression to disease occurs following failure of restriction of the initial infection, or results from a new exposure. Household contact studies of exposed children of all age groups, with longitudinal follow up and sampling provide a unique opportunity to define these phenotypes.

Research Directions

Our current understanding of risk factors for progression to disease following exposure to *M. tuberculosis* in children is limited, with few studies exploring this from epidemiological, clinical or immunological perspectives. It is clear that host responses vary with age, and research to better understand the natural history of childhood tuberculosis, accounting for age and exposure, is urgently warranted. Laboratory assays utilizing blood from children of various age-groups and stimulated with live mycobacteria or mycobacterial antigens *in vitro* could provide insight into pathways that are activated or suppressed. Animal studies could be utilized to a greater extent as few studies have investigated the impact of age on immune response in juvenile animal models. Mouse, guinea pig, rabbit and non-human primate models could all be explored.

Much of the human interaction with *M. tuberculosis* occurs initially at a mucosal and then a lymphoid level. Although studies in adults have demonstrated differences in immune responses in lung, pericardial and mucosal tissue compared to blood, and have highlighted the crucial role of resident innate cells including alveolar macrophages, mucosal associated invariant T (MAIT) cells, Th17 cells and IL17-producing γδ T cells, these studies have not been conducted in children due to ethical and physical challenges of sample collection. Novel *in vitro* approaches, including human lung explant studies and alveolar macrophage cultures could be undertaken by paediatric researchers. An additional challenge is to determine the time of exposure. The child may have been recently exposed, exposed some time ago to the identified source case, or, in a high burden setting, exposed to other infectious cases in the past. Trying to make sense of the immunological response when the time since exposure is unclear can be challenging (Figure 3). The best, and most efficient, way of exploring these responses would be to embed basic science studies within cohorts of children who are being recruited to other studies, such as epidemiological studies of household contacts or clinical trials, where the recruitment entry point is a defined exposure. Recent paediatric treatment trials such as SHINE, TB-CHAMP and
SURE, as well as other observational cohorts, have already adopted this model, collecting samples for adjunctive biomarker assays.\textsuperscript{38,39}

**DIAGNOSIS OF INFECTION**

*Currently Available Tests*

The current tests of infection, the tuberculin skin test (TST) and interferon-gamma release assay (IGRA), evaluate whether a child mounts an acquired cellular immune response to *M. tuberculosis*.\textsuperscript{40,41} However, these tests do not indicate whether a persistent or progressive infection is present, or if the infection has been cleared.\textsuperscript{42,43} In addition, in children with confirmed tuberculosis disease up to 30\% have negative tests,\textsuperscript{44} and the sensitivity of these tests is especially poor in young children living in high tuberculosis-burden settings.\textsuperscript{45} Moreover, while children with a positive test result are twice as likely to develop disease as those with a negative test, the vast majority of children with a positive test do not develop disease.\textsuperscript{43} (Figure 4). Nonetheless, epidemiological and clinical data suggest that young children with TST and/or IGRA conversion have increased risk of disease progression, supporting use of these tests to inform decision-making around use of tuberculosis infection treatment. Because the specificity of IGRAs is greater than TST in younger BCG-vaccinated children,\textsuperscript{46-49} research into decreasing the requisite blood volume for, and improving the technical test performance of, IGRA in young children, as well as developing a T cell diagnostic platform that could be used at the point-of-care for tuberculosis infection, with small quantities of blood, is warranted.

*Recent Developments*

In regions of the world where contact management and delivery of tuberculosis infection treatment is challenging due to the caseload of tuberculosis disease and limited resources, a test that could identify sub-clinical disease (Figure 1) would be useful to target tuberculosis infection treatment to those most likely to benefit from it. A recent study in South African infants demonstrated that conversion from negative to very high interferon-gamma levels (>4.00 IU/ml) in otherwise asymptomatic infants was associated with a 40 times risk of disease progression compared to non-converters.\textsuperscript{50} These results suggest that high IGRA values may be a marker of sub-clinical disease in infants. While not evaluated in young children, a recent study of 6,000 IGRA-positive South African adolescents has identified a 16-gene transcriptomic signature that defined a short-term risk of progression to tuberculosis disease.\textsuperscript{17} This signature is being taken forward in a clinical trial to validate decision-making around tuberculosis infection treatment in adults.\textsuperscript{51}
Future Directions

