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Setting priorities for a research agenda to combat drug-resistant tuberculosis in children

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Setting: Numerous knowledge gaps hamper the prevention and treatment of childhood drug-resistant tuberculosis (TB). Identifying research priorities is vital to inform and develop strategies to address this neglected problem.

Objective: To systematically identify and rank research priorities in childhood drug-resistant TB.

Design: Adapting the Child Health and Nutrition Research Initiative (CHNRI) methodology, we compiled 53 research questions in four research areas, then classified the questions into three research types. We invited experts in childhood drug-resistant TB to score these questions through an online survey.

Results: A total of 81 respondents participated in the survey. The top-ranked research question was to identify the best combination of existing diagnostic tools for early diagnosis. Highly ranked treatment-related questions centred on the reasons for and interventions to improve treatment outcomes, adverse effects of drugs and optimal treatment duration. The prevalence of drug-resistant TB was the highest-ranked question in the epidemiology area. The development type questions that ranked highest focused on interventions for optimal diagnosis, treatment and modalities for treatment delivery.

Conclusion: This is the first effort to identify and rank research priorities for childhood drug-resistant TB. The result is a resource to guide research to improve prevention and treatment of drug-resistant TB in children.

The burden of childhood tuberculosis (TB) reflects ongoing TB transmission in a community.[1] About one million children fall sick with TB every year.[2] The pattern of drug resistance in children in a community generally mirrors that of the adult population.[3] Among adults, 3.7% of new cases and 20% of previously treated cases were estimated to have multidrug-resistant TB (MDR-TB) worldwide in 2012.[4] In 2010, an estimated one million children developed TB disease, among whom 32 000 had MDR-TB.[2] Difficulties in diagnosis due to insensitive tools for microbiological confirmation in children hamper the estimation of the burden of drug-resistant TB in this population. Thus, accurate information on mortality and morbidity due to drug-resistant TB in children is lacking. This is only one among the multiple research and knowledge gaps that negatively affect children suffering from drug-resistant TB.

The goal of achieving a reduction in the global burden of TB by 2015, in line with the Millennium Development Goals, encompasses the protection of vulnerable populations, including children, from TB, TB and human immunodeficiency virus (HIV) infection and multidrug-resistant TB among its objectives.[5] Enabling and promoting research by making the best use of currently available tools and developing new tools for TB diagnosis, treatment and prevention is an important step towards achieving the goal of eliminating TB by 2050.[5] Evidence-based research priority setting is essential for effective use of funds for research and development. In this context, identification of research priorities for drug-resistant TB in children is important to address the knowledge gaps and eventually to reduce TB deaths and disease in children. A global partnership of researchers, care givers and advocates who share a vision of a world where no child dies from this curable and preventable disease, called the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, has begun collaborating toward this end (www.sentinel-project.org).

We sought to conduct a priority-setting exercise among a group of paediatricians, experts and advocates to identify and rank priority research questions related to epidemiology, diagnostics, treatment and prevention of drug-resistant TB in children.

METHODS

We adapted the methodology developed by the Child Health and Nutrition Research Initiative (CHNRI) (http://www.chnri.org/publications.php) to define the context of the problem and categorise the research priorities.[6–8] CHNRI methodology has been used to set research priorities in child health in several areas, including childhood pneumonia, diarrhoea, neonatal infections, zinc supplementation and asphyxia.[8–12]

Categorisation of drug-resistant tuberculosis research priorities in children

As a first step, a list of potential research priorities was prepared by reviewing published studies, including review articles and systematic reviews.[13–21] This included questions that would need to be answered to understand the burden of drug-resistant TB in children and its determinants, to improve the performance of existing strategies and to develop new strategies for diagnosis and management. The initial list of 79 questions was compressed to 53 questions in broad consultation with TB experts and paediatricians.

A total of 10 experts, including paediatricians, identified based on their experience in childhood TB, drug-resistant TB or both, was consulted to finalise the

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TABLE 1 Methodology used for development and categorisation of research

Research area	Research type	Research avenue	Research options	Research questions
Epidemiology Diagnosis Treatment Prevention	Research on disease burden and determinants (descriptive) Research for improving performance of existing strategies (development) Research to develop new strategies (discovery)	Measuring the disease burden Understanding risk factors Evaluating existing strategies Improving affordability, deliverability, and sustainability of existing strategies Basic, clinical, and public health research	Research options were identified within the research avenue	Specific research questions were framed based on consensus among the experts A total of 79 research questions were initially identified which were subsequently reduced to 53 questions

list of questions. The finalised questions were pilot-tested among 10 other clinicians to achieve better clarity in framing and wording. The two groups of respondents included in the formal ranking process were not involved in finalising the questions, nor were they involved in pilot testing the questions.

The questions were then organised using the CHNRI framework for listing research priorities. The final list used for scoring consisted of questions of three different research types: descriptive, development and discovery. These were systematically listed among four research areas, namely epidemiology, diagnostics, treatment and prevention (Table 1).

Scoring of research questions

In July 2013, the final list of research questions was e-mailed to two groups of respondents who were asked to score the questions via an online survey (Survey Monkey, Palo Alto, CA, USA). The first group consisted of the 304 individual members of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis; the second group was a convenience sample of 48 medical doctors from all over India who participated in a workshop on childhood drug-resistant TB held at the National Institute for Research in Tuberculosis (Chennai, India) in June 2013. The resulting group of respondents had expertise in the field of TB, drug-resistant and/or childhood TB. Online survey responses were accepted until 30 September 2013.

The respondents were asked to assess the research questions based on five criteria: answerability, feasibility, effectiveness, deliverability and equitability (Table 2). These criteria were selected from a list of all possible criteria that could be used for setting priorities in health research investments.[4] The priority-setting criteria were modified to reflect the context and subject of drug-resistant TB in children. For each criterion, the respondents were requested to tick any one of the following responses: yes, probably yes, probably no, no, do not know (Appendix Figure A). The respondents answered the questions independently of each other and were sent two reminders before being classified as non-responders.

