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Commentary

A targets framework: Dismantling the invisibility trap for children with drug-resistant tuberculosis

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Abstract Tuberculosis (TB) is an airborne infectious disease that is both preventable and curable, yet it kills more than a million people every year. Children are highly vulnerable, but often invisible casualties. Drug-resistant forms of TB are on the rise globally, and children are as vulnerable as adults but less likely to be counted as cases of drug-resistant disease if they become sick. Four factors make children with drug-resistant TB 'invisible': first, the nature of the disease in children; second, deficiencies in existing diagnostic tools; third, overreliance on these tools; and fourth, our collective failure to deploy one effective tool for finding and treating children – *contact investigation*. We describe a nascent science-advocacy network – the Sentinel Project on Pediatric Drug-Resistant Tuberculosis – whose goal is to end child deaths from this disease. Provisional annual targets, focused on children exposed at home to multidrug-resistant TB, to be updated every year, constitute a framework to focus attention and collective actions at the community, national, and global levels. The targets in two age groups, under 5 and 5–14 years old, tell us the number of: (i) children who require complete evaluation for TB disease and infection; (ii) children who require treatment for TB disease; and (iii) children who would benefit from preventive therapy.
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Introduction

Burden of tuberculosis (TB) and drug resistance

The global burden of TB disease is enormous. In 2012, the World Health Organization estimated that 8.6 million people became sick with TB

(new cases) and 1.3 million people died from TB.[1] At least 1 million children become sick with TB every year,[2,3] and at least 8 million children are infected every year.[4] In any year, children in high TB-burdened communities account for more than 25 per cent of all those who become sick with TB.[5,6]

Drug-resistant tuberculosis (DR-TB) is defined as disease caused by an *M. tuberculosis* strain resistant to one or more TB drugs. A subset, *multidrug-resistant* TB (MDR-TB), is caused by a strain resistant to at least isoniazid and rifampin, the two drugs that presently form the basis of first-line therapy. Strains resistant to more drugs have been called *extensively drug-resistant TB* (XDR-TB) or *totally drug-resistant TB* (TDR-TB), both subsets of MDR-TB. WHO estimates that at least half a million people become sick with MDR-TB each year.[1] Official estimates of all forms of DR-TB probably grossly underestimate the true burden of this problem.[7–12] A recent survey in China suggests a much larger DR-TB disease burden than expected.[13] China, along with India and Russia, are thought to bear about 60 per cent of the global burden of MDR-TB disease.[1]

The work we describe here began after an April 2011 workshop in Delhi to examine barriers to scaling up treatment for DR-TB in India.[10] Other workshops to better understand DR-TB in South Africa, Russia, and China[8–10,12] all drew attention to a hidden epidemic of DR-TB in children. The Delhi workshop led us to grasp that the near invisibility everywhere of children with DR-TB was itself a barrier to expanded research and improved treatment access.

Our systematic review[14] found that children sick with isoniazid-resistant TB have been reported in at least 40 countries. WHO surveillance reports make it clear that MDR-TB is as common in children as in adults, yet government reports capture very few children with the disease.[15] The first estimates of how many children become sick with MDR-TB each year suggest 32 000 (95 per cent CI: 26 000–39 000).[3] No one has estimated the larger number of children who become sick with other forms of DR-TB.

TB Treatment Saves Lives and Prevents New Infections, but Access to DR-TB Treatment is Limited

TB is curable, even highly drug-resistant *M. tuberculosis*. Nearly all those sick with TB organisms susceptible to first-line drugs can be cured.

When someone is sick with a drug-resistant strain, cure remains possible using drugs to which the infecting strain is susceptible. Knowing which drugs to use, however, requires the sick person's strain be isolated and tested for drug-susceptibility.

At least 60 per cent of those sick with MDR-TB can be cured using existing drugs; some programs have achieved better than 75 per cent cure.[16] Children with MDR-TB do better than adults, with cure achieved in over 80 per cent.[17] Individuals sick with TB strains resistant to many drugs can still be cured with prompt treatment and a potent drug combination.[18] Inadequate treatment selects TB organisms resistant to yet more drugs.[19] These also spread by the airborne route.[20]

Guidance for how to cure people sick with DR-TB and stop further spread has been available for nearly 20 years.[21–24] Low and middle income countries bear the greatest burden of TB and DR-TB.[1] Richer countries have programs to stem the spread of DR-TB, but such programs are rare in the rest of the world.[25]

Between 2000 and 2009, fewer than 1 per cent of all those sick with MDR-TB were treated with drugs of known good quality.[11,26] Children likely accounted for very few of those treated. The US Institute of Medicine, in a series of workshops, has examined barriers and proposed ways to get effective DR-TB treatment to all those who require it.[6,8–11] Yet today, most people sick with DR-TB remain undetected and untreated.[26,27] They continue to spread DR-TB strains through the air – to family, friends, and strangers.

Why are Children with Drug-Resistant TB Invisible?