The study of candidate biomarkers of sub-clinical disease has the potential to reduce morbidity and mortality from tuberculosis in young children. However, designing studies that could lead to tests able to discriminate between children who ultimately will develop disease and those that will not is challenging. As most children with tuberculosis infection will not progress to disease, studies need to be large. Also, the standard of care for young children (<5 years) and for children with immunosuppressive conditions is to provide tuberculosis infection treatment. Therefore, it is ethically unacceptable to observe children without treatment in order to identify biomarkers. Recent guidance is to additionally consider treating older children with evidence of tuberculosis infection. One option would be to evaluate children contacts of drug-resistant tuberculosis, as most guidelines advocate close observation without treatment. The study of children treated for tuberculosis infection may also be informative, to determine if biomarker changes signify mycobacterial clearance, potentially of use in the evaluation of novel regimens or treatment shortening trials. Finally, translating the complex laboratory procedures necessary to measure immunological parameters or identify differentially expressed transcripts into affordable true point-of-care tests, for widespread use in low resource settings, will require collaboration between multiple disparate scientific and commercial partners.

Efforts to date have mainly sought to validate diagnostic biomarkers in children that have been discovered in adults. However, accurate diagnostic biomarkers in adults may not translate well into diagnostic accuracy in children, as young children have differently regulated immune systems, have a pre-pubertal hormonal status, may more frequently suffer from malnutrition, have received BCG immunization and other childhood vaccinations more recently, and may lack the immunological memory conferred from lifetime exposures to microbial and other environmental antigens. Therefore, efforts should not only be directed at biomarker validation, but also at biomarker discovery in young children. Challenges around the timing of sampling in relation to exposure are similar as for the evaluation of the immune response (Figure 3) and there are significant transcriptomic changes with age, co-infections, nutritional status, recent vaccination and even time of day.

TREATMENT OF TUBERCULOSIS INFECTION

Treatment Strategies

Children with tuberculosis infection are clinically well, and most do not progress to tuberculosis disease. Therefore, unpalatable or intolerable medications would not be acceptable from a risk-
benefit perspective. This leaves only a handful of currently available drugs for tuberculosis infection treatment - the rifamycins, isoniazid, and the fluoroquinolones. When pharmacokinetic parameters and safety profiles are better understood in the youngest children, it may also include delamanid, bedaquiline and other novel drugs. The ideal tuberculosis infection treatment regimen would be safe, short, well-tolerated, effective, compatible with antiretroviral medications and affordable, while easy to implement for health services and families. If this ideal is not possible, then it may be appropriate to sacrifice some degree of efficacy for safety, duration, or tolerability. Multiple options, including easier administration (such as a cutaneous patch etc.) or a very long acting agent (only needed to be given once every week) would also be advantageous.

The evidence base for current treatments of tuberculosis infection has largely been gained from large-scale clinical trials, employing effectively a 'trial and error' approach. A more mechanistic and considered strategy, however, may provide advantages. Several mechanisms can be employed to treat tuberculosis infection. These may include: 1) eliminating all mycobacteria; 2) killing enough of the mycobacteria, or weakening them sufficiently to allow the immune system to eliminate or contain them; 3) stimulating the mycobacteria out of their non-replicating state so that they can be eliminated by other drugs or the immune system; 4) stimulating/manipulating the immune system so it is better able to eliminate or contain the mycobacteria; or 5) some combination of the above. All current drugs used for the treatment of tuberculosis infection (or presumed infection) act by killing mycobacteria. However, they do this by disrupting different elements of the mycobacterial metabolism or structure. Selecting the best drug or combinations to kill different populations, including metabolically inactive organisms, requires careful consideration and evaluation. It is possible that this might permit more effective or shorter treatment with less toxicity.

Dosages of Medications

Optimizing tuberculosis infection treatment also requires optimization of dosage. Increasing the milligram per kilogram dosage may mean greater efficacy, permit intermittent dosing, or allow shorter treatment. Isoniazid given at higher doses (e.g. 15-20mg/kg) has been used to treat multidrug-resistant organisms (resistant to rifampicin and isoniazid) causing both infection and disease. Comparing efficacy of this dosage with standard (10mg/kg) dosing has not been performed for the treatment of tuberculosis infection. Investigators are using increasingly high dosages of rifampicin (now up to 50mg/kg) for the treatment of tuberculosis disease in adults. These higher dosages have not been evaluated in the treatment of tuberculosis infection.
Additional and Host-Directed Therapies

It is also important to evaluate host-directed therapies and/or vaccines that do not aim to kill mycobacteria directly but assist to eliminate organisms. These might include drugs and/or vaccines that modulate parts of the immune system, inhibit efflux pumps or ‘wake’ inactive mycobacteria. The unique changes across the age-groups of children also need to be included in these evaluations as distinct immunological changes during puberty and early adolescence may alter these responses.