Computing the research priority score and average expert agreement

The following scores were given to each of the responses at the time of analysis: yes (1), probably yes (0.75), probably no (0.25), no (0), and do not know (blank). The research priority score (RPS) was used to rank the research priorities. RPS is the overall value of each research question when all the criteria are taken into account. The overall RPS was computed as the mean of the scores for the five criteria using the following formula:

(criterion 1 score) + (criterion 2 score) + (criterion 3 score) + (criterion 4 score) + (criterion 5 score) / 5

The average expert agreement (AEA) score refers to the proportion of respondents who gave the same answer most frequently, and helped to achieve discrimination between levels of agreement among respondents on the prioritisation of the research questions. The AEA was calculated for each research question as the average proportion of respondents who gave the most common answer on the five questions asked, using the following formula:

$$5 \times \sum_{q=1}^{5} N \text{ (participants who provided the most frequent response)} \; / \; n \text{ (participants)}$$

where q is the criteria question that respondents used to evaluate competing research options ranging from 1 to 5.

The research questions were then ranked based on the RPS.

RESULTS

Of the 81 individuals who responded to the survey, the vast majority were clinicians (n = 63, 78%) (Appendix Table A.1). Of the 63 clinicians, 52 (83%) had expertise in TB or multidrug-resistant (MDR) TB and 26 (41%) were paediatricians. Of the 18 non-clinicians, 11 (61%) had expertise in TB or MDR-TB. Of the total 81 respondents, 63 (78%) had expertise in TB or MDR-TB. Of the 79

TABLE 2 Criteria used to assess the research questions

Criteria	Description
Answerability	Can this research question be answered in an ethical way, i.e., protecting the rights of patients, avoiding harming them and maximising their well-being?
Feasibility	Is it feasible to answer this research question?
Effectiveness	Will answers to the research question provide knowledge, evidence and strategic directions for reducing the disease burden most effectively?
Deliverability	Will answers to the research question provide suitable data, knowledge, evidence and strategies for a deliverable output?
Equitability	Will answers to the research question provide knowledge, evidence and strategies to reduce the disease burden equitably in all population settings, particularly in high-risk populations and populations in resource-poor settings?

TABLE 3 The 10 top-ranked research questions with RPS and AEA

Rank	Proposed research question	Answerability	Feasibility	Effectiveness	Deliverability	Equitability	RPS	AEA
1	What are the best combinations of existing diagnostic tools to enhance early diagnosis of drug-resistant TB in children at the community level, in settings with different levels of resources, malnutrition and HIV prevalence?	87.33	84.72	90.49	89.08	88.38	88.00	0.62
2	What are the adverse effects of second-line anti-tuberculosis drugs in children?	88.93	85.21	89.29	85.51	85.87	86.96	0.68
3	What are the risk factors associated with death and the causes of death in children being treated for drug-resistant TB?	82.75	81.94	85.92	84.78	85.51	84.18	0.55
4	What are the reasons for poor treatment outcomes in the treatment of drug-resistant TB in children?	83.68	82.39	85.92	83.57	81.88	83.49	0.56
5	What is the role of nutritional intervention in improving treatment outcomes and adherence among children on treatment for drug-resistant TB?	83.09	82.58	85.61	82.20	83.58	83.41	0.60
6	What is the prevalence of drug-resistant TB in children in different clinical settings and geographical locations?	83.86	76.92	90.38	83.23	81.33	83.15	0.58
7	What are the reasons for default in children being treated for drug-resistant TB?	83.21	82.86	85.36	81.99	82.25	83.13	0.55
8	What are the social determinants of drug-resistant TB transmission in children?	85.67	85.27	80.14	79.11	83.68	82.77	0.55
9	Do children with HIV infection have a greater risk of drug-resistant TB infection and disease compared to children without HIV infection?	83.33	82.37	82.69	80.77	83.65	82.56	0.57
10	What is the optimal duration of treatment and combination of anti-tuberculosis drugs necessary to treat children with drug-resistant TB/MDR-TB/XDR-TB in different settings?	83.22	76.06	84.15	82.75	85.00	82.24	0.60

RPS = research priority score; AEA = average expert agreement; TB = tuberculosis; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

who reported their location, 30 (38%) were based in Asia, 29 (37%) in the Americas and 13 (17%) in Africa.

Among the 53 research questions, each research area—epidemiology, diagnosis, treatment and prevention—contained respectively 17, 9, 21 and 6 questions. The number of questions according to the research type—descriptive, development and discovery—was respectively 25, 16 and 12. The ranking of the 53 research questions with their RPS and AEA scores is provided in Appendix Table A.2. The scores ranged from 46 to 88 (potential 0–100), with scores of >80 for about 40% of the questions.

Table 3 shows the 10 highest-ranked questions based on the RPS and AEA. Of the 10 questions, 6 were related to treatment, 3 to epidemiology and 1 to diagnosis. The RPS ranged from 82 to 88 for the top 10 ranked questions and the AEA varied from 0.55 to 0.68. The top-ranked research question referred to the best combinations of existing tools for the early diagnosis of drug-resistant TB in children, which had an AEA of 0.62. The highest AEA, of 0.68, was for the question about the adverse effects of anti-tuberculosis drugs, which had an RPS of 87 and ranked second. Questions pertaining to treatment covered the reasons for poor treatment outcomes, optimal treatment duration and interventions for improving treatment outcomes. The prevalence of drug-resistant TB was the highest-ranked question in the epidemiology grouping, with an AEA of 0.58.

The 10 lowest-ranked questions had an RPS ranging from 46 to 66 and an AEA varying from 0.30 to 0.44 (Table 4). There were 6 questions pertaining to epidemiology, 3 to treatment and 1 to diagnosis. In terms of question type, 7 questions were the discovery type, 2 the descriptive type and 1 the development type. The questions related to discovery were on basic research for understanding the disease pathogenesis, transmission and biomarkers. Management of drug-resistant TB in the private sector featured among one of the lowest ranked questions, with an AEA of 0.41.

The highest-ranked questions according to research area and research type are shown in Tables 5 and 6. The epidemiology questions were related to estimating the burden, risk and determinants of disease, while the diagnostic questions evaluated existing and new diagnostic tools. Optimal screening modalities and preventive therapy were the highest-ranked questions for prevention, while adverse effects of second-line drugs and reasons for poor treatment outcomes were predominant in the treatment research area. The highly ranked questions of the descriptive type referred to treatment outcomes, whereas the development type questions were primarily about interventions for optimal diagnosis, treatment and modalities for treatment delivery. New drug evaluation and models for preventive therapy and for preventing new infections were predominant among the discovery type questions.

DISCUSSION

We report on the first effort to identify and rank research priorities specifically for preventing childhood disease and death due to

TABLE 4 The 10 lowest ranked research questions with RPS and AEA

Rank	Proposed research question	Answerability	Feasibility	Effectiveness	Deliverability	Equitability	RPS	AEA
44	How is drug-resistant TB in children treated in the private sector in terms of the duration of treatment and combination of anti-tuberculosis drugs?	73.48	67.42	64.55	61.74	61.19	65.68	0.41
45	Can protective factors (e.g., genetic/immunological/nutritional) for tuberculous infection or TB disease be determined in children who are household contacts of patients with drug-resistant TB?	71.28	62.15	69.79	61.81	62.50	65.51	0.44
46	How can the complications related to immune reactivation inflammatory syndrome or interactions between antiretroviral and anti-tuberculosis drugs be identified in HIV-infected children with drug-resistant TB?	63.43	54.92	64.77	61.15	66.92	62.24	0.39
47	What are the different innate and adaptive immune parameters that underlie infection with drug-susceptible and drug-resistant *Mycobacterium tuberculosis* in children?	64.19	59.03	59.51	55.28	56.34	58.87	0.34
48	Do biomarkers have a role in the diagnosis of drug-resistant TB in children?	63.67	54.17	60.42	56.60	55.63	58.10	0.36
49	Can mathematical modelling of dynamics and transmission of drug-resistant TB in children be computed in settings with high and low rates of HIV co-infection?	58.77	53.00	58.00	59.12	59.21	57.62	0.39
50	Can mathematical modelling of dynamics and transmission of drug resistant TB in children be computed in settings with high and low rates of drug-resistant TB?	58.97	54.00	57.89	58.22	59.00	57.62	0.38
51	What is the role of adjunct immunotherapy in children with drug-resistant TB?	60.29	57.20	58.33	54.62	53.79	56.85	0.31
52	Which biomarker or combination of biomarkers can determine the development of drug-resistant TB in children?	53.04	47.60	58.33	53.38	52.74	53.02	0.33
53	Can the location of *M. tuberculosis* in host tissues and its contribution to the development of drug-resistant or -susceptible TB be determined?	46.23	43.06	47.60	45.14	49.65	46.34	0.30

RPS = research priority score; AEA = average expert agreement; TB = tuberculosis; HIV = human immunodeficiency virus.

drug-resistant TB in children. This is important because it can support more informed conversations among practitioners, investigators and funders who share an interest in pursuing collaborative work in this area.

Early diagnosis and prompt treatment initiation reduce morbidity and mortality due to TB disease. The highest ranked research priority in this survey was to identify the best combinations of existing diagnostic tools to enhance early diagnosis of drug-resistant TB in children. The utility of newer diagnostic tools and non-invasive specimen collection methods for diagnosing drug resistance were identified as other high-priority diagnostic research questions. For example, the use of more sensitive tools for earlier diagnosis should be explored in children, such as the Xpert® MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA, USA), as well as earlier identification by whole genome sequencing of drug susceptibility profiles. The difficulties of establishing a diagnosis of drug-resistant TB in children are well known, and our findings reiterate the need for more research that can produce child-appropriate tests.

In the epidemiology research area, the prevalence of drug-resistant TB among children in different settings was a priority question. Conducting TB prevalence studies in children, although challenging, is essential, as this information is important to estimate the disease burden and assess the impact of interventions. Research involving the identification of children at high risk for drug-resistant TB, including household contacts and those with HIV infection, was ranked as high priority. Understanding the disease burden through monitoring high-risk groups is important for early identification of disease and for planning prophylactic strategies to prevent development of disease.

The treatment-related questions that were considered high priority were mainly descriptive and were related to reasons for poor

TABLE 5 The top three research questions in each research area and their rank

Research area	Rank
Epidemiology	
What is the prevalence of drug-resistant TB in children in different clinical settings and geographical locations?	6
What are the social determinants of drug-resistant TB transmission in children?	8
Do children with HIV infection have a greater risk of drug-resistant tuberculous infection and TB disease compared to children without HIV infection?	9
Diagnosis	
What are the best combinations of existing diagnostic tools to enhance early diagnosis of drug-resistant TB in children at the community level, in settings with different levels of resources, malnutrition and HIV prevalence?	1
What are the non-invasive specimen collection methods that can effectively diagnose drug-resistant TB in children?	13
Can new diagnostic techniques and management guidelines (scoring systems/algorithms, possibly incorporating new diagnostic tests) be adapted for different settings to diagnose drug-resistant TB in children?	16
Treatment	
What are the adverse effects of second line anti-tuberculosis drugs in children?	2
What are the risk factors associated with death and the causes of death in children being treated for drug-resistant TB?	3
What are the reasons for poor treatment outcomes in the treatment of drug-resistant TB in children?	4
Prevention	
What is the optimal duration of treatment and combination of anti-tuberculosis drugs for chemoprophylaxis of children in close contact with MDR-TB patients in different settings?	26
What are the best models for preventive therapy delivery and clinical monitoring to reduce default, the incidence of breakthrough TB and the occurrence of severe adverse events?	30
What are the best infection control measures that effectively reduce drug-resistant TB transmission at home and in health care settings?	31

TB = tuberculosis; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB.

treatment outcomes and adverse effects of anti-tuberculosis drugs. This type of information is essential for planning appropriate interventions that can increase cure rates and reduce mortality due to the disease. The development-type questions related to treatment that were highly prioritised were identifying the optimal treatment duration, child-friendly formulations of second-line anti-tuberculosis drugs and newer interventions for treatment delivery for favourable treatment outcomes. Treatment in children in terms of dosages of drugs, their combination and duration are derived mainly from studies done in adults, from which data are extrapolated to children. This exercise has prioritised the need to study optimal treatment and effective treatment delivery strategies for drug-resistant TB in children, which is important to reduce TB-related mortality and disease sequelae.

The six research questions pertaining to prevention of disease ranked between 26 and 37. The reasons for this could be the paucity of data even among adults on the optimal preventive therapy regimen and its duration. Effective screening algorithms to safely

TABLE 6 The top five questions in each research type and their rank

Research area	Rank
Descriptive	
What are the adverse effects of second-line anti-tuberculosis drugs in children?	2
What are the risk factors associated with death and the causes of death in children being treated for drug-resistant TB?	3
What are the reasons for poor treatment outcomes in the treatment of drug-resistant TB in children?	4
What is the prevalence of drug-resistant TB in children in different clinical settings and geographical locations?	6
What are the reasons for default in children being treated for drug-resistant TB?	7
Developmental	
What are the best combinations of existing diagnostic tools to enhance early diagnosis of drug-resistant TB in children at the community level, in settings with different levels of resources, malnutrition and HIV prevalence?	1
What is the role of nutritional intervention in improving treatment outcomes and adherence among children on treatment for drug-resistant TB?	5
What is the optimal duration of treatment and combination of anti-tuberculosis drugs necessary to treat children with drug-resistant TB/MDR-TB/XDR-TB in different settings?	10
What is the efficacy and safety of child-friendly formulations of second-line anti-tuberculosis drugs in children?	11
What interventions aimed at parents and guardians (a family-oriented approach) can be developed to improve treatment outcomes of drug-resistant TB in children?	12
Discovery	
What is the efficacy and safety of new anti-tuberculosis drugs in children with drug-resistant TB?	20
What are the best models for preventive therapy delivery and clinical monitoring to reduce default, the incidence of breakthrough TB and occurrence of severe adverse events?	30
What are the best infection control measures that effectively reduce drug-resistant TB transmission at home and in health care settings?	31
What innovative community-based interventions are available to reduce the transmission of drug-resistant TB in children?	37
What are the markers for response to treatment as surrogates/correlates of clinical efficacy in children being treated for drug-resistant TB?	43

TB = tuberculosis; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

initiate preventive therapy and the optimal preventive therapy regimens ranked higher in the preventive area of research.

Descriptive and development types of research questions received a high RPS of >80%, highlighting the need for research in evaluating and improving existing strategies, while discovery research questions (5/10) in terms of understanding the host susceptibility to disease and identification of biomarkers ranked lower. The reason for this could be that the translational benefits of discovery in basic research take longer to have an impact on reductions in mortality and morbidity. However, discovery research involving new TB drugs and models for prevention of disease scored high, emphasising that respondents consider that discovery research is imperative to reduce the burden of drug-resistant disease in children.

Understanding the current management of childhood drug-resistant TB in the private sector featured among the 10 lowest ranked questions. This is an interesting finding given that TB is managed equally in both the private and public sector in many countries, including India. The lower priority ranking may reflect a misperception that childhood TB is infrequently managed in the private sector,[22] or it may reflect the respondents' assessment that producing evidence in other areas (i.e., how best to diagnose or treat childhood drug-resistant TB) will have more impact on improving care for children. Certainly, poor prescription practices have been documented among private practitioners,[23,24] and in some countries any sustainable impact on TB burden must necessarily involve the private sector.

Limitations of this survey include the relatively small pool of survey respondents, whose overall profile is that of clinicians or researchers interested in drug-resistant TB. However, this characteristic is also an advantage, as the group of respondents includes individuals with experience in programmes aiming to treat and prevent drug-resistant TB specifically in children. The fact that 44 of the 53 questions had a score of >70% showed that most of the research questions were already deemed important by the experts. Further, the survey used a modified criterion assessment scale to suit the context and operational feasibility.

Another potential limitation to the generalisability of the ranked question list is that 23 of the 79 (29%) respondents who reported their country were based in a single country (India). This was a result of including the convenience sample afforded by the workshop participants from across India, which is home to 25–30% of global childhood drug-resistant TB cases,[2,25,26] but where very few data are available on MDR-TB in children.[27] It is important to note that our survey was not designed to represent countries according to their relative disease burden. Our survey was designed to synthesise the opinions of individuals with expertise or interest specifically in childhood drug-resistant TB—many of whom have worked in multiple countries—who were willing to rank research gaps that presently impact children with drug-resistant TB. Future priority-setting exercises that aim to update this ranking may be designed differently; for example, they may purposely recruit respondents based in specific countries or according to other types of geographic or institutional settings.

In summary, the problem of drug-resistant TB in children is poorly understood, and the optimal approach is unknown for reducing the toll of this disease specifically in children. Diagnosis of TB in children is challenging due to difficulties in collecting samples, while the paucibacillary nature of the disease reduces the sensitivity of testing. The treatment options for children are based on expert opinion, case series and cohort studies, with small sample sizes.[28] Treatment is expensive and remains associated with poor prognosis and a high risk of toxic effects.[29] Thus, prevention of progression to MDR-TB disease in children could be a practical and cost-effective solution from the public health perspective.[30]

Our results suggest that, for the time being, priority should be given to more descriptive and development types of research studies related to the diagnosis and treatment of drug-resistant TB in children. The prioritisation of funding for TB research projects will ultimately be determined by each organisation's investment context, i.e., the balance between those results needed within a short term and those that are more long-term. This is the first effort to establish research priorities in this area of child health through a systematic survey of expert stakeholders based in multiple countries. The results may serve as a framework that can be updated periodically and as a shared resource to guide new research to improve the prevention and treatment of drug-resistant TB in children.

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APPENDIX

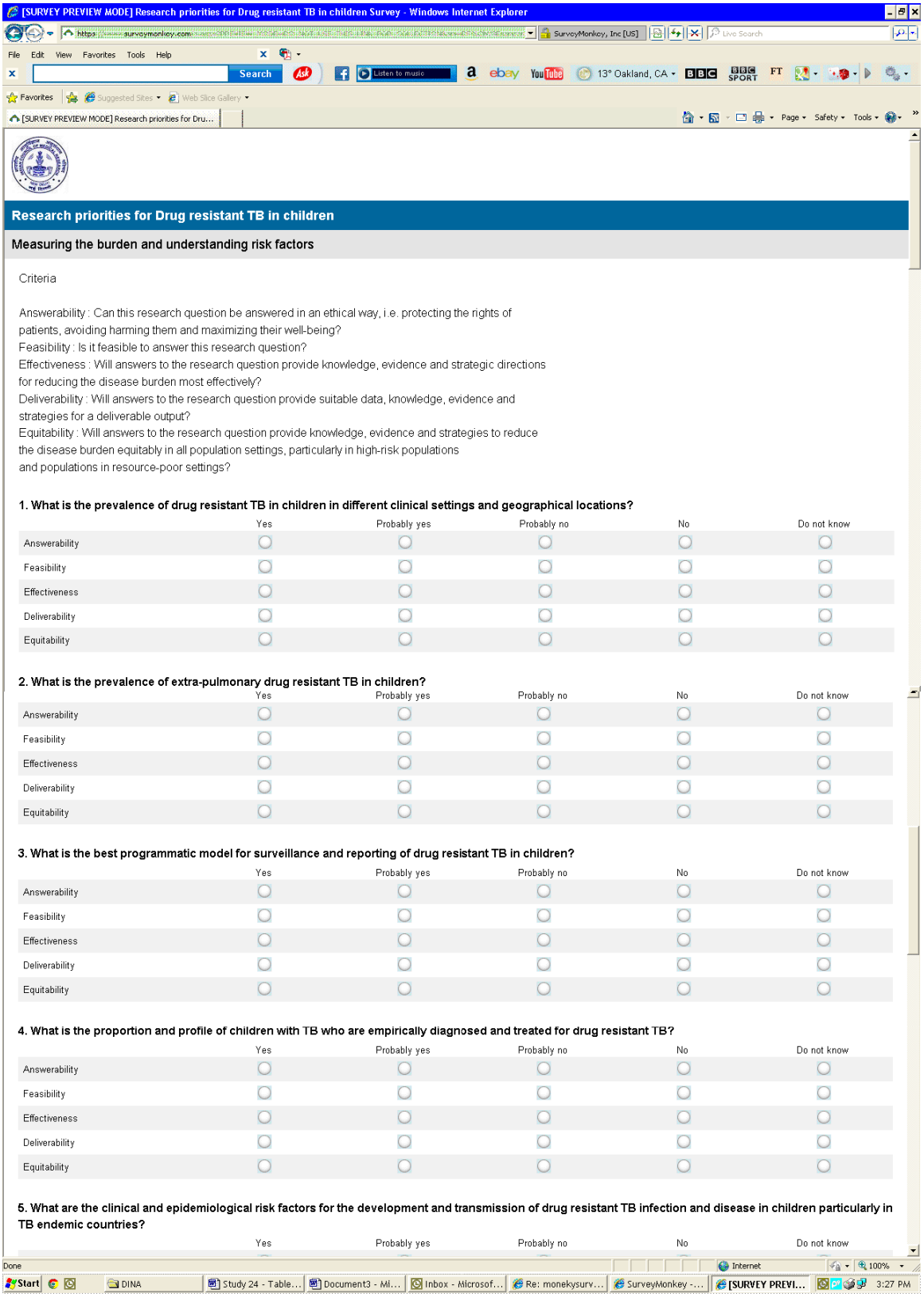

FIGURE A Screenshot of the Survey Monkey questionnaire.

TABLE A.1 Qualification, expertise, and country of survey respondents

ID	Qualification	Expertise	Country
1	MBBS MPH	Public health	India
2	MBBS	TB	India
3	MD, MPH	Paediatric TB, global health, paediatric infectious diseases	USA
4	MD, PhD	Child TB	Australia
5	Tropical Public Health and epidemiology	TB epidemiology and diagnostics	Colombia
6	MBBS, MSc	TB	India
7	Public Health and Epidemiology	TB diagnostics and epidemiology	Colombia
8	MD/DPH	Training officer	India
9	MPH	TB and HIV	Nepal
10	MD	Paediatric TB-HIV	USA
11	MD/PhD	Diagnostics and disease prevention	India
12	MS in Social Administration and Planning	Program development	Pakistan
13	MD	Infectious Disease Fellow	USA
14	MBChB, MPH	TB control, epidemiology and disease control	Africa
15	MD	MDR-TB	India
16	MD (Paediatrics), DCH	Paediatrics	India
17	MBBS DTCD	TB	Switzerland
18	MD Paediatrics	HIV, nutrition	India
19	MD (Internal Medicine)	Public health, TB, HIV, MCHN, malaria, leprosy	India
20	Pharmacist	Infectious disease; clinical trials	USA
21	PhD	Epidemiology	USA
22	MD Paediatrics	Paediatrics	India
23	MD, MPH	Basic operational research, few publications	Colombia
24	MD, MPH	Adult infectious disease consultant and paediatric TB researcher	USA
25	Paediatric infectious disease	NTP assistant and consultant	Africa
26	Paediatrician	General paediatrics	Africa
27	Master of Public Health	TB and HIV	Nepal
28	MBBS, DTCD	Chest specialist	India
29	MA	Social work	India
30	Assistant Director, TB-HIV Project	Drugs	USA
31	LLB	Social service	India
32	MD	TB	Kenya
33	MBChB	MDR-TB	Africa
34	MD	Public health, infectious and tropical diseases	USA
35	PhD	Mycobacteriologist	Ethiopia
36	Regional Lead	Infectious diseases	NR
37	TB doctor	Clinical, programme management	USA
38	Bachelor in Statistics	MDR-TB	India
39	Paediatric Infectious Disease	TB, HIV	USA
40	MD, PhD, ScM	TB, MDR-TB, health systems, medical anthropology	USA
41	MD, DrPH	Drug safety	USA
42	MD	Paediatric TB-HIV	USA
43	MD	Consultant TB expert	Sweden
44	FCPaed(SA) MMed(Paed)	Paediatrician, research clinician, pharmacokinetics studies, Childhood TB	South Africa
45	MD	Paediatrics	India
46	MD (Paediatrics)	Paediatrics	India
47	Master in Medical Sociology	TB programme management	Nepal
48	MD	Professor and head	India
49	MBBS, MD (Paediatrics)	Paediatrics	India
50	MBBS, DPH	Public health, HIV, TB	India
51	DCH	General paediatrician	India
52	MD, MPH	Paediatric TB	USA
53	NR	Market dynamics, guideline development/implementation	USA
54	MD/HRD-Training officer	NR	NR
55	Paediatric infectious disease specialist	Treatment and management of childhood TB; TB clinical drug trials	USA
56	MBChB, MMed Paed, DCM, MD Paed	Childhood TB and drug-resistant TB	South Africa
57	Medicine	Paediatric HIV and TB	South Africa
58	Medical Officer	TB-HIV, childhood TB	USA

TABLE A.1 (continued)

ID	Qualification	Expertise	Country
59	MD	TB, epidemiology, drug resistance, guidelines	Switzerland
60	MD	Infectious diseases, public health, epidemiology, clinic	Switzerland
61	Doctor of Public Health	Research/public health	India
62	Infectious Diseases Specialist	TB control	USA
63	MD, MPH	TB-HIV, drug-resistant TB	USA
64	MBBS, DTCD, PhD	Clinical DR-TB	Bangladesh
65	MD, PhD in Epidemiology	HIV, TB/MDR-TB, operational research	India
66	MBBS, MPhil (Microbiology)	Laboratory medicine	Bangladesh
67	MD	Paediatric infectious diseases	Africa
68	MBBS (DU), DTCD (DU), DTCE (Japan)	TB and chest diseases specialist	Bangladesh
69	MBBCh, FCPaed, MMed (Paed), Cert ID (Paed) SA, MPhil (Paed ID)	Paediatric infectious diseases	South Africa
70	MBBCh, FCPaed, DCH, DTM&H	Paediatric infectious diseases subspecialist, including DR-TB	South Africa
71	Treat children with TB	Childhood TB	USA
72	PhD	Paediatric infectious diseases	UK
73	MD MSc	MDR-TB, TB treatment, M&E	USA
74	MD	MDR-TB and TB diagnostics	UK
75	MPH, Pharmacy	Supply chain management, quantification of TB drug needs, M&E, pharmacovigilance	USA
76	PhD	Basic science, diagnostics, infectious diseases	USA
77	MPH	Epidemiology; policy analysis	USA
78	MD	HIV/AIDS, infectious diseases	Congo
79	MBBS, MD (Ped)	Children's environmental health, childhood TB	India
80	ScD (Epidemiology)	Research on treatment outcomes and contact evaluations	USA
81	MD, PhD	MDR-TB	USA

MBBS = Bachelor of Medicine, Bachelor of Surgery; MPH = Master of Public Health; TB = tuberculosis; MD = Doctor of Medicine; PhD = Doctorate of philosophy; MSc = Master of Science; DPH = Doctor of Public Health; HIV = human immunodeficiency virus; MS = Master of Science; MBChB = Bachelor of Medicine, Bachelor of Surgery; MDR-TB = multidrug-resistant TB; DCH = Diploma in Child Health; DTCD = Diploma in tuberculosis and chest diseases; MCHN = Maternal Child Health and Nutrition; NTP = national tuberculosis programme; MA = Master of Arts; LLB = Bachelor of Law; NR = no response; ScM = Master of Science; FCPaed (SA) = Fellow of the College of Paediatrics (South Africa); MMed = Master of Medicine; HRD = human resources development; DCM = Diploma in Community Medicine; DU = Delhi University; DTCE = digital technologies, communication and education; Cert ID = Certificate in Infectious Diseases; MPhil = Master of Philosophy; DTM&H = Diploma in tropical medicine and hygiene; DR-TB = drug-resistant TB; M&E = monitoring and evaluation; ScD = Doctor of Science; AIDS = acquired immune-deficiency syndrome.

TABLE A.2 Final ranking of all 53 research questions with RPS and AEA

Rank	Question number	Research question	Research area	Research type	Answerability	Feasibility	Effectiveness	Deliverability	Equitability	RPS	AEA
1	q18	What are the best combinations of existing diagnostic tools to enhance the early diagnosis of DR-TB in children at the community level, in settings with different levels of resources, malnutrition and HIV prevalence?	Diagnosis	Development	87.33	84.72	90.49	89.08	88.38	88.00	0.62
2	q30	What are the adverse effects of second line anti-tuberculosis drugs in children?	Treatment	Descriptive	88.93	85.21	89.29	85.51	85.87	86.96	0.68
3	q31	What are the risk factors associated with death and the causes of death in children being treated for DR-TB?	Treatment	Descriptive	82.75	81.94	85.92	84.78	85.51	84.18	0.55
4	q29	What are the reasons for poor treatment outcomes in the treatment of DR-TB in children?	Treatment	Descriptive	83.68	82.39	85.92	83.57	81.88	83.49	0.56
5	q45	What is the role of nutritional intervention in improving treatment outcomes and adherence among children on treatment for DR-TB?	Treatment	Development	83.09	82.58	85.61	82.20	83.58	83.41	0.60
6	q1	What is the prevalence of DR-TB in children in different clinical settings and geographical locations?	Epidemiology	Descriptive	83.86	76.92	90.38	83.23	81.33	83.15	0.58
7	q32	What are the reasons for default in children being treated for DR-TB?	Treatment	Descriptive	83.21	82.86	85.36	81.99	82.25	83.13	0.55
8	q11	What are the social determinants of DR-TB transmission in children?	Epidemiology	Descriptive	85.67	85.27	80.14	79.11	83.68	82.77	0.55
9	q7	Do children with HIV infection have a greater risk of DR-TB infection and disease compared to children without HIV infection?	Epidemiology	Descriptive	83.33	82.37	82.69	80.77	83.65	82.56	0.57
10	q27	What is the optimal duration of treatment and combination of anti-tuberculosis drugs necessary to treat children with DR-TB/MDR-TB/XDR-TB in different settings?	Treatment	Development	83.22	76.06	84.15	82.75	85.00	82.24	0.60
11	q44	What is the efficacy and safety of child-friendly formulations of second line anti-tuberculosis drugs in children?	Treatment	Development	80.88	80.30	86.94	82.95	78.36	81.89	0.58
12	q41	What interventions aimed at parents and guardians (a family-oriented approach) can be developed to improve treatment outcomes of DR-TB in children?	Treatment	Development	82.25	78.68	84.33	81.54	82.42	81.84	0.52
13	q22	What are the non-invasive specimen collection methods that can effectively diagnose DR-TB in children?	Diagnosis	Descriptive	82.53	81.69	80.21	81.07	82.04	81.51	0.56
14	q40	What are the best intervention models for treatment delivery in the management of DR-TB in children?	Treatment	Development	83.96	79.92	84.70	81.06	76.87	81.30	0.57
15	q6	Do children who are household contacts of adults with DR-TB have a greater risk of tuberculous infection and TB disease compared with children who are household contacts of adults with drug-susceptible TB?	Epidemiology	Descriptive	85.49	84.09	78.57	77.92	79.87	81.19	0.59
16	q19	Can new diagnostic techniques and management guidelines (scoring systems/algorithms, possibly incorporating new diagnostic tests) be applied for different settings to diagnose DR-TB in children?	Diagnosis	Development	84.59	78.13	82.39	79.58	81.07	81.15	0.52

TABLE A.2 (continued)

Rank	Question number	Research question	Research area	Research type	Answerability	Feasibility	Effectiveness	Deliverability	Equitability	RPS	AEA
17	q5	What are the clinical and epidemiological risk factors for the development and transmission of DR-TB?	Epidemiology	Descriptive	83.33	74.62	83.46	80.00	80.86	80.45	0.55
18	q23	What is the diagnostic yield from different specimens that is feasible, cost-effective and point-of-care to diagnose TB and DR-TB in children?	Diagnosis	Descriptive	82.88	78.82	80.28	77.82	80.28	80.02	0.55
19	q33	What is the optimal duration of treatment and combination of anti-tuberculosis drugs necessary to treat children with DR-TB co-infected with HIV?	Treatment	Development	78.57	75.00	82.75	79.64	80.71	79.34	0.52
20	q42	What is the efficacy and safety of new TB drugs in children with DR-TB?	Treatment	Discovery	75.37	74.62	84.47	81.34	78.03	78.77	0.51
21	q21	What is the effectiveness of current practices in the diagnosis of TB and DR-TB in children?	Diagnosis	Descriptive	79.11	77.11	78.17	77.46	77.86	77.94	0.53
22	q4	What is the proportion and profile of children with TB who are empirically diagnosed and treated for DR-TB?	Epidemiology	Descriptive	77.30	73.36	81.17	77.33	77.67	77.37	0.47
23	q38	What are the pharmacokinetics of second-line anti-tuberculosis drugs in children?	Treatment	Descriptive	77.61	77.73	79.30	75.38	76.59	77.32	0.56
24	q3	What is the best programmatic model for surveillance and reporting of DR-TB in children?	Epidemiology	Development	76.27	72.78	80.00	75.63	78.16	76.57	0.48
25	q10	Can improved techniques to identify transmission hot spots of drug-susceptible and DR-TB within communities be developed?	Epidemiology	Development	74.06	72.44	77.92	76.95	80.84	76.44	0.47
26	q48	What is the optimal duration of treatment and combination of anti-tuberculosis drugs for chemoprophylaxis of children in close contact with MDR-TB patients in different settings?	Prevention	Development	72.35	71.09	80.38	78.91	76.19	75.78	0.51
27	q39	What are the effects of age, nutritional status and HIV co-infection on drug pharmacokinetics?	Treatment	Descriptive	76.47	72.69	76.89	75.77	76.15	75.60	0.55
28	q28	What is the optimal duration of treatment and combination of anti-tuberculosis drugs necessary to treat children with DR-EPTB?	Treatment	Development	75.00	69.93	77.50	73.55	77.90	74.78	0.53
29	q35	What are the rates of treatment failure and recurrence in HIV co-infected children being treated for DR-TB?	Treatment	Descriptive	73.24	73.55	77.21	73.53	75.75	74.65	0.45
30	q50	What are the best models for preventive therapy delivery and clinical monitoring to reduce default, the incidence of breakthrough TB and occurrence of severe adverse events?	Prevention	Discovery	75.77	71.54	76.56	73.41	75.00	74.46	0.44
31	q51	What are the best infection control measures that effectively reduce DR-TB transmission at home and in health care settings?	Prevention	Discovery	75.00	71.48	74.22	75.39	76.17	74.45	0.48
32	q24	What are the diagnostic tools and algorithms for diagnosing DR-EPTB in children?	Diagnosis	Descriptive	73.97	70.77	75.71	72.54	76.47	73.89	0.46
33	q49	In children living with HIV, what is the optimal duration and timing of initiation of preventive therapy for DR-TB in relation to ART to reduce the risk of active TB?	Prevention	Development	71.64	63.49	75.79	75.40	77.38	72.74	0.45
34	q20	How can the symptoms, signs and other characteristics used in diagnostic approaches for DR-TB in children be clearly defined and standardised?	Diagnosis	Development	75.69	67.36	71.83	73.94	73.57	72.48	0.42

TABLE A.2 (continued)

Rank	Question number	Research question	Research area	Research type	Answerability	Feasibility	Effectiveness	Deliverability	Equitability	RPS	AEA
35	q52	What is the optimal TB screening algorithm to be used to safely initiate preventive TB therapy for DR-TB in children across settings with different burdens of TB and HIV disease?	Prevention	Development	71.59	66.67	75.39	72.27	75.00	72.18	0.44
36	q34	What are the pharmacokinetic interactions between and toxicity of anti-tuberculosis treatment and ART in HIV-infected children treated for DR-TB?	Treatment	Descriptive	75.00	68.12	72.10	70.29	70.22	71.15	0.44
37	q53	What innovative community-based interventions are available to reduce transmission of DR-TB in children?	Prevention	Discovery	72.35	66.80	72.27	70.16	73.08	70.93	0.45
38	q36	What is the influence of commonly seen co-morbidities (such as diarrhoea, malabsorption syndrome, hepatitis and parasitic infections) on the metabolism of anti-tuberculosis drugs and clinical outcomes of DR-TB in HIV-infected children?	Treatment	Descriptive	71.58	65.71	73.91	68.84	70.29	70.07	0.42
39	q25	How is DR-TB in children diagnosed in the private sector?	Diagnosis	Descriptive	73.33	71.53	70.83	65.63	63.19	68.90	0.40
40	q2	What is the prevalence of DR-EPTB in children?	Epidemiology	Descriptive	70.83	56.88	75.00	69.48	71.75	68.79	0.41
41	q13	What are the genotypic and phenotypic characteristics of *M. tuberculosis* strains associated with drug resistance in children?	Epidemiology	Descriptive	73.99	67.47	68.15	63.54	66.32	67.89	0.42
42	q12	What is the relationship between molecular strain patterns and drug resistance in children?	Epidemiology	Descriptive	73.31	63.85	68.06	67.12	65.94	67.66	0.41
43	q46	What are the markers for response to therapy as surrogates/ correlates of clinical efficacy in children being treated for DR-TB?	Treatment	Discovery	66.91	59.85	70.83	66.29	69.03	66.58	0.41
44	q47	How is DR-TB in children treated in the private sector in terms of the duration of treatment and combination of anti-tuberculosis drugs?	Treatment	Descriptive	73.48	67.42	64.55	61.74	61.19	65.68	0.41
45	q15	Can protective factors (e.g., genetic/immunological/ nutritional) for tuberculous infection or TB disease be determined in children who are household contacts of patients with DR-TB?	Epidemiology	Discovery	71.28	62.15	69.79	61.81	62.50	65.51	0.44
46	q37	How can the complications related to immune reactivation inflammatory syndrome or interactions between antiretroviral and anti-tuberculosis drugs be identified in HIV-infected children with DR-TB?	Treatment	Discovery	63.43	54.92	64.77	61.15	66.92	62.24	0.39
47	q14	What are the different innate and adaptive immune parameters that underlie infection with drug-susceptible and DR *M. tuberculosis* in children?	Epidemiology	Discovery	64.19	59.03	59.51	55.28	56.34	58.87	0.34
48	q26	Do biomarkers have a role in the diagnosis of DR-TB in children?	Diagnosis	Discovery	63.67	54.17	60.42	56.60	55.63	58.10	0.36
49	q8	Can mathematical modelling of dynamics and transmission of DR-TB in children be computed in settings with high and low rates of HIV co-infection?	Epidemiology	Development	58.77	53.00	58.00	59.12	59.21	57.62	0.39