The 'Roadmap for childhood tuberculosis: Towards zero deaths'[28] is the latest guidance from a dedicated group of experts and advocates who, for more than a decade, has worked to bring more systematic attention to the plight of children affected by TB.[29–31] Children sick with TB have been neglected to the point of invisibility.[28,32–36] The confluence of four factors makes children sick with drug-resistant strains of *M. tuberculosis* even more difficult to 'see' and treat:

- *Childhood TB is different from adult TB*: Children typically have fewer mycobacteria (bacillary burden) than adults and are more likely to have extra-pulmonary TB.[37–40] Young children have difficulty producing testable sputum, the specimen most used for testing. Without sputum, a

bacteriological diagnosis of *M. tuberculosis,* which requires viewing or growing the TB organism, is infrequent.[41] A diagnosis of TB disease in a child can, without sputum, be assembled using a combination of clinical (including radiographic), immunological (skin testing), and epidemiological criteria (known contact with a person who is sick with TB). Doctors usually decide whether to treat without a bacteriological confirmation of *M. tuberculosis* and even when confirmed by culture, treatment is begun without drug susceptibility data.[42–44]

- *Today's diagnostic tools are fundamentally limited.*[45–48] Without isolating the organism, drug-susceptibility testing of the child's TB strain cannot be performed. Although growing *M. tuberculosis* in culture media is the 'gold standard', a microscopic examination of a specimen, usually sputum, can be useful. As it is less expensive and requires less complex technology compared with culture, smear microscopy has become the principal diagnostic tool in most TB programs.[49] But smear microscopy performs poorly in individuals with low bacillary burdens – children and those with HIV co-infection. Fewer than 20 per cent of children with TB disease will have a smear-positive sputum test result.[50] Even culture, far more sensitive than smear microscopy, performs poorly in children: fewer than half of children with TB disease will have *M. tuberculosis* isolated in sputum cultures.[51] Yet culturing the bacterium has been a pre-requisite for testing drug susceptibility. New rapid molecular tests (CB NAAT or Xpert MTB/Rif), designed to detect TB disease and drug resistance without culturing, still depend on sputum specimens.[52] Despite their limitations for diagnosing children, experts suggest these tests should be the first used for children suspected of having TB disease and/or drug resistance.[31,53]
- *Children sick with TB and DR-TB are under-represented in systematic information sources.*[54,55] Researchers use routinely reported TB case data to estimate disease burden. But these data are not consistently available by age group. Data are available by age group for TB cases detected by smear microscopy. But, as noted above, children with TB are unlikely to be detected by this test. Two other potential sources of data might be used to inform childhood TB estimates, but neither includes child-specific information:

    - Systematic TB prevalence surveys from many countries exclude children (age<15 years) by design.[56]

- Systematic DR-TB surveys and surveillance studies have required positive smear microscopy test results. As children are far less likely than adults to meet this inclusion criterion, fewer than 2 per cent of TB cases included in systematic DR-TB surveys were children.[15]

It can be argued that including children in either TB or DR-TB prevalence surveys is not the most efficient way to improve estimates of the childhood disease burden, but no other systematic data collection has been used to inform robust estimates of childhood TB and DR-TB. For the same reasons, it is exceedingly difficult to quantify how much TB contributes to child mortality.[57] A sizeable proportion of child deaths attributed to malnutrition, pneumonia, or HIV infection may be due to undiagnosed TB. That would make it one of the most important causes of death in young children, worldwide.

- *TB contact investigation has yet to be deployed in most of the world.* The one reliable tool for promptly finding and treating children with TB is not used in much of the world. *Contact investigation* is the systematic identification and evaluation of individuals known to be exposed to someone sick with TB, permitting treatment of clinical disease or treatment of latent infection (the latter is also known as preventive therapy).[21,58] Contact investigation is standard practice in some places;[23] and a cornerstone of the TB elimination strategy in the United States.[59–61] Adult and pediatric household contacts are at high risk for both infection and disease.[62,63] This is similarly true for those living with someone sick with DR-TB.[64] Recent global guidelines emphasize contact tracing in all households of those sick with TB,[65] particularly households where someone is sick with MDR-TB.[1,66] Although no controlled trials have examined preventive therapy for persons exposed to MDR-TB,[67] experts who have reviewed observational data suggest management of close contacts include preventive therapy regimens for MDR-TB.[68–73]

Contact investigation has, for half a century,[74] been the best way to find children newly infected with TB and those with early disease. It remains so today.[21,75–79] Unfortunately, despite global policy recommendations,[30,65,66] countries with high TB burdens rarely use contact investigation.[80,81] It is in these places where most children with TB live.

How often do we find TB in children living with someone who is sick with TB? In some high-burden settings, as many as one-third of children

had TB disease.[82,83] Contact investigations can find children sick in early stages of TB, increasing the chances of cure.[84] Furthermore, preventive therapy is highly effective in children[59] and cost-effective as well.[79] Failure to deploy contact investigation everywhere means we are not using the one tool that could allow us to 'see' and treat promptly otherwise invisible children sick with TB.

For more than two decades, the dominant strategy for confronting TB in high-burden countries attempted to treat the most infectious people and thereby prevent TB transmission to children.[85] All agree that it has failed to do so.[28] To repeat, TB in children – and DR-TB in particular – is invisible because we are systematically blinded to it by the:

- nature of childhood TB disease;
- inadequate tools available for diagnosis in children;
- inadequate data available for estimating the childhood disease burden; and
- large-scale failure to implement the one programmatic strategy that can efficiently 'see' children with TB.

Children as Sentinels of Transmission and Policy Response

Given this gloomy assessment, is there a way out of the invisibility trap? Yes, and another peculiarity of childhood TB offers the key. A child who is infected with TB is likely to progress to disease and death more rapidly than an adult.[86] Compared with adults, a child sick with TB is more likely to reflect recent transmission.[38,54] Children can be 'sentinels' for TB. The word 'sentinel' originates from the Latin word *sentire*, 'to perceive' or 'to see'. It holds within it a fundamental and radical idea.

Children rapidly embody actionable information about the underlying TB epidemic. Rising TB rates among children are windows on increased transmission.[86] In the United States, for example, pediatric TB rates reflected the late 1980s' upsurge in adult rates,[87,88] and were slow to drop even after adult rates declined.[89] Many TB workers have talked of 'sentinel events',[37,38,47] 'Geiger counters',[74] and 'litmus tests'[90] when referring to children sick with TB.

Children are also sentinels for *drug-resistant* TB. DR-TB in children reflects the profile of strains circulating in a community.[38,46,91–95] In some very high TB-burden communities, children presenting with

DR-TB may have been infected with a DR-TB strain from someone outside the home.[96] But the few reports of children exposed to DR-TB at home suggest they were infected from the sick person with DR-TB living with that child.[97–99]

As children with DR-TB disease are the most difficult group to 'see' and to treat effectively, they may be 'sentinels', but ironically, invisible ones. How do we go about dismantling this invisibility trap – both for the benefit of individual children and to capture the actionable information that can be obtained from this group?

The Sentinel Project on Pediatric Drug-Resistant TB

Will the invisibility of childhood DR-TB yield to a new collaborative science-advocacy network that we have helped assemble? Certainly, children sick with DR-TB constitute a small group that is more difficult to see than other children with TB. Yet improved care for those with DR-TB would surely mean rising quality of care for all children with TB. The idea of 'children as sentinels' requires a radically different approach to science and action against TB in all forms. Rather than expecting a focus on infectious adults to improve outcomes and reduce risks to children, it is time to give priority to treating sick children and preventing disease among children at highest risk. The old strategy has been dominant for more than two decades, and done little to benefit immediately individual children.[100]

In October 2011 we convened colleagues to form the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, a collection of researchers, caregivers, and advocates who shared a vision of a world where no child dies from this curable disease.[101] More than 300 individuals in more than 60 countries are now connected as a *virtual community of concern* (www.sentinel-project.org). Network members, all volunteers, collaborate globally to raise the visibility of this deadly threat to children, and to share evidence and resources that can increase prompt and effective treatment of children. They also produce new knowledge. Within the Sentinel Project, designated task forces take on projects, including the following:

- *Advocacy resources*: The Sentinel Project gathered and disseminated two collections of stories of children with DR-TB.[102,103] It has posted online an interactive global map to display the personal stories of

nearly 70 children in more than 30 countries (www.sentinel-project.org). Each individual child with DR-TB merits attention – not only because each child requires treatment, but because each child's story reveals specific gaps in care delivery affecting many, many others.

- *Field handbook for practitioners*: We have also produced a practical 50-page field handbook for practitioners[104] buttressed by a review paper with clinical management recommendations.[44] Together they may increase practitioners' knowledge about how to evaluate children at risk and how to design and deliver effective drug regimens. To disseminate the handbook and review, we have conducted several courses, workshops, and webinars (www.sentinel-project.org).
- *Definitions for pediatric DR-TB research*: To promote more consistent and better quality data, we have proposed definitions for use in pediatric DR-TB research.[105] We suggest a systematic approach to classifying children as 'probable' cases of pediatric DR-TB, in addition to bacteriologically confirmed child cases.

Next steps include developing research priorities focused on the needs of children with DR-TB. To make this population more visible, we must gather better data and apply best practices through multi-site projects.

Targets for Evaluation, Treatment, and Prevention

Improved access to care for children with DR-TB will be impossible if the need remains invisible. Robust estimates of the DR-TB burden are hard to create,[106] and it is more difficult to do so for children. The absence of treatment targets for children with any form of TB – as these targets depend on disease burden estimates – remains a barrier.[32,33,55] We learned from the HIV experience. Initially estimates to project global resource needs for HIV prevention and treatment programs were generated with broad-stroke parameters.[107,108] Advocacy efforts at the time fundamentally depended on these. The new campaign to end child deaths from TB[28] will require putting on paper more concrete treatment goals. Simply put: we argue that, without targets, it will be impossible to reverse the neglect of children with TB.

Yes, even rough targets will help improve treatment access for children with DR-TB. But is there a practical strategy? Household contact investigation is an underused but effective tool to detect and treat sick children promptly and efficiently. Most children will have been infected

Table 1: Parameters used for estimation

Number	*Description of parameter*	*Value*	*Reference*
(1)	Average number of children (age less than 15 years) per household	2	OECD (2012)
(2)	Proportion of child contacts age 0–4 years	0.333	—
(3)	Proportion of child contacts age 5–14 years	0.666	—
(4)	Proportion of TB disease in child contacts age 0–4 years	0.100	Fox (2013)
(5)	Proportion of TB disease in child contacts age 5–14 years	0.084	Fox (2013)
(6)	Proportion of latent TB infection in child contacts age 5–14 years	0.531	Fox (2013)

by their closest contacts, by those with whom they share homes.[86] A consensus exists about best practices to treat DR-TB disease in children,[44] and experience is accumulating in the use of preventive therapy in child MDR-TB contacts.[69,71–73,109]

For an exercise to estimate targets, we will use the subset of children exposed at home to MDR-TB. A set of provisional annual targets will be updated every year. Initial parameters are listed in Table 1. The provisional targets are listed in Table 2 by country and Table 3 by WHO region.

To arrive at these provisional targets, we begin with official estimates available for each country in 2012: the number of MDR-TB cases among all notified pulmonary TB cases.[1] It is important to underscore that this is only a subset of the expected true number of individuals sick with MDR-TB in each country.[27] Because this number – MDR-TB cases expected among notified pulmonary TB cases – is the only estimate available consistently across countries, we use it as the starting point for a targets framework. (See Box 1 for a summary of the simple calculations we describe just below.)

Number of children who require evaluation: We multiply the number of individuals with MDR-TB by an average of the number of children we might expect to find in a household. To be conservative, we use an average of two children per household.[110] This product is a first target, children to be enumerated and screened: 600 000 have known household exposure to someone sick with pulmonary MDR-TB. This target comprises two groups of child contacts: those less than 5 years old and those 5–14 years old. To estimate child contacts in the two groups, we assumed equal distribution over age: 33.3 per cent (about 200 000) of all child contacts would be in the younger group (0–4 year olds) and 66.7 per cent (about 400 000) in the older group (5–14 year olds). All require complete evaluations, including at least, physical examination,

Table 2: Estimated MDR-TB child-contact targets by country or territory, grouped by WHO region

	Estimated number of MDR-TB cases among all notified pulmonary TB cases, 2012	*Target 1*			*Target 2*			*Target 3*		
		Number of children who require evaluation			*Number of children who require treatment for TB disease*			*Number of children who require preventive therapy*		
		0–4 year olds	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*
African region										
Algeria	180	120	240	360	12	20	32	108	117	225
Angola	1700	1132	2268	3400	113	190	304	1019	1103	2122
Benin	54	36	72	108	4	6	10	32	35	67
Botswana	140	93	187	280	9	16	25	84	91	175
Burkina Faso	150	100	200	300	10	17	27	90	97	187
Burundi	150	100	200	300	10	17	27	90	97	187
Cameroon	670	446	894	1340	45	75	120	402	435	836
Cabo Verde	10	7	13	20	1	1	2	6	6	12
Central African Republic	130	87	173	260	9	15	23	78	84	162
Chad	320	213	427	640	21	36	57	192	208	399
Comoros	3	2	4	6	0	0	1	2	2	4
Congo	250	167	334	500	17	28	45	150	162	312
Cote d'Ivoire	580	386	774	1160	39	65	104	348	376	724
Democratic Republic of the Congo	2900	1931	3869	5800	193	325	518	1738	1882	3620
Equatorial Guinea	0	0	0	0	0	0	0	0	0	0
Eritrea	79	53	105	158	5	9	14	47	51	99
Ethiopia	2000	1332	2668	4000	133	224	357	1199	1298	2497
Gabon	170	113	227	340	11	19	30	102	110	212
Gambia	10	7	13	20	1	1	2	6	6	12
Ghana	390	260	520	780	26	44	70	234	253	487
Guinea	250	167	334	500	17	28	45	150	162	312
Guinea-Bissau	45	30	60	90	3	5	8	27	29	56
Kenya	2800	1865	3735	5600	186	314	500	1678	1817	3495

Lesotho	170	113	227	340	11	19	30	102	110	212
Liberia	130	87	173	260	9	15	23	78	84	162
Madagascar	170	113	227	340	11	19	30	102	110	212
Malawi	96	64	128	192	6	11	17	58	62	120
Mali	140	93	187	280	9	16	25	84	91	175
Mauritania	59	39	79	118	4	7	11	35	38	74
Mauritius	0	0	0	0	0	0	0	0	0	0
Mozambique	2000	1332	2668	4000	133	224	357	1199	1298	2497
Namibia	630	420	840	1260	42	71	113	378	409	786
Niger	270	180	360	540	18	30	48	162	175	337
Nigeria	3600	2398	4802	7200	240	403	643	2158	2336	4494
Rwanda	240	160	320	480	16	27	43	144	156	300
Sao Tome and Principe	15	10	20	30	1	2	3	9	10	19
Senegal	400	266	534	800	27	45	71	240	260	499
Seychelles	0	0	0	0	0	0	0	0	0	0
Sierra Leone	220	147	293	440	15	25	39	132	143	275
South Africa	8100	5395	10 805	16 200	539	908	1447	4855	5256	10 111
Swaziland	730	486	974	1460	49	82	130	438	474	911
Togo	77	51	103	154	5	9	14	46	50	96
Uganda	1000	666	1334	2000	67	112	179	599	649	1248
United Republic of Tanzania	510	340	680	1020	34	57	91	306	331	637
Zambia	620	413	827	1240	41	69	111	372	402	774
Zimbabwe	930	619	1241	1860	62	104	166	557	603	1161
Region of the Americas										
Anguilla	0	0	0	0	0	0	0	0	0	0
Antigua and Barbuda	0	0	0	0	0	0	0	0	0	0
Argentina	340	226	454	680	23	38	61	204	221	424
Aruba	1	1	1	2	0	0	0	1	1	1
Bahamas	1	1	1	2	0	0	0	1	1	1
Barbados	0	0	0	0	0	0	0	0	0	0
Belize	3	2	4	6	0	0	1	2	2	4
Bermuda	0	0	0	0	0	0	0	0	0	0
Bolivia (Plurinational State of)	150	100	200	300	10	17	27	90	97	187
Bonaire, Saint Eustatius and Saba	0	0	0	0	0	0	0	0	0	0
Brazil	1700	1132	2268	3400	113	190	304	1019	1103	2122
British Virgin Islands	0	0	0	0	0	0	0	0	0	0

Table 2: *Continued*

	Estimated number of MDR-TB cases among all notified pulmonary TB cases, 2012	*Target 1*			*Target 2*			*Target 3*		
		Number of children who require evaluation			*Number of children who require treatment for TB disease*			*Number of children who require preventive therapy*		
		0–4 year olds	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*
Canada	7	5	9	14	0	1	1	4	5	9
Cayman Islands	0	0	0	0	0	0	0	0	0	0
Chile	19	13	25	38	1	2	3	11	12	24
Colombia	310	206	414	620	21	35	55	186	201	387
Costa Rica	6	4	8	12	0	1	1	4	4	7
Cuba	11	7	15	22	1	1	2	7	7	14
Curacao	0	0	0	0	0	0	0	0	0	0
Dominica	0	0	0	0	0	0	0	0	0	0
Dominican Republic	330	220	440	660	22	37	59	198	214	412
Ecuador	380	253	507	760	25	43	68	228	247	474
El Salvador	16	11	21	32	1	2	3	10	10	20
Grenada	0	0	0	0	0	0	0	0	0	0
Guatemala	140	93	187	280	9	16	25	84	91	175
Guyana	48	32	64	96	3	5	9	29	31	60
Haiti	390	260	520	780	26	44	70	234	253	487
Honduras	71	47	95	142	5	8	13	43	46	89
Jamaica	3	2	4	6	0	0	1	2	2	4
Mexico	480	320	640	960	32	54	86	288	311	599
Montserrat	0	0	0	0	0	0	0	0	0	0
Nicaragua	46	31	61	92	3	5	8	28	30	57
Panama	56	37	75	112	4	6	10	34	36	70
Paraguay	55	37	73	110	4	6	10	33	36	69
Peru	2200	1465	2935	4400	147	247	393	1319	1427	2746

Puerto Rico	1	1	1	2	0	0	0	1	1	1
Saint Kitts and Nevis	0	0	0	0	0	0	0	0	0	0
Saint Lucia	0	0	0	0	0	0	0	0	0	0
Saint Vincent and the Grenadines	1	1	1	2	0	0	0	1	1	1
Sint Maarten (Dutch part)	0	0	0	0	0	0	0	0	0	0
Suriname	3	2	4	6	0	0	1	2	2	4
Trinidad and Tobago	11	7	15	22	1	1	2	7	7	14
Turks and Caicos Islands	0	0	0	0	0	0	0	0	0	0
United States of America	81	54	108	162	5	9	14	49	53	101
Uruguay	1	1	1	2	0	0	0	1	1	1
Venezuela (Bolivarian Republic of)	100	67	133	200	7	11	18	60	65	125
Eastern Mediterranean region										
Afghanistan	1300	866	1734	2600	87	146	232	779	844	1 623
Bahrain	3	2	4	6	0	0	1	2	2	4
Djibouti	81	54	108	162	5	9	14	49	53	101
Egypt	330	220	440	660	22	37	59	198	214	412
Iran (Islamic Republic of)	750	500	1001	1500	50	84	134	450	487	936
Iraq	420	280	560	840	28	47	75	252	273	524
Jordan	15	10	20	30	1	2	3	9	10	19
Kuwait	0	0	0	0	0	0	0	0	0	0
Lebanon	10	7	13	20	1	1	2	6	6	12
Libya	36	24	48	72	2	4	6	22	23	45
Morocco	300	200	400	600	20	34	54	180	195	374
Oman	6	4	8	12	0	1	1	4	4	7
Pakistan	11 000	7326	14 674	22 000	733	1233	1965	6593	7137	13 731
Qatar	6	4	8	12	0	1	1	4	4	7
Saudi Arabia	84	56	112	168	6	9	15	50	55	105
Somalia	770	513	1027	1540	51	86	138	462	500	961
South Sudan	250	167	334	500	17	28	45	150	162	312
Sudan	580	386	774	1,160	39	65	104	348	376	724
Syrian Arab Republic	97	65	129	194	6	11	17	58	63	121
Tunisia	19	13	25	38	1	2	3	11	12	24
United Arab Emirates	2	1	3	4	0	0	0	1	1	2
Yemen	150	100	200	300	10	17	27	90	97	187

Table 2: *Continued*

	Estimated number of MDR-TB cases among all notified pulmonary TB cases, 2012	*Target 1*			*Target 2*			*Target 3*		
		Number of children who require evaluation			*Number of children who require treatment for TB disease*			*Number of children who require preventive therapy*		
		0–4 year olds	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*
European region										
Albania	2	1	3	4	0	0	0	1	1	2
Andorra	0	0	0	0	0	0	0	0	0	0
Armenia	250	167	334	500	17	28	45	150	162	312
Austria	18	12	24	36	1	2	3	11	12	22
Azerbaijan	2800	1865	3735	5600	186	314	500	1678	1817	3495
Belarus	2200	1465	2935	4400	147	247	393	1319	1427	2746
Belgium	15	10	20	30	1	2	3	9	10	19
Bosnia and Herzegovina	13	9	17	26	1	1	2	8	8	16
Bulgaria	100	67	133	200	7	11	18	60	65	125
Croatia	2	1	3	4	0	0	0	1	1	2
Cyprus	2	1	3	4	0	0	0	1	1	2
Czech Republic	10	7	13	20	1	1	2	6	6	12
Denmark	3	2	4	6	0	0	1	2	2	4
Estonia	70	47	93	140	5	8	13	42	45	87
Finland	3	2	4	6	0	0	1	2	2	4
France	45	30	60	90	3	5	8	27	29	56
Georgia	630	420	840	1260	42	71	113	378	409	786
Germany	63	42	84	126	4	7	11	38	41	79
Greece	6	4	8	12	0	1	1	4	4	7
Greenland	2	1	3	4	0	0	0	1	1	2

Hungary	31	21	41	62	2	3	6	19	20	39
Iceland	1	1	1	2	0	0	0	1	1	1
Ireland	2	1	3	4	0	0	0	1	1	2
Israel	22	15	29	44	1	2	4	13	14	27
Italy	43	29	57	86	3	5	8	26	28	54
Kazakhstan	7000	4662	9338	14 000	466	784	1251	4196	4542	8738
Kyrgyzstan	1800	1199	2401	3600	120	202	322	1079	1168	2247
Latvia	120	80	160	240	8	13	21	72	78	150
Lithuania	300	200	400	600	20	34	54	180	195	374
Luxembourg	0	0	0	0	0	0	0	0	0	0
Malta	0	0	0	0	0	0	0	0	0	0
Monaco	0	0	0	0	0	0	0	0	0	0
Montenegro	0	0	0	0	0	0	0	0	0	0
The Netherlands	9	6	12	18	1	1	2	5	6	11
Norway	3	2	4	6	0	0	1	2	2	4
Poland	48	32	64	96	3	5	9	29	31	60
Portugal	35	23	47	70	2	4	6	21	23	44
Republic of Moldova	1700	1132	2268	3400	113	190	304	1019	1103	2122
Romania	800	533	1067	1600	53	90	143	480	519	999
Russian Federation	46 000	30 636	61 364	92 000	3064	5155	8218	27 572	29 847	57 420
San Marino	0	0	0	0	0	0	0	0	0	0
Serbia	20	13	27	40	1	2	4	12	13	25
Slovakia	2	1	3	4	0	0	0	1	1	2
Slovenia	0	0	0	0	0	0	0	0	0	0
Spain	31	21	41	62	2	3	6	19	20	39
Sweden	11	7	15	22	1	1	2	7	7	14
Switzerland	9	6	12	18	1	1	2	5	6	11
Tajikistan	910	606	1214	1820	61	102	163	545	590	1136
The Former Yugoslav Republic of Macedonia	5	3	7	10	0	1	1	3	3	6
Turkey	520	346	694	1040	35	58	93	312	337	649
Turkmenistan	0	0	0	0	0	0	0	0	0	0
Ukraine	6800	4529	9071	13 600	453	762	1215	4076	4412	8488
United Kingdom of Great Britain and Northern Ireland	69	46	92	138	5	8	12	41	45	86
Uzbekistan	4000	2664	5336	8000	266	448	715	2398	2595	4993

Table 2: *Continued*

	Estimated number of MDR-TB cases among all notified pulmonary TB cases, 2012	*Target 1*			*Target 2*			*Target 3*		
		Number of children who require evaluation			*Number of children who require treatment for TB disease*			*Number of children who require preventive therapy*		
		0–4 year olds	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*
South-East Asia region										
Bangladesh	4200	2797	5603	8400	280	471	750	2517	2725	5243
Bhutan	25	17	33	50	2	3	4	15	16	31
Democratic People's Republic of Korea	3800	2531	5069	7600	253	426	679	2278	2466	4743
India	64 000	42 624	85 376	128 000	4262	7172	11 434	38 362	41 527	79 888
Indonesia	6900	4595	9205	13 800	460	773	1233	4136	4477	8613
Maldives	2	1	3	4	0	0	0	1	1	2
Myanmar	6000	3996	8004	12 000	400	672	1072	3596	3893	7490
Nepal	990	659	1321	1980	66	111	177	593	642	1236
Sri Lanka	21	14	28	42	1	2	4	13	14	26
Thailand	1800	1199	2401	3600	120	202	322	1079	1168	2247
Timor-Leste	82	55	109	164	5	9	15	49	53	102
Western Pacific region										
American Samoa	0	0	0	0	0	0	0	0	0	0
Australia	17	11	23	34	1	2	3	10	11	21
Brunei Darussalam	0	0	0	0	0	0	0	0	0	0
Cambodia	380	253	507	760	25	43	68	228	247	474
China	59 000	39 294	78 706	118 000	3929	6611	10 541	35 365	38 282	73 647
China, Hong Kong SAR	48	32	64	96	3	5	9	29	31	60
China, Macao SAR	8	5	11	16	1	1	1	5	5	10
Cook Islands	1	1	1	2	0	0	0	1	1	1

Fiji	0	0	0	0	0	0	0	0	0	0
French Polynesia	0	0	0	0	0	0	0	0	0	0
Guam	0	0	0	0	0	0	0	0	0	0
Japan	240	160	320	480	16	27	43	144	156	300
Kiribati	15	10	20	30	1	2	3	9	10	19
Lao People's Democratic Republic	220	147	293	440	15	25	39	132	143	275
Malaysia	18	12	24	36	1	2	3	11	12	22
Marshall Islands	4	3	5	8	0	0	1	2	3	5
Micronesia (Federated States of)	7	5	9	14	0	1	1	4	5	9
Mongolia	170	113	227	340	11	19	30	102	110	212
Nauru	0	0	0	0	0	0	0	0	0	0
New Caledonia	0	0	0	0	0	0	0	0	0	0
New Zealand	4	3	5	8	0	0	1	2	3	5
Niue	0	0	0	0	0	0	0	0	0	0
Northern Mariana Islands	0	0	0	0	0	0	0	0	0	0
Palau	0	0	0	0	0	0	0	0	0	0
Papua New Guinea	1100	733	1467	2200	73	123	197	659	714	1373
Philippines	12 000	7992	16 008	24 000	799	1345	2144	7193	7786	14 979
Republic of Korea	2200	1465	2935	4400	147	247	393	1319	1427	2746
Samoa	0	0	0	0	0	0	0	0	0	0
Singapore	36	24	48	72	2	4	6	22	23	45
Solomon Islands	12	8	16	24	1	1	2	7	8	15
Tokelau	0	0	0	0	0	0	0	0	0	0
Tonga	0	0	0	0	0	0	0	0	0	0
Tuvalu	1	1	1	2	0	0	0	1	1	1
Vanuatu	0	0	0	0	0	0	0	0	0	0
Viet Nam	3800	2531	5069	7600	253	426	679	2278	2466	4743
Wallis and Futuna Islands	0	0	0	0	0	0	0	0	0	0

Table 3: Estimated MDR-TB child-contact targets in six WHO regions

Region	*Estimated number of MDR-TB cases among all notified pulmonary TB cases, 2012*	*Target 1*			*Target 2*			*Target 3*		
		Number of children who require evaluation			*Number of children who require treatment for TB disease*			*Number of children who require preventive therapy*		
		0–4 year olds	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*	*0–4 year olds*	*5–14 year olds*	*Total 0–14 year olds*
South-East Asia	87 820	58 488	117 152	175 640	5849	9 841	15 690	52 639	56 982	109 622
Western Pacific	79 281	52 801	105 761	158 562	5280	8884	14 164	47 521	51 442	98 963
European	76 525	50 966	102 084	153 050	5097	8575	13 672	45 869	49 653	95 523
African	33 088	22 037	44 139	66 176	2204	3708	5911	19 833	21 469	41 302
Eastern Mediterranean	16 209	10 795	21 623	32 418	1080	1816	2896	9716	10 517	20 233
Americas	6961	4636	9286	13 922	464	780	1244	4172	4517	8689
Total	299 884	199 723	400 045	599 768	19 972	33 604	53 576	179 750	194 580	374 331

Box 1: Estimating three child-specific targets in households of MDR-TB patients

If:

M = number of notified pulmonary MDR-TB patients in one year,
the subscript a indicates children age 0–4 years, and
the subscript b indicates children age 5–14 years.

Then let

$T_{1a+1b} = M \times 2$

$T_{1a} = T_{1a+1b} \times 0.333$

$T_{1b} = T_{1a+1b} \times 0.667$

$T_{2a} = T_{1a} \times 0.100$

$T_{2b} = T_{1b} \times 0.084$

$T_{2a+2b} = T_{2a} + T_{2b}$

$T_{3a} = T_{1a} - T_{2a}$

$T_{3b} = (T_{1b} - T_{2b}) \times 0.531$

$T_{3a+3b} = T_{3a} + T_{3b}$

rapid molecular testing, and chest radiograph according to current global guidelines.[31,104]

Treatment target: For the treatment target, we multiply the first 'evaluation' targets by the proportion of each group expected to have TB disease. For this proportion, we use the pooled TB disease risk estimated in the two age groups of child contacts in the 2013 systematic review and meta-analysis of TB contact investigations, namely, 10.0 per cent in those less than 5 years old and 8.4 per cent in those 5–14 years old.[63] The disease risk among close contacts of individuals sick with any type of TB that is synthesized in that meta-analysis is consistent with observations in DR-TB household contact investigations.[64,68,98,99] We then multiply the disease risk in each group by the number of child contacts. This constitutes a treatment target: about 50 000 children require treatment for TB disease at the time the 'index' MDR-TB patient is found and enrolled on treatment; about 20 000 children less than 5 years old and about 30 000 who are 5–14 years old. In both groups, the child contacts will include some who have a bacteriological confirmation of TB and drug resistance. There will also be many without bacteriological confirmation who meet the recently advanced definition of a 'probable' case of TB in a child.[111] Because their household exposure was to DR-TB, these children can be classified as 'probable' cases of DR-TB.[105] Because the child contacts in the MDR-TB

households who become sick are very likely to have MDR-TB disease, but unlikely to have microbiological confirmation,[68,98,99] effective treatment for most means presumptive treatment of MDR-TB, based on drug-susceptibility data from the individual sick with MDR-TB who is most likely to have infected the children in that household.[21,69,112]

MDR-TB preventive therapy target: Finally, we calculate a third target, the number of child contacts who should receive preventive therapy for MDR-TB. All child contacts less than 5 years old without TB disease are included in this target. This age-specific recommendation is consistent with current guidelines on TB preventive therapy in child contacts of individuals sick with TB.[31] For child contacts who are 5–14 years old, we take two steps to quantify the target, those with a positive tuberculin skin test (evidence of latent TB infection) who could benefit from preventive therapy. First, we subtract the second target (treatment for TB disease) from the first (evaluation target). Next, to this difference we apply the estimate of the proportion with evidence of latent TB infection among child contacts age 5–14 years old (53.1 per cent) from the aforementioned systematic review and meta-analysis.[63] This preventive therapy target consists of nearly 400 000 children who are exposed to or latently infected with MDR-TB and who would benefit from preventive therapy: globally, nearly 200 000 child contacts less than 5 years old and another 200 000 who are 5–14 years old. Preventive therapy regimens for both groups of child contacts could be designed according to expert guidance, based on growing observational evidence of benefit and safety.[68–73] If any drug or drug combination can come even close to the spectacular efficacy of isoniazid for treating isoniazid-susceptible latent TB infection in children,[59,113] then it will avert every year large numbers of child cases and deaths due to DR-TB.

Utility of a Targets Framework

We present a set of provisional country-level targets of child household contacts (Table 2) by WHO region in Table 3. The targets in two age groups indicate the numbers of: (i) children who require complete evaluation for TB disease and infection; (ii) children who require treatment for TB disease; and (iii) children who would benefit from preventive therapy. These are actionable targets for a single year: an approximation of how many children exposed to MDR-TB could be found and started on treatment using household contact investigations.

The shortcomings of these 'back-of-the-envelope' estimates are several. First, we started with estimates of MDR-TB among *notified* pulmonary TB cases in a year rather than *all* MDR-TB cases estimated to occur in that year. Yet our estimated target of child contacts with MDR-TB disease in a year exceeds other recent estimates that put the number of children with MDR-TB around 32 000 globally.[3] They were lower because they used routine TB notifications and existing estimates of global incidence as inputs. Possible biases in those inputs could result in underestimation of childhood disease. To get a sense of how many child contacts would need to be screened in a year, our targets framework begins with an estimate of the number of pulmonary MDR-TB cases we expect would be notified in each country.

Second, we applied a single median for the number of children per household, yet the median number of children per household is variable and higher in most countries with larger populations and also in those with higher TB incidence.

Finally, we applied a single estimate of disease risk in each of two age groups of child contacts. But we know that disease risk varies within the age groups.[114] The average risk of TB disease among child contacts may be higher than the proportion we applied, exceeding in some settings a third of all the children in the home.[82,83]

For all these reasons, this first set of provisional targets is likely to underestimate the number of children who could be found through MDR-TB household contact investigations and who require screening and care.

Notwithstanding the limitations, our exercise produces a simple framework with pragmatic value: First, it provides a sense of the magnitude of the problem in understandable terms. Knowing the absolute numbers of sick children in a single year in identifiable households might serve to galvanize attention more effectively than the idea of TB elimination decades in the future. Short-term, 1-year targets are useful for communicating with diverse interested parties seeking to develop joint strategies. The number of child cases treated or prevented serves as a key indicator of the quality for any strategy. With better data, this simple framework could be used at many levels (community, sub-national, national) to build a shared vision, a vision that can galvanize new collaborative actions to reach short-term targets.

Second, our framework highlights concrete gaps in action. It reminds us that there is one effective tool not currently used widely to stop disease and deaths in children: TB contact investigation. Other interventions

exist whose potential can be tapped to prevent TB disease and death in both women and young children.[115–119] Contact investigation in TB patient households constitutes an effective screening strategy to find more TB cases;[65] it is also high yield in the households of individuals sick with DR-TB.[64] The highest yields should be expected among the youngest children,[84] who are the least likely to be recognized as TB cases without contact investigation. Given sufficient resources, we can begin immediately to screen child contacts and provide TB treatment.

Third, the framework points to critical gaps in knowledge, and can drive an ambitious scientific agenda that gives children priority. The lack of a tool that can reliably detect TB infection, disease, and drug resistance in children is a major gap. Treatment for children with MDR-TB disease can have good outcomes, but has yet to be optimized. Can today's regimens be shortened and otherwise simplified, without compromising efficacy? A lack of child-friendly formulations of key drugs restricts treatment.[120] Evidence suggests that preventive therapy in children exposed to DR-TB is effective.[68,71,72] But what is the optimal approach? Children at high risk for DR-TB disease and infection, like those who live with an adult sick with DR-TB, are a high-yield, high-priority population for demonstrating the value of any new test, vaccine, or preventive regimen.

In sum, this framework is a tool for convening interested parties to act jointly toward shared targets. It can reinforce collaborative efforts to apply existing knowledge immediately and produce new knowledge. Enumerating cohorts of household members of MDR-TB patients for evaluation – and then applying all existing tools – would itself break from the past and serve as a 'pilot' for optimizing contact investigations around all TB patients, not only those with MDR-TB. Monitoring progress on the proposed targets can inform efforts against the larger global TB pandemic. Most importantly, children will no longer be an afterthought; finding and treating children will be at the core by design.

Conclusions

The global burden of DR-TB in children is invisible. No easy solution exists. The confluence of four factors has produced the invisibility:

- the nature of pediatric TB;
- our wholly inadequate armamentarium of diagnostic tools;

- the absence of data to inform robust disease burden estimates; and
- a large-scale failure to deploy TB contact investigations.

Fortunately, the nature of pediatric TB also offers clues to solving the problem: each child with DR-TB is a sentinel event, both for recent transmission and for opportunities to improve TB care.

To raise the visibility of children with DR-TB, a collaborative network, the *Sentinel Project on Pediatric Drug-Resistant Tuberculosis*, is building on the concept of TB cases in children as sentinel events. We propose a first set of treatment and prevention targets – among children exposed at home to MDR-TB – to begin monitoring gaps in TB care and to spur new collective actions. Setting these child-focused targets, although imperfect, promotes a focus on actionable information. Working jointly to meet short-term targets, we may move away from strategies that have persistently failed children sick with TB. Efforts to meet and update these new targets can forge a policy response to the global pandemic of DR-TB. It will ensure that children with DR-TB are no longer invisible.

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