Unintended Consequences

When considering treatment of tuberculosis infection, the concept of ‘first do no harm’ needs to extend beyond tolerability and toxicity. Drugs which have broad antibacterial activity and are taken for long durations are likely to have other effects. These might be negative, in terms of the promotion of drug resistance in non-mycobacterial bacteria, or disruption of a ‘healthy’ microbiome. These unintended effects may also be positive, in terms of reduction in other bacterial infections, improved growth, better development and a reduction in life-threatening infections. These effects are rarely captured in current treatment trials and any study which seeks to evaluate new therapies for tuberculosis infection should evaluate such non-specific actions.

Developing Regimens

A relatively limited number of regimens are currently recommended to treat drug-susceptible tuberculosis infection and no regimen is widely recommended to treat drug-resistant tuberculosis infection. It is generally accepted that if a regimen is effective in an adult population, it will be effective in children. However, the formulation is far more important in children than adults and the historical crushing of adult tablets should no longer be an acceptable solution. The dosing in children required to achieve serum concentrations equivalent to effective serum concentrations in adults need to be elucidated, as do child-specific safety parameters. In the evaluation of rifapentine, a large initial study was conducted to demonstrate efficacy, with recruitment of children continuing after the primary trial had closed to make sure that enough data were available to document safety in the paediatric population. Knowledge gaps, however, remain in very young children <2 years, who have the highest risk of tuberculosis disease progression. Given that children have less concomitant pathology (such as existing lung damage that might act as a site difficult to clear of mycobacteria) and are able to tolerate higher dosages of most tuberculosis medications, it may be possible to treat children with even shorter durations of therapy than adults. To evaluate such regimens, efficacy trials would be required. However, creative trial designs are needed as the conventional approach
used to evaluate new tuberculosis infection treatments is to perform a non-inferiority trial comparing the new regimen with an established regimen. Given the rarity of disease endpoints in the absence of any treatment, and even fewer with established regimens, these trials are necessarily large, expensive and of long duration. Duration response trials have been suggested as one way that treatments of different durations could be evaluated.  

CONCLUSIONS

There is a pressing need to better understand the pathophysiology and natural history of tuberculosis infection in children from birth to adulthood, to develop tests that better identify those at the highest risk of disease progression, to target the delivery of tuberculosis infection treatment to those most likely to benefit from it, and to develop and implement treatments that are shorter and easier to give. Much can be learnt from studies in adults, but for many questions, research needs to be conducted in children specifically. One of the most efficient methods of investigating these questions is to embed basic science research into already established clinical cohorts and clinical trials and collect relevant specimens during the conduct of such studies.
CONFLICTS

DAL: Dr. Deborah Lewinsohn and Oregon Health and Science University (OHSU) have financial interests in ViTi, Inc, a company that is developing biomarkers of TB progression in children, and therefore may have a commercial interest in the contents of this manuscript. This potential individual and institutional conflict of interest have been reviewed and managed by the OHSU Conflict of Interest in Research committee. ViTi had no role in the decision to publish or preparation of the manuscript. JAS, EW, BK, MO, ACH, RR and FA: no conflicts.

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AUTHOR CONTRIBUTION

JAS, BK, DAL, ACH, RR and FA defined the scope of the article. JAS produced the first draft and all figures. All authors gave critical input and all authors approved the final version.

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FIGURE LEGENDS

Figure 1. The dynamic spectrum from *M. tuberculosis* exposure to tuberculosis disease in children.

Footnote: It should be noted that for some children severe disease can be caused by a low bacillary load that has disseminated widely, such as in miliary tuberculosis or tuberculosis meningitis.

Figure 2. Four of many potential responses to tuberculosis infection.

Footnote: **Top left panel:** Following exposure, organisms cleared by physical mechanism or by the innate immune system without sensitizing the adaptive immune system. This child will be TST or IGRA negative. **Top right panel:** Following exposure, the organisms breech the physical and innate defenses with local proliferation. The organism is then contained but not cleared by the adaptive immune system with subsequent cycles of proliferation and containment. This child will be TST/IGRA positive but does not have tuberculosis disease. **Bottom left panel:** Following exposure, the organisms breech the physical and innate defenses with local proliferation. At a future time, the organism proliferates without containment and disease results. **Bottom right panel:** Following exposure, the organisms breech the physical and innate defenses and then proliferate without effective containment by the adaptive immune system. Rapid progression to tuberculosis disease follows.

Figure 3. The natural history following exposure to an infectious tuberculosis case.

Footnote: A child is shown sampled at three time-points following exposure. At all points the child is clinically well. However, the stage of tuberculosis infection natural history would be unclear, and the immune responses may be very different between the different time-points. This is a simplified representation and in a high tuberculosis burden setting this situation could be complicated by re-exposure and re-infection.