TABLE A.2 (continued)

Rank	Question number	Research question	Research area	Research type	Answerability	Feasibility	Effectiveness	Deliverability	Equitability	RPS	AEA
50	q9	Can mathematical modelling of dynamics and transmission of DR-TB in children be computed in settings with high and low rates of DR-TB?	Epidemiology	Descriptive	58.97	54.00	57.89	58.22	59.00	57.62	0.38
51	q43	What is the role of adjunct immunotherapy in children with DR-TB?	Treatment	Discovery	60.29	57.20	58.33	54.62	53.79	56.85	0.31
52	q17	Which biomarker or combination of biomarkers can determine the development of DR-TB in children?	Epidemiology	Discovery	53.04	47.60	58.33	53.38	52.74	53.02	0.33
53	q16	Can the location of *M. tuberculosis* in host tissues and its contribution to the development of DR or drug susceptible TB be determined?	Epidemiology	Discovery	46.23	43.06	47.60	45.14	49.65	46.34	0.30

RPS = research priority score; AEA = average expert agreement; DR = drug-resistant; TB = tuberculosis; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB; EPTB = extra-pulmonary TB; ART = antiretroviral therapy.

Contexte : De nombreuses lacunes en matière de connaissances entravent la prévention et le traitement de la tuberculose (TB) pharmacorésistante. L'identification des priorités de recherche est vitale pour informer et développer des stratégies afin de répondre à ce problème négligé.
Objectif : Tenter d'identifier systématiquement et de classer par ordre les priorités en matière de recherche sur la TB pharmacorésistante de l'enfant.
Schéma : Ayant adapté la méthode de *Child Health and Nutrition Research Initiative (CHNRI)* (Initiative de recherche en santé et en nutrition de l'enfant), nous avons compilé 53 questions de recherche dans quatre domaines, puis les avons classées en trois types de recherche différents. Nous avons invité des experts en TB pharmacorésistante de l'enfant à classer ces questions grâce à une enquête en ligne.
Résultats : Un total de 81 personnes ont participé à l'enquête. La question de recherche qui a été classée première était l'identification des meilleures associations d'outils de diagnostic existants pour permettre un diagnostic précoce. Les questions considérées comme prioritaires en matière de traitement étaient centrées sur des interventions visant à améliorer les résultats du traitement, à réduire les effets secondaires des médicaments et à déterminer la durée idéale du traitement. La prévalence de la TB pharmacorésistante était la priorité dans le domaine de l'épidémiologie. Les questions relatives au développement ont été considérées comme hautement prioritaires et se sont focalisées sur des interventions d'amélioration du diagnostic, du traitement et des modalités de délivrance du traitement.
Conclusion : Cette enquête est la première qui vise à identifier et à hiérarchiser les priorités de recherche relatives à la TB pharmacorésistante de l'enfant. Son résultat constitue une ressource pour guider la recherche afin d'améliorer la prévention et le traitement de la TB pharmacorésistante de l'enfant.

Marco de referencia: Numerosas lagunas de conocimiento obstaculizan la prevención y el tratamiento de la tuberculosis drogorresistente (TB-DR) en niños. Es esencial identificar cuales son las áreas prioritarias de investigación para informar y desarrollar estrategias para hacer frente a este problema descuidado.
Objetivo: Identificar sistemáticamente las prioridades de investigación en la TB-DR en niños, y construir una clasificación jerárquica de ellas.
Diseño: Se adaptó la metodología de la Iniciativa de Investigación en Salud y Nutrición Infantil (CHNRI). Recopilamos 53 preguntas de investigación en cuatro áreas de investigación y luego las clasificamos entre tres tipos de investigación. Invitamos a expertos en TB-DR en niños a que asignen puntajes a cada una de estas preguntas usando una encuesta en línea.
Resultados: Un total de 81 individuos participaron en la encuesta. La pregunta de investigación con el puntaje más alto fue de identificar la mejor combinación de existentes herramientas de diagnosis para llegar a un diagnóstico precoz. Preguntas con altos puntajes relacionadas al tratamiento se centraron en entender las razones y las intervenciones para mejorar los resultados del tratamiento, los efectos adversos de los fármacos y la duración óptima del tratamiento. La prevalencia de la TB-DR fue la pregunta con el más alto puntaje en el área de epidemiología. Las preguntas de tipo desarrollo con puntajes más altos se centraron en las intervenciones para el diagnóstico óptimo, el tratamiento óptimo y las modalidades óptimas de prestación del tratamiento.
Conclusión: Este ha sido el primer esfuerzo de identificar y clasificar jerárquicamente las prioridades de investigación en la TB-DR en niños. El resultado es un recurso para orientar la investigación para mejorar la prevención y el tratamiento de la TB-DR en niños.

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