Figure 4. A conceptual framework for understanding the relationship between ‘true’ tuberculosis infection, a positive test of infection, and a child at risk of future disease progression.
<table>
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<th>Research Need</th>
<th>Study Suggestions</th>
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| Define immuno-phenotypes most likely to progress to tuberculosis disease (in  | Large household contact studies & large prospective longitudinal analyses of immuno-phenotypes*  
| particular sub-clinical tuberculosis) in order to identify those children and | Bio-banking of samples from ongoing tuberculosis household contact studies in children.                                                                                                                         |
| adolescents who would benefit most from tuberculosis infection treatment      |                                                                                                                                                                                                                   |
| Investigate if previous tuberculosis infection and containment protects against | Studies in animal models through exposure, infection testing and re-exposure                                                                                                                                         |
| disease development in the face of further exposure and, if so, whether      |                                                                                                                                                                                                                   |
| treatment of tuberculosis infection might impair this immunity                | In children heavily exposed to tuberculosis, compare innate immune responses in children with persistently negative IGRA/TST results and those with positive test results |
| Explore reasons for persistently negative tests of infection (IGRA and TST)   | Juvenile animal studies to define ontogeny of mycobacterial immune responses  
|                                                                              | in vitro human studies exploring ontogeny of mycobacterial immune responses                                                                   |
| Understand the impact of age on mycobacterial immune responses               | Animal and in vitro human studies of mycobacterial mucosal immunity in children of different ages*                                                                                                 |
| Understand the role of mucosal immunity in tuberculosis infection following   |                                                                                                                                                                                                                   |
| exposure to determine role of alternative vaccine routes                      |                                                                                                                                                                                                                   |
| Technical improvement of IGRAs to diagnose tuberculosis infection in young    | Technical research to: 1) Reduce requisite blood volumes; 2) decrease incidence of indeterminate results among young children                                                                                          |
| children                                                                      | Technical research to develop a point-of-care diagnostic platform for detection of *M tuberculosis* infection that minimizes blood volume                                                                 |
| Improvement of access to a diagnostic of tuberculosis infection in children    | Large prospective observational study of young children for development of tuberculosis disease with longitudinal collection of biological specimens.* |
| Validation in young children of a diagnostic biomarker of sub-clinical disease  |                                                                                                                                                                                                                   |
| discovered in older children or adults.                                      |                                                                                                                                                                                                                   |
| Biomarker discovery in young children for diagnostic biomarkers of sub-       | As for validation studies of diagnostic biomarkers of subclinical tuberculosis disease*                                                                                                                             |
| clinical tuberculosis                                                        |                                                                                                                                                                                                                   |
| Explore the shortest, effective regimen for treatment of drug-susceptible     | Randomized cluster non inferiority study  
| tuberculosis infection                                                        | Prevention of infection trials – either with novel vaccines or BCG re-vaccination                                                                                                                                   |
|                                                                              | Duration randomization trials                                                                                                                                                                                     |
| Explore the shortest, effective regimen for treatment of drug-resistant       | Randomized cluster superiority study  
<p>| tuberculosis infection                                                        | Prevention of infection trials – either with novel vaccines or BCG re-vaccination                                                                                                                                   |
|                                                                              | Duration randomization trials                                                                                                                                                                                     |</p>
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<tr>
<th>Obtain pharmacokinetic data on all regimens for all ages of children</th>
<th>Embed pharmacokinetic studies in all cohorts and trials</th>
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<tr>
<td>Conduct rifapentine pharmacokinetic studies in children &lt;2 years</td>
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<td>Palatability and acceptability of proposed new formulations or regimens</td>
<td>Nested social science evaluations within randomized study</td>
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<tr>
<td>Explore non-specific effects of current and novel anti-tuberculosis treatment, both positive and negative, including impact on the microbiome</td>
<td>Nested within randomized cluster superiority or non-inferiority study</td>
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<tr>
<td>Explore role of host directed therapies, with a focus on different effects with age</td>
<td>Prevention of infection trials – either with novel vaccines or BCG re-vaccination</td>
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<td>Trials of host-directed therapies in addition to antimicrobial agents</td>
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<tr>
<td>Implementation research outcomes evaluation with robust monitoring and evaluation</td>
<td>Step wedge design within routine implementation settings evaluate cost, coverage and sustainability</td>
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TST: tuberculin skin test; IGRA: interferon-gamma release assay; BCG: Bacillus Calmette-Guérin

*These studies would address more than one research need. These studies would ideally be embedded within vaccine trials, diagnostic biomarker studies or household contact studies with a common entry point of household exposure*
REFERENCES


52. World Health Organization, Geneva, Switzerland. Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. Available at:


