THE LANCET

How to eliminate tuberculosis · October, 2015

The Lancet—London
125 London Wall,
London EC2Y 5AS,
UK
T +44 (0)20 7424 4910
F +44 (0)20 7424 4911

The Lancet—New York
360 Park Avenue South,
New York, NY 10010–1710,
USA
T +1 212 633 3810
F +1 212 633 3853

The Lancet—Beijing
Unit 1–6, 7F, Tower W1,
Oriental Plaza, Beijing 100738,
China
T + 86 10 85208872
F + 86 10 85189297

editorial@lancet.com

Previously published online

See www.thelancet.com for supplementary material

Version verified by CrossMark

Tuberculosis—getting to zero

Published Online
October 26, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00401-8

See Online/Series
http://dx.doi.org/10.1016/S0140-6736(15)00321-9,
http://dx.doi.org/10.1016/S0140-6736(15)00322-0,
http://dx.doi.org/10.1016/S0140-6736(15)00323-2, and
http://dx.doi.org/10.1016/S0140-6736(15)00324-4

Reviewing research *The Lancet* has published on the global tuberculosis epidemic, one will be struck by how little the situation has changed over the years, and how the same calls to action get repeated from one year to the next. For decades, a piecemeal approach with a narrow treatment focus and a cost imperative has prevailed. The result? A global epidemic of disease. For more than a decade the global tuberculosis incidence rate has declined, but only slowly by about 1·65% annually.[1,2] Meanwhile, the worst legacy of this disease has become multidrug resistance.[3] The *Lancet* Series on how to eliminate tuberculosis[4–7] is a response to the fact that business as usual can no longer be an option in the fight against tuberculosis.

This latest *Lancet* Series is led by Salmaan Keshavjee, from Harvard Medical School's Department of Global Health and Social Medicine. He helped bring together researchers and advocates to answer an urgent question: how do we translate existing knowledge, strategies, and approaches into effective programmatic interventions in the communities most afflicted by tuberculosis? His group decided on a goal—to work towards achieving zero deaths from tuberculosis, and to create a scientifically based roadmap outlining the steps that would need to be taken to reach this goal.

Four Series papers[4–7] describe the scientific underpinnings of this roadmap and address changes in the current strategy that will be necessary to achieve zero deaths from tuberculosis, and to reach 2050 elimination targets in high-burden settings.[8] The authors repackage current interventions into a comprehensive epidemic-control strategy that consists of targeting local hotspots of transmission, active case-finding, initiating the correct therapy promptly, and preventing future transmission by treating high-risk individuals and contacts of affected individuals.

Interestingly, most of the data in this Series are not new. Despite their imperfections, the tuberculosis strategies and interventions described have brought down the epidemic in several different settings, from Karachi in Pakistan to New York City in the USA. Furthermore, a comprehensive approach is already being used successfully to tackle HIV/AIDS and malaria. So clearly something has gone wrong for tuberculosis, where comprehensive approaches have not been applied consistently and to scale. Countries are not getting the message that this approach should be taken and donors are also not insisting upon it. Often the message is that tuberculosis is too complex, or that newer technologies are needed. But as this Series shows, there is no reason not to use existing interventions that do work and can stop the epidemic. Despite the evidence, there is a gap between data and implementation. The policy and implementation frameworks that have been adopted in the past decades have just not worked.

There needs to be a change in mindset. Perhaps this transformation needs to come from countries themselves, especially those which have their own resources, such as Brazil, Russia, India, and China. Given the huge economic burden that tuberculosis has exacted on patients and their families,[7,9] countries should recognise that using a comprehensive approach will be good for the economy. Tuberculosis is an airborne disease. Treating only the most infectious individuals with active disease, which is mainly the current approach, and not those in the latent phase who continue to transmit the disease is bad epidemic control. There is no disease in history that has been stopped without treating the latent phase, from yaws to malaria.

This Series will be used to create a strategy to combat tuberculosis in cities. The Zero TB Cities Project is a new initiative formed in 2014 that will commit to a comprehensive tuberculosis elimination strategy, be it in a large metropolitan conurbation, a small island, or an isolated community. Key partners will be municipalities and local governments that have their own resources and

For the **Zero TB Cities Project** see http://www.advanceaccessanddelivery.org/overview/

Farooq Khan/EPA/Corbis

can be more responsive to their populations than central government. The Zero TB Cities Project will provide independent funding in addition to country resources. Chennai in India and Lima in Peru are the first cities to take part and progress will be assessed at 3-year intervals. The goal is to help communities move to zero deaths from tuberculosis in their own way, and create "islands of elimination", which will hopefully reverse the overall tuberculosis epidemic.

The final Series paper by Katrina Ortblad and colleagues[7] reminds us that tuberculosis is the quintessential disease of poverty in modern times. It is a result of poverty and is itself a driver of poverty. To date, interventions to tackle tuberculosis have largely been biomedical. But other risk factors, such as malnutrition, overcrowding, and poor health services, also need to be addressed. The Sustainable Development Goals offer an opportunity to rethink the fight against tuberculosis and to move to a more biosocial model that focuses not only on supply side interventions but also on demand side interventions at the individual level—for example, cash transfers and microcredit—to address the social determinants of this disease.

This *Lancet* Series is launched at the inauguration of the Harvard Medical School Center for Global Health Delivery—Dubai. The aim of this new centre is to promote research that will address the health delivery gap. Tuberculosis will be one of the disease areas of focus. We hope this Series will be a springboard that can help shift the global tuberculosis epidemic from incremental annual improvements to an accelerating global movement for tuberculosis elimination.

For the **Harvard Medical School Center for Global Health Delivery—Dubai** see http://ghsm.hms.harvard.edu/ghd-dubai/hms-center-for-global-health-delivery-dubai

Pamela Das, Richard Horton
The Lancet, London EC2Y 5AS, UK

1 Ortblad KF, Lozano R, Murray CJL. An alternative estimation of tuberculosis incidence from 1980 to 2010: methods from the Global Burden of Disease 2010. *Lancet* 2013; **381:** S104.
2 Murray CJL, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384:** 1005–70.
3 WHO. Multidrug-resistant tuberculosis (MDR-TB) 2014 update. Geneva: World Health Organization, 2014. http://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf?ua=1 (accessed Sept 30, 2015).
4 Theron G, Jenkins HE, Cobelens F, et al. Data for action: collection and use of local data to end tuberculosis. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00321-9.
5 Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00322-0.
6 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00323-2.
7 Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00324-4.
8 WHO. WHO STOP TB strategy. http://www.who.int/tb/strategy/stop_tb_strategy/en/ (accessed Sept 29, 2015).
9 Lönnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. *Lancet* 2010; **375:** 1814–29.

Stopping the body count: a comprehensive approach to move towards zero tuberculosis deaths

Published Online
October 26, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00320-7

See Online/Series
http://dx.doi.org/10.1016/S0140-6736(15)00321-9,
http://dx.doi.org/10.1016/S0140-6736(15)00322-0,
http://dx.doi.org/10.1016/S0140-6736(15)00323-2, and
http://dx.doi.org/10.1016/S0140-6736(15)00324-4

Tuberculosis has been a curable disease since the 1950s. In the more than six decades since then, knowledge has been amassed about how to ameliorate its social causes, prevent its transmission, and treat both its clinical and quiescent forms.[1,2] In many high-income settings, this knowledge has been used with great success. Elsewhere, this is far from the case: more than 4000 people die from this curable and preventable airborne disease each day, mostly in low-income and middle-income settings.[3] Distressed by the status quo, in 2012 more than 500 scientists, policy makers, and advocates from around the world signed the Zero TB Declaration, which called for "a new global attitude" in the fight against tuberculosis, and argued that, with the right set of interventions, the planet could move rapidly towards zero deaths from tuberculosis.[4]

Although tuberculosis incidence has declined over the past 25 years, it has done so at a glacial pace of about 1·65% annually.[5] At this rate, it will take another two centuries to eliminate the disease.[5] This reality reflects the limited set of interventions recommended for, and implemented in, low-income and middle-income settings, a shadow of the comprehensive set of strategies that has brought the tuberculosis epidemic to heel in other places.[1,2] Rather than aggressively finding all cases of tuberculosis, preventing the disease in those at highest risk, and focusing on populations and places of highest transmission, most low-income and middle-income settings have focused narrowly on the diagnosis and treatment of those patients with tuberculosis who manage to access care on their own. An over-reliance on standardised treatment and sputum smear microscopy—a low-sensitivity visual diagnostic test that cannot determine drug resistance—has sidelined not only individuals whose illness is characterised by a lower bacillary load, such as children and individuals with HIV, but also those with extrapulmonary or drug-resistant tuberculosis.[6] Early detection and treatment of both active disease and quiescent (so-called latent) infection, along with efforts to control transmission in health-care and congregate settings, have been belatedly recommended for some groups in limited settings, but have yet to be widely scaled up.[7] Much of the policy framing to date has been driven by concerns over cost, which has overridden both the scientific and moral imperatives to implement proven interventions that could inflect the global tuberculosis curve more rapidly.[6-8]

Although standardisation of treatment contributed to improved clinical outcomes for some people with tuberculosis, the absence of a comprehensive approach for fighting tuberculosis in high-burden settings has led to predictable and alarming results.[3,9,10] At least 9 million people fall sick from tuberculosis every year, including 1 million children.[3,11] More than 3 million patients with tuberculosis remain undetected and continue to transmit the disease in their families and communities. Appropriate treatment for drug-resistant tuberculosis remains the exception rather than the rule, allowing further transmission of these strains. Most known contacts receive no post-exposure therapy, a standard intervention in most high-income settings. Finally, and most damning of all, almost 1·5 million people still die each year from tuberculosis—a preventable and curable disease.[3]

Ending the tuberculosis epidemic requires the urgent deployment of a comprehensive package of effective, tried and tested interventions in low-income and middle-income settings. This comprehensive approach must happen in tandem with the development of effective

Tony Karumba/Stringer

A mother and child who both have multidrug-resistant tuberculosis at a clinic in Nairobi, Kenya, in March, 2015

point-of-care diagnostics, highly effective and shorter treatment regimens, and vaccines. The *Lancet* Series on how to eliminate tuberculosis[12–15] reviews a set of proven epidemic-control strategies for combating the disease. Their wider and more systematic application, evidence suggests, will result in quantitatively greater and more rapid progress in tackling the global tuberculosis epidemic.[1,2,16–22] These strategies include: stopping transmission through active identification of sick patients and prompt initiation of the correct therapy; treating infection in close contacts and high-risk individuals; using data from tuberculosis programmes to improve use of current resources and to better target interventions; and addressing some of the social mechanisms that fuel tuberculosis. Each Series paper presents examples of places where these epidemic-control strategies have been successfully used, as well as practical recommendations for implementation. Separately, the effect of these approaches might be modest; in combination, however, global experience and mathematical modelling suggest that they will have a swift and dramatic effect on tuberculosis incidence and mortality.[1,2]

The goals laid out in both the Stop TB Partnership's Global Plan to Stop TB 2016–2020[23] and WHO's End TB Strategy[24] will require "a new global attitude" in the fight against tuberculosis.[4] Part of that shift means moving beyond piecemeal approaches, and deploying a comprehensive epidemic-control strategy that has been shown to work. Beyond courage and vision, the success of this approach will depend on an unwavering commitment to programmatic quality, fidelity, and equity, with all the methods required to stop an airborne epidemic being used at the same time. Moreover, all people who require treatment must be included in this comprehensive approach: children, people with drug-resistant strains, individuals with extrapulmonary disease, those co-infected with HIV, others at high risk of acquiring the disease, and infected contacts. Failure to seize this opportunity now will constitute both a scientific and moral failure. Waiting another two centuries for a curable and preventable disease to disappear is not an option.

*Salmaan Keshavjee, David Dowdy, Soumya Swaminathan
Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA 02115, USA (SK); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (DD); and Office of Director General, Indian Council of Medical Research and Department of Health Research, New Delhi, India (SS)
salmaan_keshavjee@hms.harvard.edu

We declare no competing interests. We thank Carly Rodriguez for coordination and research assistance in the preparation of this Comment.

1 Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009; **68:** 2240–46.
2 Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. *Annu Rev Public Health* 2013; **34:** 271–86.
3 WHO. Global tuberculosis report 2014. Geneva: World Health Organization, 2014.
4 Treatment Action Group. Zero TB declaration. July 22, 2012. http://www.treatmentactiongroup.org/tb/advocacy/zero-declaration (accessed July 19, 2015).
5 Ortblad KF, Lozano R, Murray CJL. An alternative estimation of tuberculosis incidence from 1980 to 2010: methods from the Global Burden of Disease 2010. *Lancet* 2013; **381:** S104.
6 Keshavjee S, Farmer PE. Tuberculosis, drug resistance and the history of modern medicine. *N Engl J Med* 2012; **367:** 931–36.
7 McMillan CW. Discovering tuberculosis: a global history 1900 to the present. New Haven, CT: Yale University Press, 2015.
8 Walsh JA, Warren KS. Selective primary health care: an interim strategy for disease control in developing countries. *N Engl J Med* 1979; **301:** 967–74.
9 Obermeyer Z, Abbott-Klafter J, Murray CJL. Has the DOTS strategy improved case finding or treatment success? An empirical assessment. *PLoS One* 2008; **3:** e1721.
10 De Cock KM, Chaisson RE. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. *Int J Tuberc Lung Dis* 1999; **3:** 457–65.
11 Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet* 2014; **383:** 1572–79.
12 Theron G, Jenkins HE, Cobelens F, et al. Data for action: collection and use of local data to end tuberculosis. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00321-9.
13 Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00322-0.
14 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00323-2.
15 Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00324-4.
16 Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City—turning the tide. *N Engl J Med* 1995; **333:** 229–33.
17 Cavalcante SC, Durovni B, Barnes GL, et al. Community-randomised trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2010; **14:** 203–09.
18 Bamrah S, Brostrom R, Dorina F, et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012. *Int J Tuberc Lung Dis* 2014; **18:** 912–18.
19 Graham NM, Galai N, Nelson KE, et al. Effect of isoniazid chemoprophylaxis on HIV-related mycobacterial disease. *Arch Intern Med* 1996; **156:** 889–94.
20 Keshavjee S, Gelmanova I, Pasechnikov A, et al. Treating multi-drug resistant tuberculosis in Tomsk, Russia: developing programs that address the linkage between poverty and disease. *Ann N Y Acad Sci* 2008; **1136:** 1–11.
21 Rocha C, Montoya R, Zevallos K, et al. The innovative socio-economic interventions against tuberculosis (ISIAT) project: an operational assessment. *Int J Tuberc Lung Dis* 2011; **15:** S50–57.
22 Comstock GW. Isoniazid prophylaxis in an underdeveloped area. *Am Rev Respir Dis* 1962; **86:** 810–22.
23 Stop TB Partnership. The global plan to stop TB 2016–2020. 2015. http://www.stoptb.org/global/plan/plan2/ (accessed Sept 11, 2015).
24 WHO. Introducing the End TB Strategy. Geneva: World Health Organization, 2015.

No one with HIV should die from tuberculosis

Published Online
October 26, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00319-0

See Online/Series
http://dx.doi.org/10.1016/S0140-6736(15)00321-9,
http://dx.doi.org/10.1016/S0140-6736(15)00322-0,
http://dx.doi.org/10.1016/S0140-6736(15)00323-2, and
http://dx.doi.org/10.1016/S0140-6736(15)00324-4

Tuberculosis is the leading cause of mortality among individuals infected with HIV, killing more than 1000 people every day.[1] Even if they receive treatment for tuberculosis, people with HIV are more likely to die from tuberculosis than people without HIV,[2] especially if they are not receiving antiretroviral therapy or if they have multidrug-resistant tuberculosis.[3,4] They do not die because we cannot treat HIV or cure tuberculosis. They die because of substantial gaps in the delivery of care and innovation, despite decades of knowledge about the synergy between tuberculosis and HIV, about how to stop the spread of tuberculosis, and how to optimise HIV treatment.[5]

In 2008, WHO endorsed the Three I's strategy[6]—intensified case-finding, isoniazid prophylaxis therapy, and infection control—to address the crisis of tuberculosis deaths among people with HIV. Intensified case-finding and isoniazid prophylaxis therapy save both lives and resources, given the number of tuberculosis cases prevented.[7] A "fourth I", representing integrated care at the facility level for individuals co-infected with HIV and tuberculosis, has also been shown to improve treatment outcomes for both tuberculosis and HIV.[8,9] Despite endorsement of these almost decade-old strategies, people with HIV continue to die from tuberculosis at an alarming rate because not enough is being done to ensure optimum prevention, detection, and treatment.

How do we change this dynamic? The Stop TB Partnership's Global TB Plan 2016–2020, now under development, calls for mass scale-up of tuberculosis screening, diagnosis, and treatment for people living with HIV—with coverage targets of at least 90%.[10] But much more is needed than just ambitious targets.

First, and at a minimum, known strategies for stopping the spread of tuberculosis have to be prioritised, implemented, and scaled up in low-income and middle-income settings for both adults and children. As the papers in the *Lancet* Series on tuberculosis[11–14] show, these strategies include active case-finding, rapid diagnosis, post-exposure treatment (both isoniazid prophylaxis therapy and treatment for drug-resistant strains), and early initiation of optimum treatment for all strains of tuberculosis. These strategies have driven rates of tuberculosis down substantially among vulnerable patients in settings such as New York City and Baltimore in the USA, and Rio de Janeiro in Brazil.[15–17]

Second, innovative approaches must be adopted to halt the deadly toll of tuberculosis in people with HIV. For example, initiation of antiretroviral therapy needs to become an urgent priority among all people living with HIV, including in areas of high tuberculosis and HIV co-infection, to prevent tuberculosis incidence, progression, and mortality.[18–21] An overwhelming evidence base now clarifies the need for any patient with HIV, irrespective of CD4 count, to be started on antiretroviral therapy as soon as possible after diagnosis.[22–25] Some in the medical and public health communities have added immediate initiation of antiretroviral therapy as the "fifth I" in the strategy to halt tuberculosis mortality. There is also a need for better ways to treat tuberculosis in patients with HIV, which will involve evaluating innovative treatment strategies and improving the science of tuberculosis clinical trials. Furthermore, there should be greater inclusion of people with HIV in tuberculosis drug trials, since this population is often excluded from such research. These exclusions mean there are limited indications for the use of new tuberculosis drugs in HIV-infected individuals—those with the highest rates of mortality—and there is little information about drug–drug interactions with antiretroviral therapy.

Third, better screening and diagnostic strategies are needed to detect tuberculosis in people with HIV co-infection. A simple symptom screen, if correctly

Dieter Telemans/Panos

implemented, could identify many people with tuberculosis for diagnostic referral;[26] by contrast, sputum-based diagnostic methods miss most cases of tuberculosis among those with active disease and HIV.[27] There are now point-of-care tests available for the measurement of HIV viral load, but no such test is available for tuberculosis.[28]

Fourth, countries will continue to need technical and financial support to overcome the barriers to the implementation of comprehensive tuberculosis strategies. It is noteworthy, however, that in many settings, these barriers have been successfully addressed in the provision of HIV care in general, but not when it comes to tuberculosis care in the HIV-infected population.[29,30] A better understanding of the reasons for these differences in the provision of care would help target resources more effectively and improve tuberculosis prevention and treatment. So too would broader application of proven HIV strategies to tuberculosis, including community-based care, treatment as prevention, adaptive adherence support strategies, engagement with survivors, and a human rights driven approach.

Deaths from tuberculosis will be halted only if the tuberculosis community can emulate the ambitious scientific and advocacy agenda set by those working in HIV—where, in the span of 40 years, HIV went from being an unrecognised deadly pathogen to an easily diagnosed chronic condition with many prevention and treatment options. During that same period, there has been far too little innovation in tuberculosis prevention, diagnosis, and treatment. There is some cause for optimism from the recent introduction of molecular diagnostics and the approval of the first two new tuberculosis drugs, bedaquiline and delamanid,[31] in almost half a century, but transformative science for tuberculosis still has a long way to go. In the meantime, tuberculosis can be tackled by scaling up existing effective interventions.

The global expansion of comprehensive high-quality treatment for HIV has set a moral and human rights benchmark for other global health initiatives.[3] Preventable deaths from tuberculosis among people living with HIV are an unconscionable stain on this accomplishment. Well proven epidemic-control strategies for tuberculosis and the use of antiretroviral therapy have stopped deaths from tuberculosis in people with HIV in many settings. It is well past time to make this a reality for all people living with HIV and to expand the high levels of human and financial capital invested in HIV to the disease responsible for killing so many infected individuals.

*Jennifer Furin, Paula Akugizibwe, Lucica Ditiu, Glenda Gray, Domingo Palmero, Sarah Zaidi

Tuberculosis Research Unit, Case Western Reserve University, Cleveland, OH 44106, USA (JF); Clinton Health Access Initiative, Boston, MA, USA (PA); Stop TB Partnership Secretariat, World Health Organization, Geneva, Switzerland (LD); South African Medical Research Council and Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (GG); Hospital de Infecciosas Dr F J Muñiz, Buenos Aires, Argentina (DP); and Bangkok, Thailand (SZ)

jjf38@case.edu

We declare no competing interests. We thank Mark Harrington for the important comments he contributed during the drafting of this Comment, and Carly Rodriguez for coordination and research assistance in the preparation of this Comment.

1 WHO. Global tuberculosis report 2014. Geneva: World Health Organization, 2014.

2 Straetemans M, Glaziou P, Bierrenbach AL, Sismanidis C, van der Werf MJ. Assessing tuberculosis case fatality ratio: a meta-analysis. *PLoS One* 2011; **6:** e20755.

3 Odone A, Amadasi S, White RG, Cohen TC, Grant AD, Houben MGJ. The impact of antiretroviral therapy on mortality in HIV positive people during tuberculosis treatment: a systematic review and meta-analysis. *PLoS One* 2014; **9:** e112017.

4 Isaakidis P, Casas EC, Das M, Tseretopoulou X, Ntzani EE, Ford N. Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2015; **19:** 969–78.

5 Harries AD, Zachariah R, Corbett EL, et al. The HIV-associated tuberculosis epidemic—when will we act? *Lancet* 2010; **375:** 1906–19.

6 WHO. Report of a joint WHO HIV/AIDS and TB Department meeting, 2008. Three I's meeting. Geneva: World Health Organization, 2008. http://www.who.int/hiv/pub/meetingreports/WHO_3Is_meeting_report.pdf (accessed Aug 18, 2015).

7 Gupta S, Abimbola T, Date A, et al. Cost-effectiveness of the Three I's for HIV/TB and ART to prevent TB among people living with HIV. *Int J Tuberc Lung Dis* 2014; **18:** 1159–65.

8 Hermans SM, Castelnuovo B, Katabira C, et al. Integration of HIV and TB services results in improved TB treatment outcomes and earlier prioritized ART initiation in a large urban HIV clinic in Uganda. *J Acquir Immune Defic Syndr* 2012; **60:** e29–35.

9 Durovni B, Saraceni V, Moulton LH, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. *Lancet Infect Dis* 2013; **13:** 852–58.

10 Stop TB Partnership. The global plan to stop TB 2016–2020. 2015. http://www.stoptb.org/global/plan/plan2/ (accessed Sept 11, 2015).

11 Theron G, Jenkins HE, Cobelens F, et al. Data for action: collection and use of local data to end tuberculosis. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00321-9.

12 Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00322-0.

13 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00323-2.

14 Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00324-4.

15 Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City—turning the tide. *N Engl J Med* 1995; **333:** 229–33.

16 Graham NM, Galai N, Nelson KE, et al. Effect of isoniazid chemoprophylaxis on HIV-related mycobacterial disease. *Arch Intern Med* 1996; **156:** 889–94.

17 Cavalcante SC, Durovni B, Barnes GL, et al. Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2010; **14:** 203–09.

18 Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis* 2010; **10:** 489–98.

19 INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373:** 795–807.

20 Gandhi NR, Andrews JR, Brust JC, et al. Risk factors for mortality among MDR- and XDR-TB patients in a high HIV prevalence setting. *Int J Tuberc Lung Dis* 2012; **16:** 90–97.

21 Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010; **362:** 697–706.

22 Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PLoS Med* 2012; **9:** e1001270.

23 Havlir D, Kendall M, Ive P, et al. Timing of antiretroviral therapy for HIV-1 and tuberculosis. *N Engl J Med* 2011; **365:** 1482–91.

24 The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373:** 808–22.

25 Cohen M, Chen Y, McCauley M, et al. Final results of the HPTN 052 randomized controlled trial: antiretroviral therapy prevents HIV transmission. 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 19–22, 2015. Program number MOAC0106LB, track C.

26 Van't Hoog AH, Meme HK, Laserson KF, et al. Screening strategies for tuberculosis prevalence surveys: the value of chest radiography and symptoms. *PLoS One* 2012; **7:** e38691.

27 Swindells S, Komarow L, Tripathy S, et al. Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253. *Int J Tuberc Lung Dis* 2013; **17:** 532–39.

28 Ritchie AV, Ushiro-Lumb I, Edmaga D, et al. SAMBA HIV semiquantitative test, a new point-of-care viral-load-monitoring assay for resource-limited settings. *J Clin Microbiol* 2014; **52:** 3377–83.

29 Gupta S, Granich R, Date A, et al. Review of policy and status of implementation of collaborative HIV-TB activities in 23 high-burden countries. *Int J Tuberc Lung Dis* 2014; **18:** 1149–58.

30 Clinton Health Access Initiative. Survey on barriers to TB-HIV integration in 14 high-burden countries. Boston, MA: Clinton Health Access Initiative, 2014.

31 Zumla AI, Gillespie SH, Hoelscher M, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *Lancet Infect Dis* 2014; **14:** 327–40.

How to eliminate tuberculosis 1

Data for action: collection and use of local data to end tuberculosis

Grant Theron, Helen E Jenkins*, Frank Cobelens, Ibrahim Abubakar, Aamir J Khan, Ted Cohen†, David W Dowdy†*

Accelerating progress in the fight against tuberculosis will require a drastic shift from a strategy focused on control to one focused on elimination. Successful disease elimination campaigns are characterised by locally tailored responses that are informed by appropriate data. To develop such a response to tuberculosis, we suggest a three-step process that includes improved collection and use of existing programmatic data, collection of additional data (eg, geographic information, drug resistance, and risk factors) to inform tailored responses, and targeted collection of novel data (eg, sequencing data, targeted surveys, and contact investigations) to improve understanding of tuberculosis transmission dynamics. Development of a locally targeted response for tuberculosis will require substantial investment to reconfigure existing systems, coupled with additional empirical data to evaluate the effectiveness of specific approaches. Without adoption of an elimination strategy that uses local data to target hotspots of transmission, ambitious targets to end tuberculosis will almost certainly remain unmet.

Published **Online** October 26, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00321-9

See **Online/Comments** http://dx.doi.org/10.1016/S0140-6736(15)00401-8, http://dx.doi.org/10.1016/S0140-6736(15)00320-7, and http://dx.doi.org/10.1016/S0140-6736(15)00319-0

This is the first in a **Series** of four papers about how to eliminate tuberculosis

*Joint first authors

†Joint senior authors

DST/NRF Centre of Excellence for Biomedical Tuberculosis Research, and South African Medical Research Council Centre for Molecular and Cellular Biology, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa (G Theron PhD)**; Lung Infection and Immunity Unit, Department of Medicine, University of Cape Town, Observatory, Cape Town, South Africa** (G Theron)**; Department of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA** (H E Jenkins PhD)**; KNCV Tuberculosis Foundation, The Hague, Netherlands** (F Cobelens MD)**; Amsterdam Institute for Global Health and Development, Academic Medical Center, Amsterdam, Netherlands** (F Cobelens)**; University College London, London, UK** (Prof I Abubakar FRCP)**; Interactive Research & Development, Karachi, Pakistan** (A J Khan MD)**; Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA** (T Cohen DPH)**; and Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA** (D W Dowdy MD)

Introduction

The fight against tuberculosis is entering a new era, moving from one of control to one of attempting to end the tuberculosis epidemic. The international donor and policy community have embraced targets of 90–95% reductions in incidence and mortality by 2035, relative to 2015.[1] One important component of such so-called epidemic-ending approaches is an increased focus on local-level strategies, which have been instrumental during elimination of infectious diseases ranging from smallpox to polio.[2–5] The successful elimination of disease epidemics has typically involved two important components: systematic reporting of every case and identification of disease clusters or hotspots at the local level where ongoing transmission occurs. These components enable the documentation of disease trends in each community and the subsequent targeting of resources to where they are needed most. Local strategies for tuberculosis could, for example, tailor diagnosis and treatment of infection to subpopulations that are at highest risk of disease progression [6] or target case-finding to stop transmission in high-incidence populations.[7] Some countries are starting to use subnational trends to inform more tailored approaches; however, to end tuberculosis in a 20 year timeframe, this trend must be accelerated and focus increased on local empowerment with centralised (national and global) support.[8,9]

Since the 1993 adoption of a widely accepted approach to tuberculosis treatment known as DOTS (directly observed treatment, short-course), a standard set of clinical, demographic, bacteriological, and treatment outcome data have been collected and aggregated by national tuberculosis programmes and subsequently reported to WHO.[10,11] This approach, although essential to inform country-level and global estimates and to monitor the high-level progress of strategies such as DOTS, has not emphasised the use of existing data (or collection of additional data) to identify sites of ongoing transmission and target local responses accordingly. Local tuberculosis epidemics differ in intensity, drivers, and key characteristics, and approaches that are effective in some hotspots (eg, informal urban settlements) might not work in others (eg, prisons or rural villages with poor access to care). Without high-quality data and infrastructure at the local level (and support from national and global entities) to inform more locally

Key messages

- Tuberculosis epidemics, like those of other infectious diseases, vary largely across different geographical regions; to end epidemics in high-burden areas, control efforts will need to be tailored to local conditions
- To design interventions that effectively combat tuberculosis, national control programmes should shift from a centralised approach in which local data are deposited into national databases for aggregated analyses, to a bidirectional one in which local partners have the capacity to collect and analyse data and then use those data to design locally responsive interventions
- This shift requires local tuberculosis programmes to make better use of existing data, expand routine data collection, and make informed use of targeted surveys
- These efforts also require the modernisation of data collection and storage systems, substantial financial investment in infrastructure and human resources (including the use of mobile technology and social media), and the reallocation of resources to support local decision making
- Programmes will need to develop the necessary analytical and support infrastructure to measure the effect of local interventions and disseminate these findings within the national programme

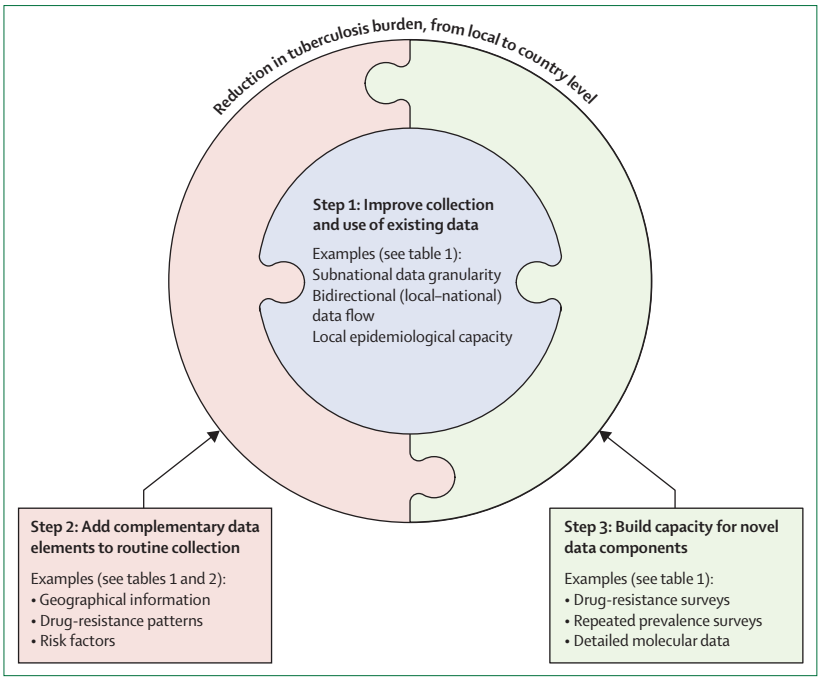

Figure 1: **A three-step approach for leveraging data to end tuberculosis**
To build locally tailored responses to effectively combat tuberculosis, three interlocking categories of activities are required. Effective local tuberculosis responses must start with improving the collection and use of existing data (blue centre), onto which additional data elements can be added (in peach). A third essential component involves building capacity to collect and use novel data at all levels of the health-care system (in green). Employing these three categories of activities in a multi-tiered and bidirectional fashion (as depicted in figure 4) should result in tuberculosis control policies that are more data driven and thus more likely to be effective.

Correspondence to:
Dr David W Dowdy, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21236, USA
ddowdy1@jhmi.edu

responsive strategies, the goal of ending tuberculosis worldwide will not be achieved.

Awareness is building of the importance of local data and capacity, but action is not being taken fast enough. WHO has championed the need for national programmes to respond to setting-specific differences, according to the scale of the epidemic in the country.[12] Three specific steps will accelerate this process (figure 1). First, countries must better use existing data on tuberculosis case notifications, risk factors, and treatment outcomes to inform local interventions. Second, national and global systems should augment the set of standard, routinely collected data with additional data elements (eg, geographical information, drug resistance, and risk factors) to target resources better, while ensuring that this additional data collection is feasible. Third, programmes must build capacity for the periodic and focused collection of novel data components (such as targeted surveys), contact investigations, and sequencing data, to inform local policy decisions.

In this, the first paper in a Series of four about how to eliminate tuberculosis, we describe how existing data and analysis systems could be improved to enable these three steps, highlighting the benefits and challenges in transitioning to a locally focused agenda to end tuberculosis (table 1).[12–16] Combined with strategies to interrupt transmission (see Series paper 2[7]), treat latent tuberculosis (see Series paper 3[6]), and improve social conditions (see Series paper 4[17]), use of local data and infrastructure to target interventions appropriately could form the basis for a coherent strategy to end tuberculosis from both a top-down and a bottom-up direction.

Improving data collection and analysis

Step one: improving the collection and use of existing programmatic data

Routinely collected data for tuberculosis vary substantially in scope and detail between countries. WHO recommends a minimum set of variables, comprising age, sex, geographical region, previous treatment, smear microscopy result, anatomical site (pulmonary or extrapulmonary), and treatment outcome, which are ideally linked to unique patient identifiers.[13,18] In many settings, data for HIV and exposure to high-risk congregate settings are also routinely collected. Although WHO recommends the use of secure, self-contained electronic systems, paper forms are still predominantly used.[13,14] Thus data analysis is often delayed until entry into a central country wide database is completed, reducing its usefulness to inform realtime programmatic decisions.[14] When such data are rapidly incorporated into policy, results can be dramatic. For example, in 2008, the tuberculosis programme in Lesotho found that more than 90% of patients diagnosed with tuberculosis were HIV seropositive.[19] The Ministry of Health, in collaboration with Médecins Sans Frontières, rapidly scaled up and integrated decentralised tuberculosis–HIV care in response. As a result, the number of adults on antiretroviral therapy (ART) in the programme doubled over 4 years, and the incidence of HIV-positive tuberculosis decreased by about 40%.[19,20]

Of particular importance to interrupting transmission is more focus on childhood tuberculosis, which is currently greatly underdetected and can serve as an important marker of ongoing transmission.[21–23] Better systems for the detection of paediatric tuberculosis and rapid notification when childhood cases rise higher than a certain threshold might not only inform specific interventions such as household contact tracing and preventive therapy for children, but could also serve as an early detection system to identify transmission hotspots.[24]

Ultimately, centralised tuberculosis data collection and reporting systems must be designed not only to inform national policy changes, but also to build local capacity to create tailored responses at the community level. Examples exist in other infectious diseases, such as with polio surveillance in India, which showed lower vaccine efficacy in high-population-density districts with poor sanitation, thereby enabling the roll-out of a different vaccine that was better suited to these areas.[25,26] This ultimately contributed to the elimination of polio where national-level policies had failed.[27] Similar targeted approaches, which are often as cost effective as broader,

	Current capacity	Potential improvements	Key challenges
Programmatic data	Strong systems for collection of aggregate data in many countries WHO guidance is available for surveillance and other systems[12–14]	Stronger systems for disaggregation of data at the subnational level Building internal capacity for epidemiological analysis and reporting to subnational tuberculosis authorities	Current incentive structures that prioritise national-level reporting Human resource constraints Infrastructure constraints (eg, reporting systems for surveillance) Little consistent data quality
Additional data that could be collected programmatically	Many clinics already informally collect additional data for internal quality control purposes	Routine data collection could expand to include patients' location, key risk factors, interactions with congregate settings, etc Increased autonomy and decision making capability at local clinics to decide data collection priorities Local stakeholders, who might have a better idea of interventions that are locally important, can be consulted in order to expand additional data collection	Standardised notification systems must be preserved in some form, but must balance the need for national reporting with local flexibility Local tuberculosis officials currently have little experience in collecting or using additional data Additional data must be able to be fed into large-scale tuberculosis elimination projects and compatible with national databases Routine (rather than targeted or time-limited) collection of additional data can be expensive and might compromise data quality
Specific surveys	Capacity to perform surveys for drug-resistant tuberculosis is increasing National prevalence surveys are being increasingly done WHO guidance is available for certain types of surveys[13,15]	Repeated surveys to better inform longitudinal analyses Routine surveillance systems that could feed back to national and subnational authorities Inclusion of data and reporting systems (eg, geographical data on drug-resistant cases) to inform local policies	Surveys can be very expensive, politically motivated, and not well integrated into existing routine tuberculosis efforts In-country capacity to do surveys without outside technical assistance is small Infrastructure for surveillance systems is often poor
Novel data	Some reference or academic laboratories can collect and analyse novel forms of data, such as the genetic distance between strains, to identify transmission events WHO guidance is available for some types of novel data[17]	Creation or adaptation of existing systems to allow for inputting of novel data Establishment of mechanisms for internal and external quality control Co-collection of other types of data (eg, social network data) must be improved to maximise the potential of novel data such as strain genotyping	IT (eg, data capturing and storage), laboratory (eg, infrastructure for culture, DST, and strain genotyping), and human resource capacity challenges need to be overcome to generate new types of data Storage and reporting of some types of novel data (eg, whole-genome sequence data) is not standardised
Systems for reporting and analysing data	Strong systems for reporting clinical laboratory data often exist, and could be adapted for epidemiological data BRICS and other middle-income countries have skilled (but highly centralised) capacity to perform epidemiological analyses Countries are increasingly moving towards individual-based electronic systems	Formal frameworks and how-to guides are needed to analyse data at a local level Better access to data and analytical support staff at the subnational or local level Better, automated systems for capturing new data on the ground in clinics (eg, electronic forms) Better integration of analytical expertise with other in-country disease control programmes Better systems for data sharing between local tuberculosis control programmes	Linkage of disparate IT systems (eg, for laboratory and patient data) Lack of human resource capacity to clean data and perform analyses, especially at the subnational level Lack of clear political, economic, or financial incentives to develop such capacity within countries
Empirical evidence to support local approaches	Reasonably strong evidence exists that tuberculosis incidence (including drug resistance) is heterogeneous at the local level Mathematical models suggest that local approaches might be more effective and efficient[16]	Programmatic evaluations and research studies could help to compare the effectiveness of locally targeted strategies against nationally standardised ones Cost-effectiveness analyses could evaluate whether the additional cost of local targeting provides sufficient health value to be justified	Generalisability of data from one epidemic and intervention to another is difficult Infrastructure and incentives (both organisational and financial) to collect such data are deficient outside of existing academic centres

IT=information technology. DST=drug-susceptibility testing. BRICS=Brazil, Russia, India, China, and South Africa.

Table 1: **Key elements of a data-driven, locally tailored approach to tuberculosis elimination**

untargeted interventions, will be needed to end epidemics of tuberculosis.[28–30]

Step two: routine collection of additional data to inform targeted responses

Although challenging in many settings, expansion of the minimum set of routinely collected tuberculosis data is essential to empower more locally responsive strategies.[12] Additional data include geographical information (eg, to assist with community-based follow-up, panel 1,[31] figure 2; or transmission-hotspot mapping, figure 3[32,33]), drug-resistance patterns (eg, for region-specific drug susceptibility testing algorithms and localised treatment regimens), and risk factors such as diabetes, smoking, or previous hospitalisation or imprisonment (eg, to inform local screening strategies).[34–36] For example, a surveillance study in Japan found high diabetes mellitus rates in some populations of elderly or homeless people with tuberculosis, thereby enabling clinics serving these individuals to do targeted screening.[37] Similarly, data from China showed a dramatic increase in the proportion of patients with tuberculosis that had recently migrated into Beijing, and that these patients rarely completed treatment.[38] This led to targeted case-finding and counselling to be carried out by clinics serving these communities. In table 2, we provide an illustrative list of

Panel 1: Data for action in Karachi, Pakistan

Interactive Research and Development, a local research organisation in Karachi, Pakistan, has used a range of electronic recording and reporting systems to improve access to and reporting from diagnostic and treatment sites.[31] For example, global positioning system (GPS) data have been used to identify the exact coordinates of private family practitioner clinics, public and private national tuberculosis programme (NTP) reporting centres, private laboratories, and pharmacies. All patients with drug-resistant tuberculosis or at high risk of loss to follow-up are mapped to approximate home locations with GPS-enabled phones, to inform assignment of community treatment supporters and to facilitate follow-up. For most of these patients, private clinics (red boxes in figure 2) are more accessible than the NTP reporting centre (NTP in figure 2) for scheduling of follow-up visits. These data have informed key programme decisions for targeted intensified case-finding, location of digital radiograph systems and GeneXpert machines, and recruitment of treatment supporters.

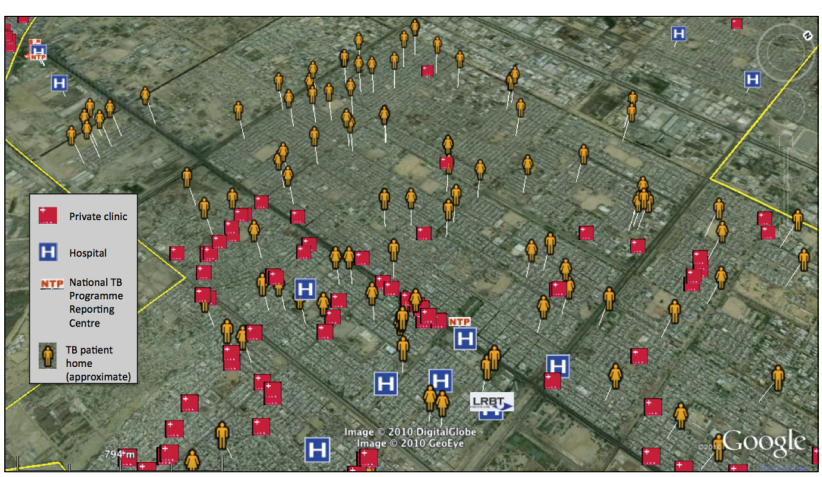

Figure 2: **GPS map of facilities and patient homes in Karachi, Pakistan (May, 2009)**
Illustrative example discussed in panel 2 showing coordinates of private family practitioner clinics, public and private national tuberculosis programme (NTP) reporting centres, and people with TB. GPS=geographical positioning system. NTP=national tuberculosis programme. TB=tuberculosis. Map data from Google, DigitalGlobe.

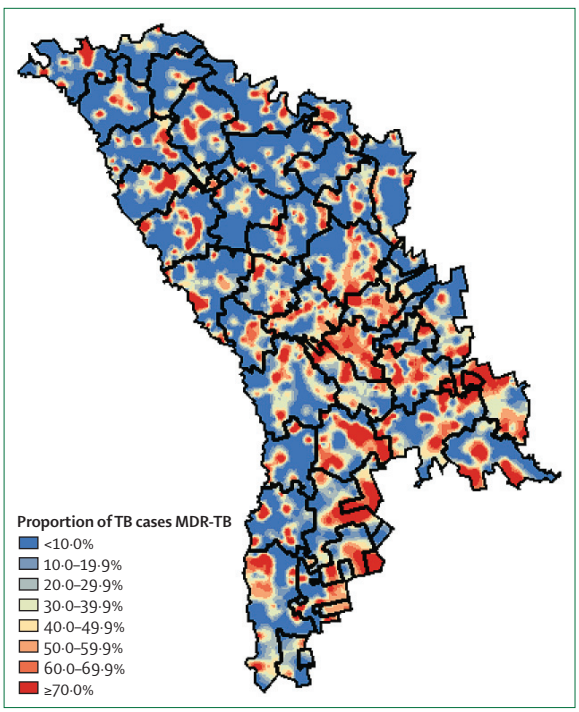

Figure 3: **Geographical hotspots of MDR-TB risk in Moldova**
Colours represent the proportion of previously treated TB cases with drug susceptibility testing data that are MDR-TB by location of residence. Maps such as this, which can help target intervention efforts and direct future research, represent the product of strengthening multiple aspects of the TB surveillance system. In the early 2000s, Moldova's TB programme updated the laboratory network, revised guidelines, and improved training to ensure universal drug susceptibility testing. Standardised reporting systems enabled more complete and accurate reporting of incidence, outcomes, and drug resistance, and a nationwide online database was introduced with access at every national TB facility.[32] Physicians and laboratory staff enter data (including routinely collecting location of residence) for individual patients with TB in realtime at the relevant points of contact. Data can then be synthesised into detailed maps of TB and drug-resistant TB, such as the one presented here, which can in turn be used to focus resources and efforts on regions of likely high ongoing transmission of drug-resistant TB (eg, see southeast represented in red). TB=tuberculosis. MDR=multidrug resistant. Reproduced with permission of the European Respiratory Society.[33]

additional data that could be collected and used for local decision making.

In routine practice, tuberculosis programmes must weigh data quantity against quality and might therefore focus additional data collection on particular patient groups or during the roll-out of new initiatives. To encourage the collection and use of relevant data, policy makers and tuberculosis programmes should promote new frameworks that use local data collection as benchmarks for clinic performance. Local tuberculosis control authorities must have sufficient autonomy, funding, and oversight to obtain data and implement interventions that will be most responsive to their unique epidemics. Examples of strategies that collect additional tuberculosis data and link these to tailored interventions are multicountry projects such as ENGAGE-TB and TB-REACH.[39,40] Importantly, local data collection can reveal other issues (eg, comorbidities such as diabetes and malnutrition) that are important for tuberculosis control and will also need to be addressed in a targeted fashion. Better integration of care is needed to address these factors; targeting them can also help to drive organisational and operational changes to strengthen local health systems.

Step three: targeted collection of novel data

Routine data will always be limited to elements that can be collected during busy clinical practice, with tight programmatic budgets, and from patients who actually present to care. To take a more comprehensive step toward ending tuberculosis, these data must be

occasionally augmented by additional investment in collecting non-routine information that can improve understanding of transmission and drug-resistance patterns.

Prevalence surveys estimate how many people have tuberculosis in a representative population sample.[9] Between 2009 and 2015, 23 countries are expected to have carried out tuberculosis prevalence surveys.[41] These surveys, with WHO guidance, can produce national (or occasionally subnational) estimates of the fraction of new cases with drug resistance, characterise broader patterns of transmission, and identify gaps in current control efforts.[13,15,42] Because surveys are expensive, logistically complex, and have relatively small sample sizes at the subnational level, they generally do not have resolution to inform local decisions. Innovative approaches to representative survey designs must therefore be considered.

One example of an alternative design in the case of drug resistance surveys is lot quality assurance sampling (LQAS).[43,44] LQAS can classify the risk of drug resistance among patients with tuberculosis at a subnational level with use of predefined thresholds of drug resistance.[45] Unlike traditional national-level drug-resistance surveys, LQAS surveys do not attempt to estimate the prevalence of resistance precisely. Instead, LQAS surveys classify areas as likely being above or below a threshold selected to guide local interventions. LQAS has shown, for example, that although Tanzania and Vietnam seem to have low multidrug-resistant (MDR) prevalence among new tuberculosis cases nationally, Vietnam has considerably subnational heterogeneity.[45–47] In particular, one province (Tây Ninh) had high MDR tuberculosis prevalence, which focused attention on areas closer to Cambodia, where MDR tuberculosis is more prevalent. Targeted surveys have also shown unusually high rates of MDR tuberculosis in some ART clinics and Tibetan refugee communities in India.[48,49] Similar methods, such as sentinel surveillance, have identified many patients with MDR tuberculosis from Somalia seeking treatment in Kenya.[50]

Other potentially useful data sources are molecular data for strain types, transmission, and drug resistance.[51] Currently, such data are only collected broadly and systematically in resource-rich settings. For example, an analysis of US national surveillance identified which racial minorities are most likely to develop tuberculosis from recent transmission and a service in the UK has used molecular typing prospectively since 2010 to identify outbreaks and estimate the proportion and identity of MDR tuberculosis cases attributable to transmission.[52–54] Locally, such data can also be used to improve both contact investigations (which might be complemented by online social network data) and the laboratory methods used to diagnose drug-resistant tuberculosis (panel 2).[60] Newer technologies, such as whole-genome sequencing (WGS), can identify strains responsible for major outbreaks, uncover highly infectious super-spreaders, and help to understand the completeness of contact investigations.[51,61–63] Although not widely implemented, BRICS countries (Brazil, Russia, India, China, and South Africa) and other middle-income countries have capacity to collect and analyse molecular data, and WHO guidance exists about strain genotyping for tuberculosis surveillance.[12] Although WGS might be more challenging to implement, it can inform the development of simpler tests, which have been used in preliminary studies to infer transmission patterns.[64] Mobile technology can also help the collection of novel geospatial information. For example, human movement (measured via mobile phone towers) has been combined with high-resolution prevalence data for malaria in Kenya to show that migration from less-developed residential areas accounts for most new cases of malaria within urban centres.[65] Importantly, the usefulness of these additional data will always be small if they cannot also be easily captured and integrated into existing data systems.

	Items
Drug resistance surveys	
Drug resistance diagnoses	Genotypic (eg, Xpert MTB/RIF) and phenotypic (eg, liquid culture) drug-susceptibility testing results, mutational analyses
Monitoring of disease severity	
Bacterial load	Smear grade, culture time-to-positivity, Xpert MTB/RIF cycle threshold values, LAM strip grade
Clinical test data	Chest radiograph, BMI, haemoglobin concentrations
Transmission mapping	
Strain genotype	MIRU-VNTR, spoligotype, RFLP pattern, WGS
Geospatial, location, and contact data	Administrative region (eg, district, city, and suburb), residential address, or GPS coordinates of residence; recent hospital admissions (name of hospital, duration, and reason for treatment); incarcerations or known tuberculous contacts
Risk factor analysis	
Comorbidities	HIV, diabetes, chronic obstructive pulmonary disease, pneumonia, diabetes
Occupational exposure	Health-care workers, miners
Substance use	Cigarette pack-years, AUDIT alcohol use scores, illicit narcotic usage

LAM=lipoarabinomannan. BMI=body-mass index. MIRU-VNTR=mycobacterial interspersed repetitive units–variable number of tandem repeats. RFLP=restriction fragment length polymorphism. WGS=whole-genome sequencing. GPS=global positioning system. AUDIT=alcohol use disorders identification test.

Table 2: **Possible data items to be collected on individual tuberculosis cases, in addition to the WHO minimum set of variables,[13] by purpose and data type**

Enhancing data systems

Systems for reporting and analysing data

An investment in surveillance systems for tuberculosis, including strengthening of WHO-supported electronic data collection systems, is needed to achieve greater local control of tuberculosis.[12,14] Maintaining a system that is sufficiently agile to be useful for heterogeneous patient populations and the levels of resource availability (eg, internet access) across all localities can be difficult. This difficulty is compounded by the long-term use of proprietary systems for which support might have ceased

Panel 2: **Strain typing to inform the local scale-up of drug susceptibility testing (DST) in South Africa**

The Western Cape province in South Africa, which has relatively strong drug-resistant tuberculosis surveillance infrastructure, has seen a change in drug-resistant tuberculosis strain diversity. Strains with an atypical Beijing genotype, which are historically scarce, have become dominant among patients with drug-resistant tuberculosis and are associated with clustered outbreaks of extensively drug-resistant (XDR) tuberculosis.[55] A series of molecular epidemiological studies[56–58] showed that these strains likely originated from an adjacent province (Eastern Cape), which has relatively weak DST surveillance infrastructure. These atypical Beijing strains in the Eastern Cape had an unusually high prevalence of inhA promoter mutations which, in addition to conferring low-level resistance to isoniazid (a key drug in the first-line regimen), also confer resistance to ethionamide (a key drug in the second-line regimen used to treat multidrug-resistant tuberculosis, but for which resistance was not routinely tested). The effectiveness of the second-line drug regimen was thus substantially weakened, and atypical Beijing strains were programmatically selected to evolve into XDR tuberculosis, which subsequently entered the Western Cape, likely via the large migrant population. Molecular tests are now used to identify inhA promoter mutations in the Eastern Cape. An alternative drug can thus potentially be substituted for ethionamide to limit the emergence of XDR tuberculosis; however, in practice, this is not yet widely adopted.[59]

and the requirement by governments for a lengthy public tender process.[66] Implementation of flexible systems for a locally tailored tuberculosis response—especially in high-burden countries that often have extreme resource limitations, little political will, and the highest need for such systems among disenfranchised populations—will be no easier.

Benchmarks and performance indicators can facilitate the collection of standardised data and identification of surveillance gaps.[12–14] These benchmarks encourage tuberculosis programmes to assess the consistency of case definitions and national data in interactive workshops with stakeholders. Such benchmarks can be internal (eg, subtotals by age group equal the total number of reported cases) or external (eg, the percentage of new cases in subgroups, such as children, is comparable with similar countries). Although linking data across disparate electronic databases (eg, laboratory results and treatment information) is challenging, guidelines for the development of national electronic tuberculosis data systems are potentially useful for local system development.[14]

Potential improvements to existing systems

Existing systems might be improved by: incorporation of more local data; enabling the easy capture of additional setting-specific data; integrating with other disease databases; and implementing features that enable rapid data analysis and linkage to intervention. Systems incorporating local data should permit the timely collection, reporting, and analysis of these data at all levels of the health-care system (figure 4). Crucially, these steps must be done while maintaining the capacity of existing systems to enable country-level reporting. This effort will require substantial new investments in human resource capacity (particularly epidemiological expertise) and technological infrastructure. Countries and cities are increasingly developing individual-based electronic data systems.[67–69] Mobile technology can also be combined with innovative methods to maximise case-finding by reimbursing tuberculosis control officers promptly or providing appropriate incentives to find additional cases.[67]

Importantly, these improved systems for local data should not only integrate with national systems but also allow for bidirectional data flow, facilitating the direct transfer of data between national to local level and control programmes. This information can also link into systems used in other sectors. For example, the INDEPTH Network provides support and guidance for the collection of community-level demographic and health-care information, which supplement the surveillance of non-communicable diseases in high-burden countries and is subsequently fed into national databases.[70,71] Data from both public and private sectors should also be considered for inclusion.[72]

If locally important data are to be analysed effectively, improved quality control and standardised best practice guidelines are required, especially for new types of data. Open-source tools are available to assist in the analysis of these data, whether, for example, it is to project the local impact and cost of diagnostic tests or to detect drug-resistance mutations from WGS data.[73,74] Wider availability and adoption of such methods could encourage the collection of local data and improve the analytical capacity of tuberculosis programmes; however, data might also need to be analysed at a more centralised level, at which analytical capacity is likely to be greater.

Unique patient identifiers are essential. Without these, linkage of routine clinical and laboratory data to those from targeted surveys, sentinel surveillance systems, and other novel data collection efforts will be challenging. This data linkage can facilitate pragmatic studies of the impact of interventions at a subdistrict level. In Brazil, data collected before and after the roll-out of Xpert MTB/RIF (a molecular test for tuberculosis and rifampin resistance) allowed for Xpert's effect on local case notification rates to be quantified and for poor-performing sites to be identified and targeted for further strengthening.[75] However, because the laboratory and treatment databases used their own internal identifiers, linking specific laboratory results with specific treatment outcomes was a challenge. Weak existing data structures have also made it difficult to generate empirical evidence for locally targeted approaches to tuberculosis control. Despite their clear benefits and potential cost savings, improvements to these systems need substantial investment.[76–78] To justify such investment, strengthening of the empirical evidence base is essential.

Empirical evidence for local approaches

Little evidence has been provided for the effectiveness of the types of locally targeted approaches described above

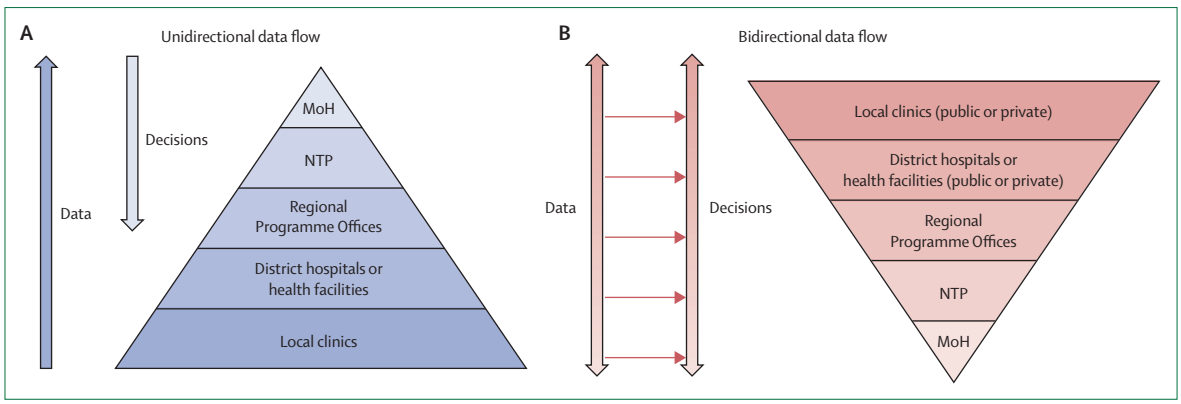

Figure 4: **Structuring data and decision making for tuberculosis elimination**
In existing systems, data is largely sent from the local level and aggregated at the central level for reporting and broad target-setting, with decisions made in top-down fashion and rarely involving individuals below the regional or district level (A). To achieve tuberculosis elimination, data structures, and decision making should arguably be centred around activities at the local level, which is the level at which tuberculosis transmission occurs. Such structures should support data and decision making that is bidirectional and mutually informative in nature, involving all levels of the tuberculosis control system (B). This flow of information should not only occur between health-care system tiers, but also between localities, to disseminate information about what works in different settings. NTP=National Tuberculosis Programme. MoH=Ministry of Health.

	Examples of potential benchmarks*	Improvements in data systems and structures required to assess progress
High HIV rate, low MDR, urban setting (eg, African city)	Percent decline in notified tuberculosis incidence in the five highest-incidence neighbourhoods	Ability to measure tuberculosis incidence by neighbourhood or postal code
Diffuse, private-sector driven, periurban setting (eg, Indian informal settlement)	Percent increase in patients notified and successfully treated (including referrals) among those diagnosed with tuberculosis in the private sector	Integration of private care notification data with routine public systems
Low HIV, moderate incidence, high MDR (eg, town in former Soviet Union)	Absolute decline in incidence of MDR tuberculosis among treatment-naive individuals	Repeat, targeted surveys to measure and stratify MDR tuberculosis according to previous tuberculosis history
Rural subdistrict with poor access to laboratory testing facilities (eg, in southeast Asia)	Absolute reductions in average time to diagnosis and the proportion of patients who test positive but do not start treatment	Integration of laboratory results with treatment initiation (yes/no, and date-stamped) data
Well resourced city with large migrant community (eg, in western Europe)	Absolute reduction in proportion of new cases due to recent infection, informed by molecular epidemiology	Inclusion of strain type data into routine notification systems

MDR=multidrug resistance. *The specific change targeted, and the duration of time provided to meet the benchmark, would depend on the current rate of tuberculosis, existing trends, and anticipated costs.

Table 3: **Examples of potential benchmarks for success of locally targeted strategies to end tuberculosis in five emblematic settings**

for tuberculosis control. Nevertheless, targeting of high-risk populations (eg, homeless people, HIV-infected people, or drug users) has been a crucial component of most major successes in tuberculosis control.[79,80] Mathematical models based on empirical data provide indirect support for targeted tuberculosis elimination strategies, as has been demonstrated for other diseases.[3,16,81,82] Data from Rio de Janeiro, Brazil, suggest that, as with other diseases, targeting hotspots containing 6% of the population on a district level (identified from local notification rates) could reduce city wide incidence to a similar degree as an intervention of equal intensity covering the remaining 94% of the population.[30]

Local control officials undoubtedly target high-risk patient groups intuitively, but to show the effectiveness of these approaches, data must be collected and compared against standardised benchmarks. Ideally, these benchmarks should be agreed upon at the local and national level, accounting for local epidemiology and existing trends (table 3). Guidance about these measures of success could come from global agencies such as WHO and implementation of these standards could drive the improvement of local data collection efforts. Targeted approaches become increasingly important as tuberculosis incidence declines and becomes more concentrated within specific subpopulations; thus, collection of empirical evidence against standardised benchmarks to inform such approaches should become a higher priority.[83]

Encouraging parallels exist for other diseases. The Tanzanian ART programme's "Know your CD4 count" campaign used a consultation process to identify clinic, patient, and infrastructural factors that limited the number of HIV-infected patients with a known CD4 count.[84] After data for each clinic were reviewed in conjunction with local staff, site-specific interventions were implemented to address administrative and laboratory barriers, strengthen staff training, and educate patients. After the roll-out of the

intervention, ART enrolment increased by an average of 62% at each clinic.

Evidence for the effectiveness of local interventions could also be collected with pragmatic trials embedded within the implementation of locally tailored responses, or before–after comparisons of communities that adopt tailored strategies for tuberculosis control. A study in Karachi showed that when community members screened patients in private health-care facilities, the number of detected tuberculosis cases doubled, compared with areas without the intervention.[31]

Ethical considerations

When designing targeted approaches to end tuberculosis locally, ethical considerations are an important challenge. Tuberculosis programmes collect anonymised data routinely and are working increasingly closely with patient advocacy groups, but local-level collection requires additional engagement with the targeted communities. Tuberculosis officers might therefore wish to consult with community organisations to ensure that data are used to address local public health priorities. For example, community consultation is a core component of the Reaching Every District approach for childhood vaccination, and many countries with the most successful vaccination programmes also have high outreach and community engagement.[85,86] Ethical considerations should also be considered when prioritising interventions such as ART to specific groups; targeting of one region or population over another might be perceived as inequitable.[28] Finally, with regard to security, data can be anonymised, but sufficient technological infrastructure is still required to protect patient privacy, especially in resource-limited settings, in which such systems might be weaker. However, systems to protect privacy do not need to be specific to tuberculosis, and cross-sector initiatives should be encouraged.

Conclusion

Traditionally, interventions to control tuberculosis have focused on providing a basic level of care to a large number of people. As global priorities shift from controlling tuberculosis to ending tuberculosis, we must rapidly develop new systems that empower interventions tailored to heterogeneous epidemics. Locally targeted approaches have been successful in other diseases, but need routine collection of local data, bidirectional flow of information and capacity between local and central level, augmentation of existing data collection efforts, and investment in the systems needed to collect and analyse disaggregated data.

In many settings, the focus of data collection is already shifting from national reporting to informing local strategy. Accelerating this expansion will require stronger links between local clinics, national tuberculosis programmes, in-country and regional institutions with specialised expertise, and global organisations such as WHO. A political commitment to increase human and information technology resources at all levels, and to collect empirical data to show the effectiveness of locally targeted strategies, will also be essential. To stop tuberculosis worldwide, variation in epidemics locally must be addressed, meaning that we must modernise data, systems, and ethical structures at all levels to empower communities to understand tuberculosis epidemics better, and ultimately to end them.

Contributors

GT, HEJ, TC, and DWD conceived the idea for this manuscript. GT and HEJ wrote the first draft, and all authors revised it for important intellectual content. All authors approved the final version as submitted for publication.

Declaration of interests

The authors declare no competing interests.

Acknowledgments

We are supported by the Wellcome Trust (grant WT099854MA) and a South African Medical Research Council Career Development Award (to GT); the US National Institutes of Health (K01AI102944, awarded to HEJ; R01AI112438 awarded to TC); the B Frank and Kathleen Polk Assistant Professorship in Epidemiology (to DWD); and the UK National Institute of Health Research, Medical Research Council, and Public Health England (IA). The funders had no role in the conception, preparation, review, approval, or submission of this manuscript. The content is solely the responsibility of the authors and does not necessarily represent the views of the US National Institute of Allergy and Infectious Diseases or the US National Institutes of Health. We thank Carole Mitnick for her review and the important comments she contributed during drafting and Carly Rodriguez for coordination and research assistance in the preparation of this manuscript.

References

1 Uplekar M, Weil D, Lonnroth K, et al. WHO's new End TB Strategy. *Lancet* 2015; **385:** 1799–801.

2 Guerra CA, Gikandi PW, Tatem AJ, et al. The limits and intensity of *Plasmodium falciparum* transmission: implications for malaria control and elimination worldwide. *PLoS Med* 2008; **5:** e38.

3 Hotez PJ, Bottazzi ME, Franco-Paredes C, Ault SK, Periago MR. The neglected tropical diseases of Latin America and the Caribbean: a review of disease burden and distribution and a roadmap for control and elimination. *PLoS Negl Trop Dis* 2008; **2:** e300.

4 Centers for Disease Control and Prevention (CDC). Progress toward elimination of Haemophilus influenzae type b invasive disease among infants and children–United States, 1998–2000. *MMWR Morb Mortal Wkly Rep* 2002; **51:** 234–37.

5 Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. World Health Organisation. Geneva, Switzerland, 1988.

6 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00323-2.

7 Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00322-0.

8 Nanoo A, Izu A, Ismail NA, et al. Nationwide and regional incidence of microbiologically confirmed pulmonary tuberculosis in South Africa, 2004–12: a time series analysis. *Lancet Infect Dis* 2015; **15:** 1066–76.

9 WHO. Global Tuberculosis Control 2014. Publication no. WHO/HTM/TB/2014.08. Geneva: World Health Organization, 2014.

10 WHO. What is DOTS: a guide to understanding the WHO-recommended TB control strategy known as DOTS. WHO/CDS/CPC/TB/99.270. Geneva: World Health Organization, 1999.

11 WHO. Definitions and reporting framework for tuberculosis—2013 revision. Publication no. WHO/HTM/TB/2013.2. Geneva: World Health Organization, 2013.

12 WHO. Understanding and using tuberculosis data. WHO/HTM/TB/2014.09. Geneva: World Health Organization, 2014.

13 WHO. Standards and benchmarks for tuberculosis surveillance and vital registration systems: checklist and user guide. WHO/JTM/TB/2014.02. Geneva: World Health Organization, 2014.

14 WHO. Electronic recording and reporting for tuberculosis care and control. WHO/HTM/TB/2011.22. Geneva: World Health Organization, 2012.

15 WHO. Tuberculosis prevalence surveys: a handbook. WHO/HTM/TB/2010.17. Geneva: World Health Organization, 2011.

16 Dowdy DW, Golub JE, Chaisson RE, Saraceni V. Heterogeneity in tuberculosis transmission and the role of geographic hotspots in propagating epidemics. *Proc Natl Acad Sci USA* 2012; **109:** 9557–62.

17 Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00324-4.

18 WHO. Global tuberculosis report 2014. WHO/HTM/TB/2014.08. Geneva: World Health Organization, 2014.

19 WHO. TB country profile: Lesotho. Geneva: World Health Organization, 2014. https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=LS&LAN=EN&outtype=html (accessed Dec 21, 2014).

20 Cohen R, Lynch S, Bygrave H, et al. Antiretroviral treatment outcomes from a nurse-driven, community-supported HIV/AIDS treatment programme in rural Lesotho: observational cohort assessment at two years. *J Int AIDS Soc* 2009; **12:** 23.

21 Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health* 2014; **2:** e453–59.

22 Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet* 2014; **383:** 1572–79.

23 Bloch AB, Snider DE Jr. How much tuberculosis in children must we accept? *Am J Public Health* 1986; **76:** 14–15.

24 WHO. Roadmap for childhood tuberculosis. WHO/HTM/TB/2013.12. Geneva: World Health Organization, 2013.

25 Grassly NC, Fraser C, Wenger J, et al. New strategies for the elimination of polio from India. *Science* 2006; **314:** 1150–53.

26 Grassly NC, Wenger J, Durrani S, et al. Protective efficacy of a monovalent oral type 1 poliovirus vaccine: a case-control study. *Lancet* 2007; **369:** 1356–62.

27 Bahl S, Kumar R, Menabde N, et al. Polio-free certification and lessons learned—South-East Asia region, March 2014. *MMWR Morb Mortal Wkly Rep* 2014; **63:** 941–46.

28 Gerberry DJ, Wagner BG, Garcia-Lerma JG, Heneine W, Blower S. Using geospatial modelling to optimize the rollout of antiretroviral-based pre-exposure HIV interventions in Sub-Saharan Africa. *Nat Commun* 2014; **5:** 5454.

29 Azman AS, Luquero FJ, Rodrigues A, et al. Urban cholera transmission hotspots and their implications for reactive vaccination: evidence from Bissau City, Guinea Bissau. *PLoS Negl Trop Dis* 2012; **6**: e1901.

30 Bousema T, Griffin JT, Sauerwein RW, et al. Hitting hotspots: spatial targeting of malaria for control and elimination. *PLoS Med* 2012; **9:** e1001165.

31 Khan AJ, Khowaja S, Khan FS, et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. *Lancet Infect Dis* 2012; **12:** 608–16.

32 Soltan V, Henry AK, Crudu V, Zatusevski I. Increasing tuberculosis case detection: lessons from the Republic of Moldova. *Bull World Health Organ* 2008; **86:** 71–76.

33 Jenkins HE, Plesca V, Ciobanu A, et al. Assessing spatial heterogeneity of multidrug-resistant tuberculosis in a high-burden country. *Eur Respir J* 2013; **42:** 1291–301.

34 Stuckler D, Basu S, McKee M, King L. Mass incarceration can explain population increases in TB and multidrug-resistant TB in European and central Asian countries. *Proc Natl Acad Sci USA* 2008; **105:** 13280–85.

35 Bantubani N, Kabera G, Connolly C, et al. High rates of potentially infectious tuberculosis and multidrug-resistant tuberculosis (MDR-TB) among hospital inpatients in KwaZulu Natal, South Africa indicate risk of nosocomial transmission. *PLoS One* 2014; **9:** e90868.

36 Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med* 2007; **167:** 335–42.

37 Uchimura K, Ngamvithayapong-Yanai J, Kawatsu L, et al. Characteristics and treatment outcomes of tuberculosis cases by risk groups, Japan, 2007-2010. *Western Pac Surveill Response J* 2013; **4:** 11–18.

38 Zhang LX, Tu DH, An YS, Enarson DA. The impact of migrants on the epidemiology of tuberculosis in Beijing, China. *Int J Tuberc Lung Dis* 2006; **10:** 959–62.

39 WHO. The ENGAGE-TB Approach: Integrating community-based TB activities into the work of NGOs and other CSOs. Geneva: World Health Organization, 2014. http://www.who.int/tb/people_and_communities/commcare/background/en/ (accessed Dec 23, 2014).

40 Stop TB. Partnership. TB Reach. 2015. http://www.stoptb.org/global/awards/tbreach/ (accessed March 13, 2015).

41 Floyd S, Sismanidis C, Yamada N, et al. Analysis of tuberculosis prevalence surveys: new guidance on best-practice methods. *Emerg Themes Epidemiol* 2013; **10:** 10.

42 WHO. Guidelines for surveillance of drug resistance in tuberculosis–5th edition. WHO/HQ/TB/2014.12. Geneva: World Health Organization, 2014.

43 Robertson SE, Valadez JJ. Global review of health care surveys using lot quality assurance sampling (LQAS), 1984–2004. *Soc Sci Med* 2006; **63:** 1648–60.

44 Lanata CF, Black RE. Lot quality assurance sampling techniques in health surveys in developing countries: advantages and current constraints. *World Health Stat Q* 1991; **44:** 133–39.

45 Hedt BL, van Leth F, Zignol M, et al. Multidrug resistance among new tuberculosis cases: detecting local variation through lot quality-assurance sampling. *Epidemiology* 2012; **23:** 293–300.

46 Chonde TM, Doulla B, van Leth F, et al. Implementation of a national anti-tuberculosis drug resistance survey in Tanzania. *BMC Public Health* 2008; **8:** 427.

47 Huong NT, Lan NT, Cobelens FG, et al. Antituberculosis drug resistance in the south of Vietnam: prevalence and trends. *J Infect Dis* 2006; **194:** 1226–32.

48 Salvo F, Dorjee K, Dierberg K, et al. Survey of tuberculosis drug resistance among Tibetan refugees in India. *Int J Tuberc Lung Dis* 2014; **18:** 655–62.

49 Isaakidis P, Das M, Kumar AMV, et al. Alarming levels of drug-resistant tuberculosis in HIV-infected patients in metropolitan Mumbai, India. *PLoS One* 2014; **9:** e110461.

50 Cain KP, Marano N, Kamene M, et al. The movement of multidrug-resistant tuberculosis across borders in East Africa needs a regional and global solution. *PLoS Med* 2015; **12:** e1001791.

51 Walker TM, Ip CL, Harrell RH, et al. Whole-genome sequencing to delineate *Mycobacterium tuberculosis* outbreaks: a retrospective observational study. *Lancet Infect Dis* 2013; **13:** 137–46.

52 Moonan PK, Ghosh S, Oeltmann JE, Kammerer JS, Cowan LS, Navin TR. Using genotyping and geospatial scanning to estimate recent mycobacterium tuberculosis transmission, United States. *Emerg Infect Dis* 2012; **18:** 458–65.

53 Mears J, Abubakar I, Crisp D, et al. Prospective evaluation of a complex public health intervention: lessons from an initial and follow-up cross-sectional survey of the tuberculosis strain typing service in England. *BMC Public Health* 2014; **14:** 1023.

54 Anderson LF, Tamne S, Brown T, et al. Transmission of multidrug-resistant tuberculosis in the UK: a cross-sectional molecular and epidemiological study of clustering and contact tracing. *Lancet Infect Dis* 2014; **14:** 406–15.

55 Chihota VN, Müller B, Mlambo CK, et al. The population structure of multi- and extensively drug-resistant tuberculosis in South Africa. *J Clin Microbiol* 2012; **50:** 995–1002.

56 Müller B, Chihota VN, Pillay M, et al. Programmatically selected multidrug-resistant strains drive the emergence of extensively drug-resistant tuberculosis in South Africa. *PLoS One* 2013; **8:** e70919.

57 Müller B, Streicher EM, Hoek KG, et al. inhA promoter mutations: a gateway to extensively drug-resistant tuberculosis in South Africa? *Int J Tuberc Lung Dis* 2011; **15:** 344–51.

58 Klopper M, Warren RM, Hayes C, et al. Emergence and spread of extensively and totally drug-resistant tuberculosis, South Africa. *Emerg Infect Dis* 2013; **19:** 449–55.

59 Bateman C. Eastern Cape treatment dysfunction boosts virulent new XDR-TB strain. *S Afr Med J* 2015; **105:** 165–67.

60 Mandeville KL, Harris M, Thomas HL, Chow Y, Seng C. Using Social Networking Sites for Communicable Disease Control: Innovative Contact Tracing or Breach of Confidentiality? *Public Health Ethics* 2014; **7:** 47–50.

61 Gardy JL, Johnston JC, Ho Sui SJ, et al. Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. *N Engl J Med* 2011; **364:** 730–39.

62 Walker TM, Lalor MK, Broda A, et al. Assessment of *Mycobacterium tuberculosis* transmission in Oxfordshire, UK, 2007–12, with whole pathogen genome sequences: an observational study. *Lancet Respir Med* 2014; **2:** 285–92.

63 Török ME, Reuter S, Bryant J, et al. Rapid whole-genome sequencing for investigation of a suspected tuberculosis outbreak. *J Clin Microbiol* 2013; **51:** 611–14.

64 Pérez-Lago L, Lirola MM, Herranz M, Comas I, Bouza E, García-de-Viedma D. Fast and low-cost decentralized surveillance of transmission of tuberculosis based on strain-specific PCRs tailored from whole genome sequencing data: a pilot study. *Clin Microbiol Infect* 2015; **21**: 249 e1–9.

65 Wesolowski A, Eagle N, Tatem AJ, et al. Quantifying the impact of human mobility on malaria. *Science* 2012; **338:** 267–70.

66 Sankoh O, Byass P. The INDEPTH Network: filling vital gaps in global epidemiology. *Int J Epidemiol* 2012; **41:** 579–88.

67 TIBU. Use of innovative technology to improve Kenya TB programme management – the first in Africa! www.tbcare1.org/pdfs/download.php?file=TIBU_factsheet.pdf (accessed Feb 3, 2015).

68 Creswell J, Khowaja S, Codlin A, et al. An evaluation of systematic tuberculosis screening at private facilities in Karachi, Pakistan. *PLoS One* 2014; **9:** e93858.

69 Lorent N, Choun K, Thai S, et al. Community-based active tuberculosis case finding in poor urban settlements of Phnom Penh, Cambodia: a feasible and effective strategy. *PLoS One* 2014; **9:** e92754.

70 Bangha M, Diagne A, Bawah A, Sankoh O. Monitoring the millennium development goals: the potential role of the INDEPTH Network. *Glob Health Action* 2010; published online Sept 13. DOI:10.3402/gha.v3i0.5517.

71 Ng N, Van Minh H, Juvekar S, et al. Using the INDEPTH HDSS to build capacity for chronic non-communicable disease risk factor surveillance in low and middle-income countries. *Glob Health Action* 2009; **2**. DOI:10.3402/gha.v2i0.1984.

72 Wells WA, Uplekar M, Pai M. Achieving Systemic and Scalable Private Sector Engagement in Tuberculosis Care and Prevention in Asia. *PLoS Med* 2015; **12:** e1001842.

73 Dowdy DW, Andrews JR, Dodd PJ, Gilman RH. A user-friendly, open-source tool to project impact and cost of diagnostic tests for tuberculosis. *eLife* 2014; **3:** 3.

74 Coll F, McNerney R, Preston MD, et al. Rapid determination of anti-tuberculosis drug resistance from whole-genome sequences. *Genome Med* 2015; **7:** 51.

75 Durovni B, Saraceni V, van den Hof S, et al. Impact of replacing smear microscopy with Xpert MTB/RIF for diagnosing tuberculosis in Brazil: a stepped-wedge cluster-randomized trial. *PLoS Med* 2014; **11:** e1001766.

76 Blaya JA, Cohen T, Rodríguez P, Kim J, Fraser HS. Personal digital assistants to collect tuberculosis bacteriology data in Peru reduce delays, errors, and workload, and are acceptable to users: cluster randomized controlled trial. *Int J Infect Dis* 2009; **13:** 410–18.

77 Blaya JA, Shin SS, Yale G, et al. Electronic laboratory system reduces errors in National Tuberculosis Program: a cluster randomized controlled trial. *Int J Tuberc Lung Dis* 2010; **14:** 1009–15.

78 Chapman AL, Darton TC, Foster RA. Managing and monitoring tuberculosis using web-based tools in combination with traditional approaches. *Clin Epidemiol* 2013; **5:** 465–73.

79 Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City--turning the tide. *N Engl J Med* 1995; **333:** 229–33.

80 Partners in Health. PIH/Russia recognized for TB achievements. Geneva: UNAIDS, 2014. http://www.pih.org/blog/pih-russia-recognized-for-tb-achievements (accessed Dec 23, 2014).

81 Wand H, Ramjee G. Targeting the hotspots: investigating spatial and demographic variations in HIV infection in small communities in South Africa. *J Int AIDS Soc* 2010; **13:** 41.

82 Gurarie D, Seto EY. Connectivity sustains disease transmission in environments with low potential for endemicity: modelling schistosomiasis with hydrologic and social connectivities. *J R Soc Interface* 2009; **6:** 495–508.

83 Colijn C, Cohen T, Murray M. Emergent heterogeneity in declining tuberculosis epidemics. *J Theor Biol* 2007; **247:** 765–74.

84 Memiah P, Shumba C, Henley Y, et al. "Know your CD4 campaign": 6-year outcomes from a quality improvement initiative to promote earlier initiation of antiretroviral therapy in Tanzania. *Int J Med Public Health* 2014; **4:** 194.

85 Vandelaer J, Bilous J, Nshimirimana D. Reaching Every District (RED) approach: a way to improve immunization performance. *Bull World Health Organ* 2008; **86:** (A–B).

86 WHO. In-Depth Evaluation of the Reaching Every District Approach in the African Region. Geneva: World Health Organization, 2007. http://www.immunizationbasics.jsi.com/Docs/AFRO_RED_Eval_Dec07.pdf (accessed Jan 6, 2015).

How to eliminate tuberculosis 2

Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment

Courtney M Yuen, Farhana Amanullah, Ashwin Dharmadhikari, Edward A Nardell, James A Seddon, Irina Vasilyeva, Yanlin Zhao, Salmaan Keshavjee, Mercedes C Becerra**

To halt the global tuberculosis epidemic, transmission must be stopped to prevent new infections and new cases. Identification of individuals with tuberculosis and prompt initiation of effective treatment to rapidly render them non-infectious is crucial to this task. However, in settings of high tuberculosis burden, active case-finding is often not implemented, resulting in long delays in diagnosis and treatment. A range of strategies to find cases and ensure prompt and correct treatment have been shown to be effective in high tuberculosis-burden settings. The population-level effect of targeted active case-finding on reducing tuberculosis incidence has been shown by studies and projected by mathematical modelling. The inclusion of targeted active case-finding in a comprehensive epidemic-control strategy for tuberculosis should contribute substantially to a decrease in tuberculosis incidence.

Published **Online** October 26, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00322-0

See **Online/Comments** http://dx.doi.org/10.1016/S0140-6736(15)00401-8, http://dx.doi.org/10.1016/S0140-6736(15)00320-7, and http://dx.doi.org/10.1016/S0140-6736(15)00319-0

This is the second in a **Series** of four papers about how to eliminate tuberculosis

*Joint senior authors

Brigham and Women's Hospital, Boston, MA, USA (C M Yuen PhD, A Dharmadhikari MD, E A Nardell MD)**; Indus Hospital Research Center, Karachi, Pakistan** (F Amanullah MD)**; Imperial College London, London, UK** (J A Seddon PhD)**; Russian Academy of Medical Sciences, Moscow, Russia** (Prof I Vasilyeva MD)**; Chinese Centre for Disease Control and Prevention, Beijing, China** (Y Zhao PhD)**; and Harvard Medical School, Boston, MA, USA** (S Keshavjee MD, M C Becerra ScD)

Correspondence to: Dr Mercedes C Becerra, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA 02115, USA **Mercedes_Becerra@hms.harvard.edu**

Present situation and rationale for change

Tuberculosis is a global epidemic with an estimated 9 million new cases and 1·5 million deaths in 2013.[1] Although tuberculosis has been curable for almost 70 years—and despite the fact that millions of individuals are treated every year—the annual rate of decline of tuberculosis incidence globally has averaged only 1·5% for more than a decade.[1,2] Part of the reason for this sluggish progress is that a substantial proportion of people who fall sick with tuberculosis are never diagnosed and treated. WHO estimates that 3 million people with tuberculosis are "missed" each year by health systems, leading to the persistence of infectious cases and the airborne disease's transmission within families and communities.[1]

Transmission of tuberculosis leads to new infections and new cases of disease. If the global tuberculosis epidemic is to be stopped, not only must existing cases be treated, but the transmission that is constantly producing new infections and cases must also be halted. Trying to eliminate tuberculosis without stopping transmission would be like trying to empty a basin full of water without first turning off the tap that fills it.

Crucial steps to stopping transmission are finding people who have the disease and ensuring that they are immediately put on effective treatment so that they can be rapidly rendered non-infectious. In low-incidence, high-resource settings such as the USA, Canada, and the European Union, policies of targeted active case-finding are in place to limit transmission of tuberculosis in households, communities, and congregate settings.[3–5] Targeted active case-finding means actively seeking out and screening individuals at increased risk of having the disease so that they can be diagnosed early, and, through correct treatment, rendered non-infectious. Targeted active case-finding is a fundamental strategy for disease control that has been used to stop epidemics ranging from smallpox to severe acute respiratory syndrome to Ebola virus disease, and has been recognised as a crucial component of the epidemic-control response to tuberculosis since the 1930s.[6–8]

By contrast, most tuberculosis programmes in low-income and middle-income countries with high burdens of tuberculosis have adopted policies that rely on passive case-finding—waiting for the sick to seek care if they are able. Driven in large part by concerns over cost, this strategy prioritises treatment success among passively detected cases and considers case detection to be of secondary importance.[9–11] However, by the time sick individuals seek treatment for their symptoms, they have been infectious for some time, and transmission in the family and community has already occurred.[12,13]

Key messages

- Stopping transmission is an essential component of halting the global tuberculosis epidemic; this requires finding individuals with tuberculosis and promptly initiating the correct treatment
- Actively searching for tuberculosis cases in high-risk groups is an efficient and effective way to improve tuberculosis case detection
- Initiation of effective treatment rapidly renders patients non-infectious
- The efficacy of strategies to actively find cases and ensure prompt effective treatment has been shown in high tuberculosis-burden settings
- The ability of targeted active case-finding and prompt treatment to reduce tuberculosis incidence in the population has been suggested by both empirical evaluations and mathematical modelling
- By applying existing knowledge comprehensively and exhaustively to stop the production of new infections and new cases, we can make a substantial impact on the tuberculosis epidemic

The reliance on passive case-finding for tuberculosis has contributed to the present failure to prevent transmission at the level required to turn the tide of the tuberculosis epidemic.[12]

Improvement of case detection by actively searching for sick individuals is only the first step in stopping transmission. The second step is to ensure that individuals with tuberculosis are rapidly diagnosed and put on an effective treatment regimen. Delays in diagnosis and treatment contribute to persisting transmission of tuberculosis.[12,13] Diagnostic and treatment policies in high tuberculosis-burden countries have largely relied on conventional sputum smear microscopy as the main diagnostic technique and on a standard empirical treatment regimen of four first-line anti-tuberculosis drugs.[14] However, sputum smear microscopy has severe limitations: it fails to detect about half of all tuberculosis cases;[15] its sensitivity in children sick with tuberculosis is about 10%;[15] its sensitivity in people living with HIV who are sick with tuberculosis is less than 30%;[16,17] it cannot diagnose patients with extrapulmonary tuberculosis, who represented 15% of notified cases in 2013;[1] and it cannot detect drug resistance. Furthermore, although cases that are detectable by sputum smear microscopy are generally more infectious than those that are not, the non-detectable cases have been shown to cause 13–17% of transmission in low-incidence settings.[18,19] Reliance on smear microscopy rather than more sensitive procedures for diagnosis thus allows infectious cases to remain undetected in the community for longer. In addition, policies that rely on both sputum smear microscopy and empirical treatment with a standard first-line anti-tuberculosis regimen can result in long periods of ineffective treatment for patients with drug-resistant tuberculosis.

The tuberculosis epidemic cannot be successfully and rapidly curbed without use of recognised control measures for communicable diseases, including targeted active case-finding and prompt initiation of the correct treatment. These activities are both feasible and effective in high tuberculosis-burden settings at present, despite the challenges facing health systems in many of these countries. Thus, with adequate resource investment and political will, substantial decreases in tuberculosis incidence are possible.

	Expected prevalence of newly diagnosed tuberculosis in people assessed
Household contact investigation in low-income and middle-income countries[22–24]	1–5%
Screening of outpatients in general health-care facilities in high tuberculosis-burden settings for tuberculosis symptoms and assessment of symptomatic individuals[25–30]	5–10%
Screening of people receiving HIV-associated health care in low-income and middle-income countries with HIV prevalence of more than 5%[31]	1–25%
Untargeted screening in general population in 22 high tuberculosis-burden countries[1]	0·1–0·7%

Table 1: **Expected yields for different active case-finding strategies**

Data and successes

Since the 1930s, a range of approaches to targeted active case-finding, tailored to local epidemiology, have been shown to improve tuberculosis case detection.[6,20,21] By focusing on populations at high risk for tuberculosis, targeted active case-finding strategies detect substantially more cases per number of people assessed than would be detected by screening in the general population. The expected yields of a few common approaches are described in table 1.

Once a tuberculosis case is identified, further transmission from that individual can be stopped almost immediately by initiation of effective treatment. A seminal prospective, randomised, controlled study[32] done at the Tuberculosis Chemotherapy Center, Madras (now Chennai), India, in the 1950s reported that household members of patients with tuberculosis who were treated at home had no greater risk of tuberculosis disease or infection after 5 years than household members of patients who were treated in sanatoria and thus restricted from contact with their families. Furthermore, since the 1950s, independent studies have measured the infectiousness of patients with tuberculosis who were being treated in hospital using an experimental model in which highly susceptible guineapigs were exposed to the air from a ward of patients with tuberculosis, and then tested for tuberculosis infection. These experiments repeatedly showed a rapid reduction in the patients' infectiousness after initiation of effective therapy, even while they might remain sputum smear positive.[33–35] In the earliest experiments, patients began treatment on the day of admission to the hospital; guineapigs exposed to patients who started effective treatment for drug-susceptible tuberculosis were only 2% as likely to be infected as guineapigs exposed to untreated patients, suggesting that the patients were rendered non-infectious almost immediately after initiation of multidrug therapy.[33] In later studies using a similar experimental set-up, rapid attenuation of infectiousness was reported for patients with drug-resistant tuberculosis who were treated effectively with regimens that contained sufficient drugs to which the infecting strains were susceptible.[34] By contrast, these guineapig exposure studies have repeatedly reported most infections to be associated with patients who have undiagnosed or ineffectively treated drug-resistant tuberculosis, underscoring the importance of rapid initiation of the correct regimen and the danger of protracted infectiousness in these patients.[33–36] Epidemiologically, the continuing transmission of drug-resistant strains that results from diagnostic failure or an absence of effective treatment is suggested by the prevalence of drug resistance in patients who have never

	Strategies
Targeted active case-finding	Perform contact investigations of patients with tuberculosis Screen clients attending health facilities Use programme data to identify groups of people that account for a disproportionate share of the tuberculosis burden; groups can be defined by individual risk factors or geography Consider, pilot, and assess different targeted active case-finding strategies to find out what works best in a given setting Increase uptake of screening through awareness campaigns, community engagement, initiatives to mitigate stigma, and incentives
Prevention of transmission in health facilities	Provide paper masks to individuals suspected of having tuberculosis until they are receiving effective treatment Reduce contact between individuals suspected of having tuberculosis and other people seeking care, particularly susceptible individuals such as young children and people with HIV; contact can be reduced by having patients wait in different areas on the basis of risk and symptoms, or by scheduling clinics for different types of patients at different times Expedite diagnosis for individuals suspected of having tuberculosis Open windows in waiting areas or use outdoor waiting areas where feasible
Prompt initiation of effective therapy	Develop protocols and strengthen health systems to ensure that results of diagnostic procedures are received and acted on promptly Use chest radiography and clinical algorithms in addition to bacteriological testing for diagnosis, especially for young children and people with HIV Use rapid molecular tests that can detect both tuberculosis and drug resistance Initiate presumptive treatment for drug-resistant tuberculosis when a contact of a patient with drug-resistant tuberculosis is diagnosed with tuberculosis
Formation of partnerships	Integrate tuberculosis care with other health-care services such as HIV care and maternal-child health programmes Engage community members who advocate for best practices, encourage health-care-seeking behaviours, and support patients through treatment Partner with private sector providers to ensure that patients with tuberculosis receive timely diagnoses and appropriate treatment, and that they are reported to the national tuberculosis programme even if they receive care in the private sector

Table 2: **Key activities and strategies to be considered for prevention of tuberculosis transmission**

been treated for tuberculosis; across the WHO European Region in 2013, 14% of patients without previous treatment had multidrug-resistant tuberculosis.[1]

The combination of active case-finding and prompt initiation of effective treatment reduces transmission by removing infectious cases from the population before additional transmission occurs. Although the effect of these activities at a population level is difficult to measure over a short timeframe, evidence suggests that they have a role in reducing tuberculosis incidence. In a community-randomised trial in Brazil, eight communities matched according to socioeconomic indicators were assigned to either an intervention or control condition. In the intervention communities, outreach workers actively sought out household contacts of tuberculosis cases for prompt screening, and treatment was given for both tuberculosis disease and infection.[37] The control communities received the local standard of care, which relied on contacts to present to health facilities for assessment, and did not routinely provide preventive therapy. At baseline, the two sets of communities had nearly identical annual tuberculosis case notification rates (340 cases per 100 000 individuals in communities receiving the intervention and 339 per 100 000 in the controls). After 5 years, the intervention communities had a statistically significant 15% lower annual tuberculosis case notification rate than the control communities (p=0·04). A community-randomised trial in Zambia and South Africa allocated 24 communities to four intervention conditions involving different combinations of case-finding interventions such that each group was similar with respect to baseline prevalence of tuberculosis and HIV infection, and demographic characteristics.[38] After 3 years, communities in which household contacts of patients with tuberculosis were systematically assessed had an 18% lower prevalence of tuberculosis in adults (p=0·095) and a 55% lower rate of tuberculosis infection in children (p=0·063) than communities in which household contacts were not assessed.

Translation of knowledge into strategy and action

Key strategies to consider

Targeted active case-finding and prompt initiation of effective treatment are crucial components of epidemic control for infectious diseases. Although optimum methods for both can vary across settings, general strategies that have proven effective in a range of settings can provide a starting point for implementation. Table 2 presents key activities and strategies to be considered for stopping tuberculosis transmission in the context of a comprehensive approach to stopping the tuberculosis epidemic.

Active case-finding in high-risk groups

In view of the inability of passive case-finding alone to halt tuberculosis transmission, targeted active case-finding is important in all settings. However, different characteristics are associated with increased tuberculosis risk in different places, and the efficacy of any single approach to active case-finding can vary widely across settings.[20] Thus, each tuberculosis programme has to identify what combination of targeted active case-finding activities is the most effective in the local context.

One high-risk group that is present in all settings is contacts of patients with tuberculosis. Contact

investigation refers to the process of systematically identifying and screening contacts of patients with tuberculosis.[39] Since the risk of transmission increases with the intensity and duration of contact, contact investigation in the household and other places where patients with tuberculosis live (eg, workers' dormitories, prisons) is a logical case-finding strategy to consider in all countries. Common components of contact investigations include patient interviews in the clinic, asking patients to bring household members and other close contacts (particularly children) to the clinic for assessment, and home visits by a health-care worker to identify and screen household members. Although programmes generally prioritise the most infectious cases for contact investigation, investigations of children, who generally have non-infectious forms of tuberculosis, can lead to detection of infectious adult cases; this is sometimes called a source case investigation since transmission is assumed to have occurred from the adult to the child. At a children's hospital in Texas, USA, 17–24% of children diagnosed with tuberculosis were accompanied to the hospital by an adult with previously undiagnosed pulmonary tuberculosis.[40,41]

Another generally applicable strategy for targeted active case-finding is regular screening of social or demographic risk groups that contribute a disproportionate number of cases to the local tuberculosis burden (panel). This strategy is important in both low-burden settings and high-burden settings. Analysis of routinely collected programme data can help identify high-risk groups in a particular location. Furthermore, in some high-burden settings, analysis of programme data can identify geographical hotspots where community-level interventions such as door-to-door screening and deployment of mobile diagnostic units could be a high-yield activity (see Theron and colleagues,[46] paper 1 in this Series). In countries where genotyping is practised, such as China, the combination of genotype and geographical data might allow even more specific identification of transmission hotspots.

One practical consideration for the implementation of targeted active case-finding activities is how to convince individuals to undergo screening for a stigmatised disease, especially if screening requires time and effort on the part of the individual. Strategies that have proven successful at encouraging uptake of services for other stigmatised health issues (eg, HIV, leprosy) have included coupling services for a stigmatised health issue with services for a non-stigmatised one, and community-based awareness campaigns to reduce stigma.[47] Several successful active case-finding initiatives for tuberculosis have incorporated advocacy and community mobilisation activities into their strategies.[20] Material incentives can also be useful in encouraging people to undergo screening; two randomised controlled trials in the USA reported that small monetary incentives doubled the proportion of homeless people who returned to the clinic to have their tuberculin skin tests read.[48]

Another practical consideration is what screening and diagnostic algorithm to use. Strategies for targeted active case-finding typically use screening algorithms that progressively reduce the number of individuals at each step of assessment to ensure that time-intensive and resource-intensive procedures such as sputum culture and full clinical assessment by a physician are done for individuals who are likely to have tuberculosis. A common first step is to ask individuals about symptoms and risk factors, and move only those who are symptomatic or high risk to the next step of assessment. However, the choice of symptoms included in the initial interview can greatly affect the performance of the symptom screen, with trade-offs between sensitivity and specificity. In a prevalence survey in western Kenya,[49] where the prevalence of bacteriologically confirmed pulmonary tuberculosis was 0·6%, the presence of cough for 2 weeks or longer had 52% sensitivity and 89% specificity in predicting tuberculosis, whereas the presence of any tuberculosis symptom (cough, haemoptysis, weight loss, fever, or night sweats) had 90% sensitivity and 32% specificity. Furthermore, for children, additional symptoms such as reduced playfulness and failure to reach an age-appropriate weight are important components of a symptom screen. Finally, the comparatively high sensitivity (94%) and specificity (73%) of an abnormal chest radiograph for predicting tuberculosis in the western Kenya survey[49] (with similar results reported from other prevalence surveys) strongly supports inclusion of chest radiography into screening algorithms.

The decision to implement targeted active case-finding activities has practical implications for the tuberculosis

Panel: Examples of targeted active case-finding policies in risk groups that contribute disproportionately to local tuberculosis burden

Across the WHO African Region in 2013, the prevalence of HIV in adults aged 15–49 years was 4·5%,[42] but an estimated 34% of tuberculosis cases were associated with HIV.[1] Screening people with HIV for tuberculosis is therefore a crucial strategy for tuberculosis case detection.

In Russia, about 0·5% of the population is incarcerated. However, prisoners accounted for 27% of tuberculosis cases in 1995.[43] Since then, Russia has focused on addressing tuberculosis in prisons, enforcing both mandatory screening and directly observed treatment.[43] These policies have been credited with reducing the proportion of tuberculosis cases that were detected in prisons to 12% in 2004.

In the USA, tuberculosis incidence among homeless people is roughly 10 times the incidence in the general population.[44] National guidelines recommend that staff in homeless shelters monitor clients for persistent cough and ensure prompt assessment either at the shelter or by providing transportation to a health-care facility.[45]

	Example of implementation
Requesting that patients with tuberculosis wear surgical masks	When admitted to hospital, patients receiving multidrug-resistant tuberculosis treatment at the Airborne Infections Research Facility in Emalahleni, South Africa, were asked to wear surgical masks during the day, excluding mealtimes; infectiousness of air from the ward was reduced after the intervention[53]
Manipulation of clinic schedules to reduce risk of transmission to susceptible individuals in waiting rooms	At the Indus Hospital in Karachi, Pakistan, before the establishment of a separate tuberculosis clinic, clinic schedules were arranged so that no paediatric clinics were run on days during which patients with tuberculosis were seen (personal experience of FA).
Opening windows or doors, or both	In various hospital spaces in Lima, Peru, the amount of ventilation was nearly 20 times higher when windows and doors were opened than when they were closed. With open windows and doors, these spaces were better ventilated than spaces with mechanical ventilation systems (eg, fan-based systems)[54]

Table 3: **Administrative and environmental strategies for airborne infection control**

programme and the health system as a whole. Active case-finding activities require staff and diagnostic resources in addition to those already in place to support passive case-finding. Additionally, if active case-finding activities are successful, the number of patients requiring treatment will increase in the short term, even though subsequent reduction in transmission should reduce the number of cases in the long term. Therefore, anticipation of increased diagnostic and treatment capacity should be part of the planning process for any active case-finding activity. Furthermore, monitoring and assessment should be planned to ensure that the people screened by an active case-finding initiative are those at the highest risk rather than those who are easiest to reach, and that increases in diagnoses represent true case detection and not overdiagnosis. Finally, while active case-finding activities have as their main goal the prompt diagnosis and treatment of tuberculosis disease, they can also provide a platform for the diagnosis and treatment of tuberculosis infection and exposure to prevent development of future cases (see Rangaka and colleagues,[50] paper 3 in this Series). Therefore, the coordination of case-finding and prevention efforts should be considered.

Prevention of transmission in health-care facilities

Health facilities are a unique setting in which targeted active case-finding can be combined with administrative and environmental infection control measures to prevent nosocomial tuberculosis transmission. Facilities where individuals who are sick spend hours waiting for health care in crowded and poorly ventilated waiting areas can promote transmission within the facility. Detection of these cases as soon as possible is thus crucial to prevent transmission. One strategy to identify cases and prevent nosocomial transmission is to screen individuals in waiting areas for tuberculosis symptoms and quickly separate symptomatic individuals from the general population. This type of rapid triage was instrumental in halting nosocomial transmission during the 2003 outbreak of severe acute respiratory syndrome in Asia.[7]

For tuberculosis, the strategy "Finding TB cases Actively, Separating safely, and Treating effectively" (FAST) has helped facilities introduce procedures that reduce the risk and duration of exposure to tuberculosis for both patients and health-care workers.[51] The FAST strategy includes cough monitoring in waiting rooms and admission wards to identify individuals who might have tuberculosis, rapid diagnosis for those with tuberculosis symptoms, prompt separation of patients with suspected drug-resistant tuberculosis, and rapid initiation of effective treatment for all forms of tuberculosis. Although designed for health-care facilities, the FAST strategy could be adapted to other congregate settings as well.[52] Additionally, a range of administrative and environmental interventions can further augment efforts to prevent transmission within facilities, without substantial additional resource investment (table 3).

Implementation of the FAST strategy in hospitals has reduced both unsuspected tuberculosis and delays in the initiation of effective treatment. After implementing FAST, the National Institute of Diseases of the Chest Hospital in Dhaka, Bangladesh, reported that 9% of patients admitted as so-called non-tuberculosis patients in fact had tuberculosis.[51] In a tuberculosis hospital in Voronezh, Russia, implementation of FAST using a molecular diagnostic test reduced the time from admission to initiation of multidrug-resistant tuberculosis treatment to less than 5 days, compared with the weeks that patients would wait to receive results from mycobacterial culture and conventional drug susceptibility testing.[51]

Diagnosis and prompt initiation of effective treatment

The FAST strategy provides an integrated and streamlined approach that combines active case-finding, diagnosis, and treatment into a single facility-based protocol. When active case-finding is focused outside a health-care facility, strategies are needed to ensure that individuals identified as being at risk for tuberculosis are linked to appropriate diagnosis and treatment, since searching for cases will not have any effect unless these cases are promptly diagnosed and effectively treated.

In view of the limitations of sputum smear microscopy, the goal to diagnose all tuberculosis cases can only be accomplished through the use of other modalities such as radiography, molecular diagnostic tests, bacteriological culture, and clinical algorithms.[21] Because children and people with HIV are less likely than others to have bacteriological confirmation of tuberculosis, use of clinical algorithms for these two groups is essential.[55–57]

In the future, rapid biomarker-based tests that do not rely on detection of bacteria in sputum could improve the speed and accuracy of diagnosis, particularly in children and people with HIV. Technologies under development at present include antigen detection tests and tests to analyse volatile organic compounds in breath or urine.[58]

Failure to suspect or identify drug resistance at the time of tuberculosis diagnosis can result in patients receiving inadequate treatment regimens, which prolongs both illness and infectiousness and potentially causes amplification of drug resistance.[59,60] Patients can deteriorate and remain infectious for months in places where policies allow treatment for drug-resistant tuberculosis to be considered only after a patient has been unsuccessfully treated with a first-line regimen. Therefore, use of new molecular diagnostic tests to rapidly diagnose drug resistance and presumptive treatment for drug-resistant tuberculosis are both integral to stopping transmission of drug-resistant strains. Molecular diagnostic tests can detect drug resistance in hours or days rather than the weeks needed for conventional culture-based drug susceptibility testing. In settings with high prevalence of drug resistance, such as Russia, Peru, and various southern African settings, universal drug susceptibility testing using molecular tests has been shown to be feasible, reducing the time to diagnosis of drug resistance and initiation of second-line treatment.[51,61,62] In settings with low rates of drug resistance in the general tuberculosis patient population, rapid molecular testing of people suspected of having tuberculosis or patients meeting certain criteria for being at an increased risk of drug resistance (eg, contacts of an individual with drug-resistant tuberculosis, individuals with a history of tuberculosis treatment, patients not responding to treatment, and refugees) has proven to be a feasible intermediate step toward universal drug susceptibility testing.

Standardised risk criteria can also be used to identify individuals who should receive treatment for drug-resistant disease, even in the absence of a drug susceptibility test result. For example, high concordance of drug susceptibility test pattern has generally been reported between the index case and secondary cases within households of patients with drug-resistant tuberculosis.[63] Therefore, presumptive treatment for drug-resistant disease is warranted for household members of patients with drug-resistant tuberculosis who are themselves diagnosed with tuberculosis, especially young children who are most likely to not have bacteriological confirmation and be infected with the same strain as the index patient.

Even a perfect diagnostic technology or algorithm cannot have an effect on transmission if patients are not rapidly started on treatment. Thus, not only is the method of diagnosis important to consider, but also the timeliness and ease with which patients receive diagnostic results and are linked to care. High rates of failure to initiate treatment after diagnosis have been reported in a range of settings.[64] Sometimes, gaps in the health-care delivery system can lead to a failure to communicate test results or an absence of action based on these results.[65,66] In KwaZulu-Natal, South Africa, only 20% of patients with rifampicin-resistant tuberculosis had started tuberculosis treatment within 2 weeks of testing using the Xpert MTB/RIF assay, which yields results within hours.[67] In other situations, patients themselves might decline treatment despite receiving a diagnosis of tuberculosis, particularly if they have no or mild symptoms or if treatment interferes with their ability to work. Nearly a quarter of patients diagnosed with sputum smear-positive tuberculosis during a community survey in India did not initiate treatment, with the two most common reasons being lack of interest in treatment and having symptoms too mild to warrant treatment.[68] Therefore, strategies are needed to ensure that all individuals diagnosed with tuberculosis are informed of their diagnoses, counselled appropriately, and promptly treated. Strategies could include the collection of accurate contact information during the initial diagnostic encounter, optimisation of diagnostic procedures and communication systems to reduce time to diagnosis and treatment, active follow-up of people who do not initiate treatment, incentives for initiation of treatment, and oversight and support for individuals requiring it during treatment. In some countries, regulations exist that allow a tuberculosis programme to compel a patient to accept treatment despite his or her refusal; the decision about how to balance the rights of a patient with the public health system's mandate to protect the public is complex and warrants careful consideration.[69]

Partnerships to extend case-finding and care

A health-care system that requires patients to seek or receive tuberculosis care within specific tuberculosis-focused settings or programmes might result in patients spending substantial time and effort accessing tuberculosis care, in addition to their other health-care needs. This burden can discourage patients from either seeking or remaining in care. Thus, a system that makes it easier for patients to access tuberculosis services in conjunction with other health-care services would probably improve both case detection and the probability of treatment initiation and completion.

Many logical points of integration between tuberculosis services and other health-care services exist. The FAST strategy offers one example of a way to integrate tuberculosis screening into primary care settings. Additionally, integration of tuberculosis and HIV services by use of a range of approaches is widely advocated, and is an obvious area for improvement in many countries with high burdens of both diseases. Maternal-child health programmes (including Integrated Management of Childhood Illness screening programmes and

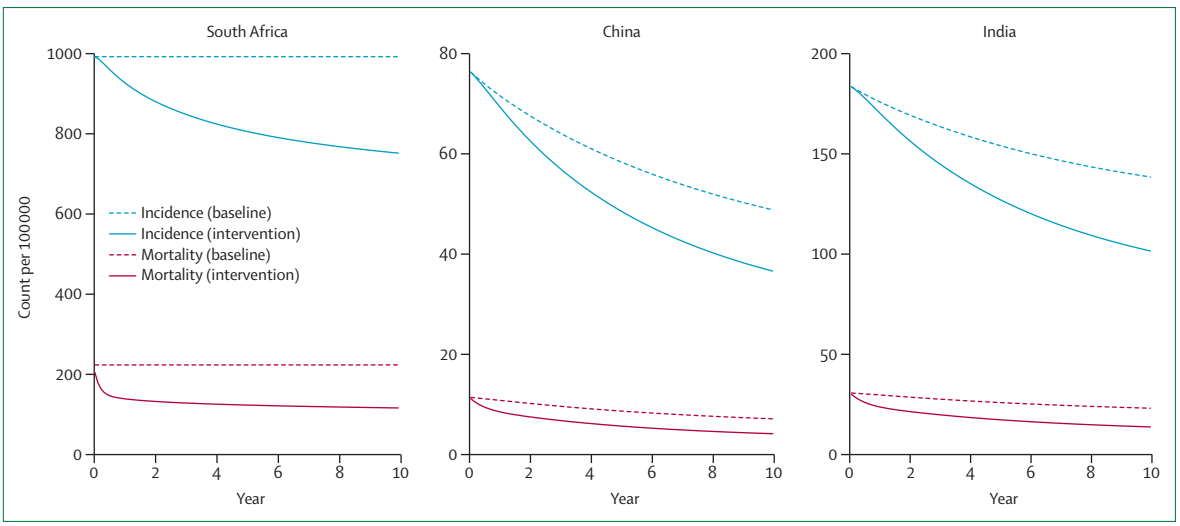

Figure: **Projected impact of sustained active case-finding after 10 years in China, India, and South Africa[76]**
Impact represents reduction after 10 years compared with baseline, assuming an active case-finding programme that detects and treats 25% more cases than would otherwise be detected and treated in view of present epidemiological trends in each country. The additional cases detected are assumed to come from a homogeneous population, with detection occurring at a random point of disease progression. Figure courtesy of David Dowdy.

malnutrition clinics) provide a platform to offer tuberculosis treatment or preventive therapy to young children.[70] Other important points of contact include clinics treating patients with diabetes, chronic obstructive pulmonary disease, or lung disorders associated with smoking, all of which are associated with an increased risk of tuberculosis.[71–74] Achievement of this sort of coordination of care will require tuberculosis programmes to partner with other stakeholders in the general health services rather than working in isolation.

Partnerships outside the public health-care sector can also improve the effectiveness of many of the strategies discussed thus far. For example, engagement of community members who advocate for best practices, encourage health-care-seeking behaviours, and support patients through treatment can help ensure that interventions initiated by the tuberculosis programme have wide-reaching and sustained effect. Additionally, partnerships with other government sectors, such as those in charge of prisons or social welfare programmes, can ease access to vulnerable or hard-to-reach populations. Finally, partnerships with the private sector are necessary in settings such as south Asia, where 80% of patients seek care from private providers.[75] In view of the large number and the heterogeneity of private providers, it is an immense undertaking for national tuberculosis programmes to effectively engage these providers to ensure that patients with tuberculosis receive timely diagnoses and appropriate treatment, and that all tuberculosis cases are reported to the national tuberculosis programme even if they are diagnosed and treated in the private sector. Although strategies will vary across settings, some approaches that have proven successful include use of large private hospitals with associated clinic networks as reporting centres for the national tuberculosis programme; use of mobile phone-based platforms to help report screening or diagnostic results from private facilities; and mass media campaigns that give publicity to private facilities that have partnered with the national programme to offer testing and treatment.[29,75]

Projection of impact

What impact would be expected from a commitment to identify and treat more people with tuberculosis than is achieved at present? Models consistent with the present tuberculosis epidemics in China, India, and South Africa predict that an increase in case detection by 25% can achieve a 40–44% reduction in tuberculosis-associated mortality, a 22–27% reduction in incidence, and a 30–33% reduction in prevalence in 10 years (figure).[76] Furthermore, these interventions were deemed to be highly cost effective, even if the costs of the interventions were as high as US$2500 per case detected in India, and $5000 per case detected in China and South Africa. Importantly, these projections show that the population-level benefits of active case-finding accumulate with time since removal of infectious cases from the population prevents the development of additional cases in both the near-term and long-term future; thus an assessment at the end of 1 year is unlikely to show a substantial effect, even though the 10 year projected benefit is substantial. These projections assume that detection is synonymous with prompt and effective treatment, so all case-finding has to be directly linked to the immediate delivery of care.

Achievement of a 25% increase in case detection is feasible in view of the strategies already discussed. Of 19 active case-finding initiatives, each lasting 1 year, undertaken in 11 countries, the median increase in notification rates of sputum smear-positive tuberculosis

cases was 35%, after controlling for historical trends in case notification rates and changes in case notification rates in control populations that did not receive the interventions.[20] In one of these initiatives, undertaken in Karachi, Pakistan, a combination of screening outpatients in clinics and a mass communication campaign encouraging people with prolonged cough to seek care more than doubled the case notification rate in the intervention area compared with the control area.[29] A model consistent with local tuberculosis epidemiological data projected that if the level of case detection achieved during the intervention year were maintained, 24% of the tuberculosis cases and 52% of the tuberculosis deaths that would have occurred in the absence of the intervention would be averted in 5 years; even if the level of case detection were to fall back to baseline immediately after the intervention year, 13% of cases and 25% of deaths would be averted.[77]

Conclusion

Stopping an epidemic requires stopping transmission. For an airborne disease without an effective vaccine, stopping transmission requires finding all cases promptly and rendering them non-infectious through treatment. The only way to accomplish this is to search actively for cases, use effective diagnostic methods and algorithms, initiate patients promptly on the correct therapy, and support them through to cure. The knowledge necessary to do these activities exists and successes have been documented across a range of settings.

While major changes to existing policies and care delivery systems will take time, action in the near future is possible. Some administrative and environmental interventions, such as providing individuals suspected of having tuberculosis with surgical masks until treatment begins and, where practical, opening windows in health facilities, can be implemented immediately without changes to existing systems or large investment of resources. Others, such as performing basic household contact investigations, implementation of the FAST strategy, and expansion of the use of molecular diagnostics, will require some additional human resources, training, and capacity building, but can be rapidly accomplished within the context of existing health-care delivery systems. Still others, such as integration of health-care services, have a slightly longer timeframe because they require the development of partnerships and the reorganisation of existing systems. The development and deployment of new point-of-care diagnostic technologies could accelerate these efforts by making diagnosis easier in the future.

By applying existing knowledge comprehensively and exhaustively, we can stop the production of new tuberculosis infections and cases and make a substantial impact on the epidemic. These efforts would certainly be aided and enhanced by the development of new diagnostic tests, vaccines, and treatments. However, with sufficient commitment of resources, engagement with stakeholders outside national tuberculosis programmes, and careful planning to ensure that all the components of a new comprehensive strategy are coordinated, tuberculosis rates can be substantially reduced.

Contributors

CMY, SK, and MCB conceived the idea for this Series paper. CMY wrote the first draft, and all other authors revised it for important intellectual content. All authors approved the final version of the manuscript as submitted for publication.

Declaration of interests

We declare no competing interests.

Acknowledgments

This work was supported by a grant from Janssen Global to Harvard Medical School (CMY, SK, MCB); the Global Fund (FA); TBREACH (FA); and the US National Institutes of Health (award K23 AI084548 to AD). The funders had no role in the conception, preparation, review, approval, or submission of this manuscript. The content is solely the responsibility of the authors and does not necessarily represent the views of the US National Institutes of Health or any other funding body. We thank Carole Mitnick for her review and the important comments she contributed during drafting, and Carly Rodriguez for coordination and research assistance in the preparation of this Series paper.

References

1 WHO. Global tuberculosis report 2014. Geneva, Switzerland: World Health Organization, 2014.

2 Ortblad KF, Lozano R, Murray CJL. An alternative estimation of tuberculosis incidence from 1980 to 2010: methods from the Global Burden of Disease 2010. *Lancet* 2013; **381:** S104.

3 Taylor Z, Nolan CM, Blumberg HM, and the American Thoracic Society, and the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR Recomm Rep* 2005; **54:** 1–81.

4 Public Health Agency of Canada, Canadian Lung Association, Canadian Thoracic Society. Canadian tuberculosis standards, 7th edn. 2013. http://www.respiratoryguidelines.ca/sites/all/files/Canadian_TB_Standards_7th_Edition_ENG.pdf (accessed July 16, 2015).

5 Migliori GB, Zellweger JP, Abubakar I, et al. European union standards for tuberculosis care. *Eur Respir J* 2012; **39:** 807–19.

6 Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. *Int J Tuberc Lung Dis* 2005; **9:** 1183–203.

7 Cheng VC, Chan JF, To KK, Yuen KY. Clinical management and infection control of SARS: lessons learned. *Antiviral Res* 2013; **100:** 407–19.

8 Tom-Aba D, Olaleye A, Olayinka AT, et al. Innovative Technological Approach to Ebola Virus Disease Outbreak Response in Nigeria Using the Open Data Kit and Form Hub Technology. *PLoS One* 2015; **10:** e0131000.

9 Toman K. Tuberculosis case-finding and chemotherapy questions and answers. Geneva, Switzerland: World Health Organization, 1979.

10 McMillan CW. Discovering tuberculosis: a global history 1900 to the present. New Haven and London: Yale University Press, 2015.

11 Keshavjee S, Farmer PE. Tuberculosis, drug resistance, and the history of modern medicine. *N Engl J Med* 2012; **367:** 931–36.

12 Golub JE, Bur S, Cronin WA, et al. Delayed tuberculosis diagnosis and tuberculosis transmission. *Int J Tuberc Lung Dis* 2006; **10:** 24–30.

13 Lin X, Chongsuvivatwong V, Lin L, Geater A, Lijuan R. Dose-response relationship between treatment delay of smear-positive tuberculosis patients and intra-household transmission: a cross-sectional study. *Trans R Soc Trop Med Hyg* 2008; **102:** 797–804.

14 Maher D, Chaulet P, Spinaci S, Harries A. Treatment of tuberculosis: guidelines for national programmes, 2nd edn. Geneva, Switzerland: World Health Organization, 1997.

15 Murray CJ, Styblo K, Rouillon A. Tuberculosis in developing countries: burden, intervention and cost. *Bull Int Union Tuberc Lung Dis* 1990; **65:** 6–24.

16 Lawn SD, Brooks SV, Kranzer K, et al. Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. *PLoS Med* 2011; **8:** e1001067.

17 Balcha TT, Sturegård E, Winqvist N, et al. Intensified tuberculosis case-finding in HIV-positive adults managed at Ethiopian health centers: diagnostic yield of Xpert MTB/RIF compared with smear microscopy and liquid culture. *PLoS One* 2014; **9:** e85478.

18 Behr MA, Warren SA, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet* 1999; **353:** 444–49.

19 Tostmann A, Kik SV, Kalisvaart NA, et al. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. *Clin Infect Dis* 2008; **47:** 1135–42.

20 Creswell J, Sahu S, Blok L, Bakker MI, Stevens R, Ditiu L. A multi-site evaluation of innovative approaches to increase tuberculosis case notification: summary results. *PLoS One* 2014; **9:** e94465.

21 WHO. Systematic screening for active tuberculosis: principles and recommendations. Geneva: World Health Organization, 2013.

22 Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; **8:** 359–68.

23 Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; **41:** 140–56.

24 Blok L, Sahu S, Creswell J, Alba S, Stevens R, Bakker MI. Comparative meta-analysis of tuberculosis contact investigation interventions in eleven high burden countries. *PLoS One* 2015; **10:** e0119822.

25 Baily GV, Savic D, Gothi GD, Naidu VB, Nair SS. Potential yield of pulmonary tuberculosis cases by direct microscopy of sputum in a district of South India. *Bull World Health Organ* 1967; **37:** 875–92.

26 Aluoch JA, Swai OB, Edwards EA, et al. Study of case-finding for pulmonary tuberculosis in outpatients complaining of a chronic cough at a district hospital in Kenya. *Am Rev Respir Dis* 1984; **129:** 915–20.

27 Aluoch JA, Swai OB, Edwards EA, et al. Studies of case-finding for pulmonary tuberculosis in outpatients at 4 district hospitals in Kenya. *Tubercle* 1985; **66:** 237–49.

28 Sánchez-Pérez HJ, Hernán MA, Hernández-Díaz S, Jansá JM, Halperin D, Ascherio A. Detection of pulmonary tuberculosis in Chiapas, Mexico. *Ann Epidemiol* 2002; **12:** 166–72.

29 Khan AJ, Khowaja S, Khan FS, et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. *Lancet Infect Dis* 2012; **12:** 608–16.

30 Claassens MM, Jacobs E, Cyster E, et al. Tuberculosis cases missed in primary health care facilities: should we redefine case finding? *Int J Tuberc Lung Dis* 2013; **17:** 608–14.

31 Kranzer K, Houben RM, Glynn JR, Bekker LG, Wood R, Lawn SD. Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10:** 93–102.

32 Kamat SR, Dawson JJ, Devadatta S, et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. *Bull World Health Organ* 1966; **34:** 517–32.

33 Riley RL, Mills CC, O'Grady F, Sultan LU, Wittstadt F, Shivpuri DN. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. *Am Rev Respir Dis* 1962; **85:** 511–25.

34 Escombe AR, Moore DA, Gilman RH, et al. The infectiousness of tuberculosis patients coinfected with HIV. *PLoS Med* 2008; **5:** e188.

35 Dharmadhikari AS, Mphahlele M, Venter K, et al. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2014; **18:** 1019–25.

36 Riley RL, Mills CC, Nyka W, et al. Aerial dissemination of pulmonary tuberculosis. A two-year study of contagion in a tuberculosis ward. 1959. *Am J Epidemiol* 1995; **142:** 3–14.

37 Cavalcante SC, Durovni B, Barnes GL, et al. Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2010; **14:** 203–09.

38 Ayles H, Muyoyeta M, Du Toit E, et al, and the ZAMSTAR team. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. *Lancet* 2013; **382:** 1183–94.

39 WHO. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva, Switzerland: World Health Organization, 2013.

40 Muñoz FM, Ong LT, Seavy D, Medina D, Correa A, Starke JR. Tuberculosis among adult visitors of children with suspected tuberculosis and employees at a children's hospital. *Infect Control Hosp Epidemiol* 2002; **23:** 568–72.

41 Cruz AT, Medina D, Whaley EM, Ware KM, Koy TH, Starke JR. Tuberculosis among families of children with suspected tuberculosis and employees at a children's hospital. *Infect Control Hosp Epidemiol* 2011; **32:** 188–90.

42 WHO. Global health observatory data repository, adult HIV prevalence (15–49 years), 2013, by WHO region. 2014. http://www.who.int/gho/hiv/hiv_013.jpg?ua=1 (accessed July 16, 2015).

43 Shukshin A. Tough measures in Russian prisons slow spread of TB. *Bull World Health Organ* 2006; **84:** 265–66.

44 Bamrah S, Yelk Woodruff RS, Powell K, Ghosh S, Kammerer JS, Haddad MB. Tuberculosis among the homeless, United States, 1994–2010. *Int J Tuberc Lung Dis* 2013; **17:** 1414–19.

45 Centers for Disease Control and Prevention. Prevention and control of tuberculosis among homeless persons. Recommendations of the Advisory Council for the Elimination of Tuberculosis. *MMWR Recomm Rep* 1992; **41:** 13–23.

46 Theron G, Jenkins HE, Cobelens F, et al. Data for action: collection and use of local data to end tuberculosis. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00321-9.

47 Hadley M, Maher D. Community involvement in tuberculosis control: lessons from other health care programmes. *Int J Tuberc Lung Dis* 2000; **4:** 401–08.

48 Lutge EE, Wiysonge CS, Knight SE, Volmink J. Material incentives and enablers in the management of tuberculosis. *Cochrane Database Syst Rev* 2012; **1:** CD007952.

49 van't Hoog AH, Meme HK, Laserson KF, et al. Screening strategies for tuberculosis prevalence surveys: the value of chest radiography and symptoms. *PLoS One* 2012; **7:** e38691.

50 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00323-2.

51 Barrera E, Livchits V, Nardell E. F-A-S-T: a refocused, intensified, administrative tuberculosis transmission control strategy. *Int J Tuberc Lung Dis* 2015; **19:** 381–84.

52 Dharmadhikari A, Smith J, Nardell E, Churchyard G, Keshavjee S. Aspiring to zero tuberculosis deaths among southern Africa's miners: is there a way forward? *Int J Health Serv* 2013; **43:** 651–64.

53 Dharmadhikari AS, Mphahlele M, Stoltz A, et al. Surgical face masks worn by patients with multidrug-resistant tuberculosis: impact on infectivity of air on a hospital ward. *Am J Respir Crit Care Med* 2012; **185:** 1104–09.

54 Escombe AR, Oeser CC, Gilman RH, et al. Natural ventilation for the prevention of airborne contagion. *PLoS Med* 2007; **4:** e68.

55 WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children—2nd edn. Geneva, Switzerland: World Health Organization, 2014.

56 WHO. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings. Geneva, Switzerland: World Health Organization, 2007.

57 Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med* 2011; **8:** e1000391.

58 Pai M, Schito M. Tuberculosis diagnostics in 2015: landscape, priorities, needs, and prospects. *J Infect Dis* 2015; **211** (suppl 2)**:** S21–28.

59 Lew W, Pai M, Oxlade O, Martin D, Menzies D. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med* 2008; **149:** 123–34.

60 van der Werf MJ, Langendam MW, Huitric E, Manissero D. Multidrug resistance after inappropriate tuberculosis treatment: a meta-analysis. *Eur Respir J* 2012; **39:** 1511–19.

61 Mendoza-Ticona A, Alarcón E, Alarcón V, et al. Effect of universal MODS access on pulmonary tuberculosis treatment outcomes in new patients in Peru. *Public Health Action* 2012; **2:** 162–67.

62 Theron G, Zijenah L, Chanda D, et al, and the TB-NEAT team. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet* 2014; **383:** 424–35.

63 Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis* 2014; **58:** 381–91.

64 Harries AD, Rusen ID, Chiang CY, Hinderaker SG, Enarson DA. Registering initial defaulters and reporting on their treatment outcomes. *Int J Tuberc Lung Dis* 2009; **13:** 801–03.

65 Botha E, Den Boon S, Verver S, et al. Initial default from tuberculosis treatment: how often does it happen and what are the reasons? *Int J Tuberc Lung Dis* 2008; **12:** 820–23.

66 Buu TN, Lönnroth K, Quy HT. Initial defaulting in the National Tuberculosis Programme in Ho Chi Minh City, Vietnam: a survey of extent, reasons and alternative actions taken following default. *Int J Tuberc Lung Dis* 2003; **7:** 735–41.

67 Naidoo P, du Toit E, Dunbar R, et al. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town. *PLoS One* 2014; **9:** e103328.

68 Gopi PG, Chandrasekaran V, Subramani R, Narayanan PR. Failure to initiate treatment for tuberculosis patients diagnosed in a community survey and at health facilities under a DOTS programme in a district of South India. *Indian J Tuberc* 2005; **52:** 153–56.

69 Amon JJ, Girard F, Keshavjee S. Limitations on human rights in the context of drug-resistant tuberculosis: a reply to Boggio et al. *Health Hum Rights* 2009. http://www.hhrjournal.org/2009/10/07/limitations-on-human-rights-in-the-context-of-drug-resistant-tuberculosis-a-reply-to-boggio-et-al/ (accessed July 16, 2015).

70 Detjen A, Gnanashanmugam D, Talens A. A framework for integrating childhood tuberculosis into community-based child health care. Washington, DC: CORE Group, 2013.

71 Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008; **5:** e152.

72 Stevenson CR, Forouhi NG, Roglic G, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BMC Public Health* 2007; **7:** 234.

73 Inghammar M, Ekbom A, Engström G, et al. COPD and the risk of tuberculosis--a population-based cohort study. *PLoS One* 2010; **5:** e10138.

74 Ferrara G, Murray M, Winthrop K, et al. Risk factors associated with pulmonary tuberculosis: smoking, diabetes and anti-TNFα drugs. *Curr Opin Pulm Med* 2012; **18:** 233–40.

75 Khan MS, Salve S, Porter JD. Engaging for-profit providers in TB control: lessons learnt from initiatives in south Asia. *Health Policy Plan* 2015; published online Jan 20. DOI:10.1093/heapol/czu137.

76 Azman AS, Golub JE, Dowdy DW. How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and India. *BMC Med* 2014; **12:** 216.

77 Dowdy DW, Lotia I, Azman AS, Creswell J, Sahu S, Khan AJ. Population-level impact of active tuberculosis case finding in an Asian megacity. *PLoS One* 2013; **8:** e77517.

How to eliminate tuberculosis 3

Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection

Molebogeng X Rangaka, Solange C Cavalcante, Ben J Marais, Sok Thim, Neil A Martinson, Soumya Swaminathan, Richard E Chaisson

The billions of people with latent tuberculosis infection serve as the seedbeds for future cases of active tuberculosis. Virtually all episodes of tuberculosis disease are preceded by a period of asymptomatic *Mycobacterium tuberculosis* infection; therefore, identifying infected individuals most likely to progress to disease and treating such subclinical infections to prevent future disease provides a crucial opportunity to interrupt tuberculosis transmission and reduce the global burden of tuberculosis disease. Programmes focusing on single strategies rather than comprehensive programmes that deliver an integrated arsenal for tuberculosis control might continue to struggle. Tuberculosis preventive therapy is a poorly used method that is essential for controlling the reservoirs of disease that drive the epidemic. Comprehensive control strategies that combine preventive therapy for the most high-risk populations and communities with improved case-finding and treatment, control of transmission, and health systems strengthening could ultimately lead to worldwide tuberculosis elimination. In this Series paper we outline challenges to implementation of preventive therapy and provide pragmatic suggestions for overcoming them. We further advocate for tuberculosis preventive therapy as the core of a renewed worldwide focus to implement a comprehensive epidemic control strategy that would reduce new tuberculosis cases to elimination targets. This strategy would be underpinned by accelerated research to further understand the biology of subclinical tuberculosis infections, develop novel diagnostics and drug regimens specifically for subclinical tuberculosis infection, strengthen health systems and community engagement, and enhance sustainable large scale implementation of preventive therapy programmes.

Published **Online** October 26, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00323-2

See **Online/Comments** http://dx.doi.org/10.1016/S0140-6736(15)00401-8, http://dx.doi.org/10.1016/S0140-6736(15)00320-7, and http://dx.doi.org/10.1016/S0140-6736(15)00319-0

This is the third in a **Series** of four papers about how to eliminate tuberculosis

Institute of Epidemiology and Health, University College London, London, UK and Department of Medicine, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa (M X Rangaka PhD)**; Evandro Chagas National Institute of Infectious Diseases, Rio de Janeiro, Brazil** (S C Cavalcante PhD)**; Children's Hospital at Westmead and the Centre for Research Excellence in Tuberculosis, University of Sydney, Australia** (B J Marais PhD)**; Cambodian Health Committee, Phnom Penh, Cambodia** (S Thim MD)**; Perinatal HIV Research Unit, University of Witwatersrand, Soweto, South Africa** (N A Martinson MBBCh)**; National Institute for Research on Tuberculosis, Chennai, India (S Swaminathan PhD); Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA** (R E Chaisson MD)

Correspondence to: Richard E Chaisson, Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
rchaiss@jhmi.edu

Current situation and rationale for change

The control of an infectious disease epidemic requires active case detection, treatment when possible, interruption of transmission, and enhancement of immunity for susceptible individuals. If elimination is desired, containment of the reservoirs, or seedbeds, of infection is essential. Tuberculosis is a disease whose pathogenesis is characterised by a period of asymptomatic subclinical infection that might last for weeks to decades; as a result, a large reservoir of infected human beings exists, among whom new cases might arise at any time. Although aggressive strategies to find and treat all cases of disease are necessary to turn the tide of the worldwide tuberculosis epidemic, these strategies alone will not be sufficient to end tuberculosis by WHO's 2035 target because they do not address the large existing reservoir of infection. The WHO policy now recognises that stopping the tuberculosis pandemic will require unprecedented efforts to address the human seedbeds of disease.[1]

Contemporary understanding of what has long been called latent tuberculosis infection has evolved. Rather than a binary distinction between latent and active states, tuberculosis infection is now understood as a dynamic multistate gradient of latent subclinical infection to clinically active disease; a process that is imperfectly represented by the dichotomous classification.[2–4] The spectrum of tuberculosis infection ranges from individuals who mount effective immune responses that eradicate all viable bacilli, to those whose responses contain the infection but who continue to harbour populations of bacilli that intermittently replicate in macrophages, granulomata, and other tissues, engaged in an intricate struggle with the host immune system.[5] There are also those with no effective immunity against tuberculosis who progress rapidly from tuberculosis infection to disease, such as young children, the chronically ill, and, HIV-infected individuals.[2,4] Differences in host immune responses affect the risk of tuberculosis infection progressing to active disease.

The population dynamics of tuberculosis begin with subclinical asymptomatic infections from which active cases arise (figure); these infections then spread to

Key messages

- Latent tuberculosis infection serves as the seedbed for virtually all new cases of active tuberculosis disease and should be addressed as an essential part of tuberculosis elimination.
- The efficacy and effectiveness of treating latent tuberculosis infection have been known for more than 50 years, but policies have not emphasised the epidemiological effect of treating these infections.
- Several clinical, administrative, and policy constraints have restricted use of preventive therapy.
- Populations at highest risk of progression from latent to active tuberculosis can be identified, and diagnostic tests and risk stratification can be used to select those individuals most likely to benefit from preventive therapy.
- New regimens for treating latent tuberculosis can simplify, shorten, and improve adherence to preventive therapy.

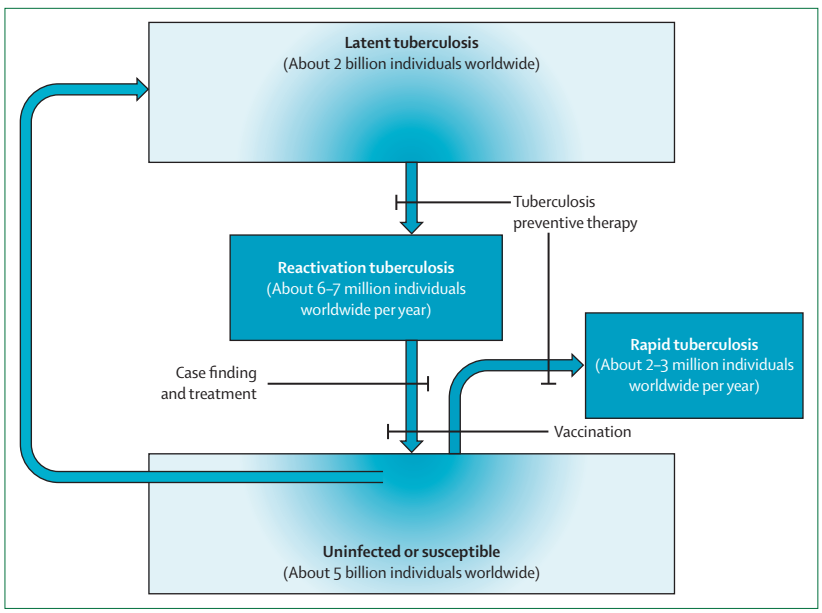

***Figure*: Population-level control strategies for tuberculosis elimination.**
Arrows show the dynamics of *M tuberculosis* in the world's population, with flow from latent infection to active disease, transmission to new hosts, followed by either rapid progression to disease and ongoing transmission or entry into the pool of latent infections. Bars show how different control measures affect these dynamics, interrupting the chain of events. Even if diagnosis and treatment of active tuberculosis is maximised and a new effective vaccine is developed, reactivation from the billions of latently infected will result in new cases for decades to come.

contacts (individuals in contact with the infectious case). Newly infected contacts might then progress to active tuberculosis disease, a process that could take weeks to more than a year, or enter the large pool of asymptomatically infected individuals and be at risk of future tuberculosis. Tuberculosis case-finding and treatment of disease prevents the spread of tuberculosis by reducing the number of secondary infections resulting from each new case, but this strategy alone cannot lead to elimination of the disease.[6] The vaccine available at present mostly mitigates disease severity in infants and young children, and despite high levels of coverage in many countries, it has not had an appreciable population-level effect on the incidence of pulmonary tuberculosis in adults worldwide. The only strategy for preventing new cases from arising in individuals sufficiently exposed to tuberculosis is to give treatment to those exposed to or infected by *M tuberculosis*, which prevents progression to active disease in the newly or remotely infected.[4,7] Thus, treatment of latent tuberculosis infection (called preventive therapy to differentiate it from treatment of active disease, which requires multidrug therapy) is an essential component of the strategy for elimination of tuberculosis, yet it is the least exercised option of all of the proven methods for combatting the worldwide epidemic because it has been underemphasised in disease control policies for several decades.

In the 1990s, Dye and colleagues estimated that a third of the world population was infected with *M tuberculosis*,[8] and a study from China found that a quarter to a third of adults in rural areas had tuberculosis infection,[9] emphasising the enormous reservoir that serves as the seedbed for new cases of active tuberculosis. Identification of high-risk epidemic locales (see Theron et al, paper 1)[10] as well as intensification of case-finding and improvements in treatment (see Yuen et al, paper 2),[11] although important, cannot alone achieve tuberculosis elimination because the reservoir of asymptomatically infected individuals will continue to produce millions of new cases of reactivation tuberculosis for decades to come. Even a highly effective new vaccine that prevents disease after new infection would not be sufficient for eliminating tuberculosis because the high prevalence of existing infections would not be affected. Thus, epidemiologically sound tuberculosis elimination strategies should include treatment of tuberculosis infection to be effective.[12]

Provision of treatment to prevent the establishment of a productive infection or progression of infection to disease is an established strategy for the control and elimination of major infectious diseases of public health relevance. For instance, eradication of smallpox was possible through a worldwide multipronged strategy to limit transmission that included finding and offering vaccination to contacts of infected people residing in epidemic hotspots.[13] Additionally, mass preventive therapy has been used to combat both *Chlamydia trachomatis* and *Onchocera volvulus*.[14] Because the human reservoir of *M tuberculosis* infection is enormous, overwhelmingly asymptomatic, and long-lived, a strategy to identify individuals who are at highest risk of progression to disease, who would thus benefit the most from preventive therapy, is widely recommended.

Some groups of people are at increased risk of progression to disease. These include close contacts of people with active tuberculosis disease, young children, elderly people, and people with HIV or other immunodeficiencies. Additionally, although tuberculosis infection tests available at present are imperfect proxies of risk, the Mantoux tuberculin skin test has been prospectively assessed to predict benefit from preventive therapy in several settings and populations.[7] Less robust evidence exists for the newer interferon γ release assays, though it is likely to be as predictive.[15]

The benefits of tuberculosis preventive therapy have been known for more than 60 years. Pioneering studies in the 1950s–60s provided overwhelming evidence of the efficacy of isoniazid preventive therapy in preventing active tuberculosis in children, Alaskan Native populations, residents of congregate living facilities such as mental hospitals, and household contacts of tuberculosis patients.[7,16–18] Subsequent work has further documented benefits of preventive therapy for individuals with evidence of recent infection, those with radiographic evidence of previous untreated tuberculosis, people with HIV infection, recipients of immunosuppressive therapy such as TNF-α inhibitors, and other immunocompromised individuals. We summarise the populations at

 Published online October 26, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00323-2

risk for tuberculosis who should benefit from preventive therapy, tests for tuberculosis infection, and available options for treatment (panel 1).

Despite abundance of evidence of its efficacy, use of preventive therapy outside North America has been restricted for the past 40 years because tuberculosis control programmes have focused almost exclusively on detection and treatment of infectious tuberculosis cases. Preventive therapy has been patchily targeted at children aged 5 years or younger with household exposure to an infected person. Although most countries have formal policies recommending treatment of these individuals, implementation in countries with a high tuberculosis burden has been near absent. Additionally, few of these countries have historically had policies addressing other high-risk individuals. WHO first recommended isoniazid preventive therapy for people living with HIV as a personal health measure in 1998, and updated this to a public health recommendation in 2010.[19] However, of the 22 high tuberculosis-burden countries, only South Africa and Brazil have ambitious national policies to provide preventive therapy to people infected with HIV.

The existence of obstacles to implementation of preventive therapy is no justification for inaction in the face of the wealth of compelling evidence supportive of preventive therapy as an essential component of disease control. Large population-based studies of preventive therapy and mathematical models both suggest that preventive treatment of tuberculosis infection, as a component of a comprehensive approach that includes active case-finding and prompt effective treatment, can produce sufficient reduction in population-level transmission and rates of active disease to interrupt the cycle of infection, illness, and death.[20,21] This Series paper thus argues for an integrated approach intended to spur widespread implementation of preventive therapy in the context of a comprehensive approach to addressing the tuberculosis epidemic. We summarise the successes of preventive therapy, provide a framework for understanding new and old challenges to implementation, and lay out a pragmatic roadmap to action.

Data and successes

Isoniazid preventive therapy, which is offered in conjunction with active screening to detect and treat cases of active tuberculosis disease, has long been recognised as an effective intervention for reducing the risk of tuberculosis at both the individual and population level. From the early 1950s and during two subsequent decades, many trials assessed the efficacy of isoniazid in preventing tuberculosis in different populations and circumstances.[7] By 1970, overwhelming evidence from several countries had shown that isoniazid was effective for reducing the risk of tuberculosis and was safe and well tolerated in both adults and children.[7] Declining incidence of tuberculosis in rural Alaska after community-wide trials of isoniazid treatment and mass screening for disease suggested a reduced force of infection attributable to mass preventive therapy during the trials. In Alaska, where tuberculosis was endemic in the 1950s, a community-wide trial of isoniazid versus placebo found a 60% decline in tuberculosis incidence for treated households that was sustained for more than two decades.[17]

The use of preventive therapy had a setback in the 1970s when case reports of isoniazid-associated hepatitis focused attention on the risks of preventive treatment, and a large US Public Health Service Study reported eight deaths in 13 838 individuals enrolled in a trial of isoniazid,[22] although subsequent analysis suggested that an unrelated epidemic of hepatitis might have contributed to the deaths recorded.[23] A series of studies using various models then argued that, for many individuals, the risks of preventive treatment outweighed the benefits.[24] Of note, none of these articles considered the public health gains of preventive therapy among the benefits.

Panel 1: Populations and individuals who benefit from tuberculosis preventive therapy, testing strategies, and treatment regimens

Populations at increased risk

- Residents of or immigrants from high-burden areas
- People with HIV infection
- Contacts of infectious cases
- Recent tuberculin skin test (TST) or interferon γ release assay (IGRA) converters
- Recipients of TNFα blockers
- Recipients of immunosuppressive therapy or transplantation
- Residents of congregate living facilities including prisons
- Homeless people
- People with diabetes
- Cigarette smokers
- Miners and people with silicosis
- Residents of congregate living facilities
- Health-care workers and people who visit health-care facilities (in high tuberculosis burden areas)

Tests for tuberculosis infection

- TST
  - ≥5 mm induration at 2–3 days deemed positive for HIV-infected individuals, close contacts of cases, and young children
  - ≥10 mm induration at 2–3 days deemed positive for other risk categories
  - ≥15 mm induration at 2–3 days for those with no identifiable risk factors
- IGRA
  - Quantiferon-Gold In Tube Assay (QGIT): >0·35 IU/mL deemed positive
  - T-SPOT Test: >8 spot-forming cells deemed positive
- Proxy measures of tuberculosis infection when testing unavailable
  - Household contact with a pulmonary tuberculosis case
- Resident of areas with high burden of latent tuberculosis

Treatment regimens for tuberculosis infection

- Isoniazid daily or twice weekly for 6, 9, 12, or 36 months
  - Rifampicin daily for 3–4 months
  - Rifampicin and isoniazid daily or two to three times per week for 3 months
  - Rifampicin and isoniazid once weekly for 12 weeks

The emergence of the worldwide HIV epidemic in the 1980's and 1990's led to a renewed interest in prevention of tuberculosis in high-risk individuals. Several observational and randomised trials showed that using isoniazid for 6–12 months reduced the risk of tuberculosis, particularly in people with positive tuberculin skin tests.[25] Guidelines developed in the USA in 2000 emphasised the importance of targeting skin testing and preventive therapy at those with highest risk of developing disease, with careful clinical monitoring to reduce toxicity.[26] Yet isoniazid treatment was still little-used worldwide, including in populations with high rates of HIV infection.

The consensus on the individual-level benefit of preventive therapy is incontrovertible. Compared with untreated individuals, the risk of clinically active tuberculosis disease is reduced by 60% in immunocompetent, HIV-uninfected individuals and by 32–62% in HIV-infected adults who are treated with preventive therapy regimens of 3–12 months duration.[25,27] The benefit of isoniazid preventive therapy in HIV-infected individuals is additive to the benefit of antiretroviral therapy, which itself reduces tuberculosis risk by about 60%; the combination of the two can achieve substantial reductions in rates of incident tuberculosis in people with HIV infection.[28–30] The risk of developing tuberculosis is reduced by about 60% in children aged 15 years or younger who receive preventive therapy.[31] Long courses reduce subsequent disease in individuals at risk of exogenous re-infection.[32] Finally, evidence is accumulating that preventive therapy with an appropriate drug can offer protection to individuals exposed to drug-resistant tuberculosis.

At a population level, studies have built on the experience in Alaska and shown that the treatment of tuberculosis infection as part of a comprehensive tuberculosis control strategy that includes active case-finding, particularly in household contacts, can reduce tuberculosis incidence. In Rio de Janeiro, Brazil, a community-randomised trial including eight urban neighbourhoods with a baseline tuberculosis incidence of roughly 340 per 100 000 people per year compared the standard procedure of informing patients with tuberculosis of the need for their household contacts to be assessed with active identification, assessment, and appropriate treatment of tuberculosis infection and tuberculosis disease in household contacts. After 5 years, tuberculosis incidence in the intervention communities was 15% lower than in the standard procedure communities.[33]

The cluster-randomised THRio trial in Rio de Janeiro, Brazil, involving HIV-infected people enrolled in 29 clinics, showed a benefit of isoniazid preventive treatment in a setting of moderate tuberculosis incidence, as part of an integrated care programme for HIV care. In this trial, strengthening the uptake of tuberculosis screening, tuberculin testing, and use of preventive therapy reduced the adjusted hazard of tuberculosis incidence and death in the study population by 25–30%.[34] Long-term follow up of individuals treated with isoniazid showed that the benefit was durable for 5 years after treatment, and modelling based on the results of this intervention predicted that targeted treatment of just 20% of HIV-infected individuals with tuberculosis infection would produce a community-wide decline in HIV-related tuberculosis incidence and mortality of about 15%.[21,35]

Observational evidence from other settings also supports the effectiveness of preventive therapy as a key component of achieving population-level reductions in tuberculosis incidence. To address a decade-long stagnation of tuberculosis incidence, Singapore started a new tuberculosis elimination initiative combining directly observed therapy, national surveillance, and treatment of latent infection in contacts. Tuberculosis incidence declined by 15–20% within 5 years, and treatment of latent infection was identified as a key contributor to this decline.[36] In a programmatic intervention targeting two neighbourhoods with historically high tuberculosis incidence (40/100 000 people per year) in Texas, USA, a door-to-door mass screening was done and isoniazid was prescribed for all infected individuals. This community-based tuberculosis screening and preventive treatment seemed to have substantially decreased subsequent tuberculosis incidence because no tuberculosis cases were detected in the two intervention communities over the next 10 years.[37]

Challenges

Although more than a half-century of data support the use of preventive therapy as an important component of tuberculosis control, several challenges, both new and old, should be addressed to energise widespread implementation of present guidelines and respond to perceived and actual barriers to implementation, which include clinical, technical, health systems, and policy and advocacy dimensions (table 1).

On a clinical level, practitioners encounter the difficulty of screening HIV-infected adults for tuberculosis disease before initiating preventive therapy, restricted access to tests for tuberculosis infection, the complexity of risk-factor driven algorithms to identify individuals at highest risk of disease, and the challenges of encouraging adherence to a treatment for an asymptomatic condition. These are accompanied by perceived problems such as fear of inducing drug resistance, even though evidence exists that this fear is unfounded,[38] and exaggerated perceptions of the risk of severe side effects.

At the health-systems level, ambiguous or ambivalent guidelines for diagnosing and treating tuberculosis infection undermine clinician confidence. Inadequate health training and insufficient numbers of health-care workers, compounded by drug stock-outs, limit use of preventive therapy. Additionally, the absence of effective monitoring and assessment surveillance systems to oversee uptake, side effects, adherence, resistance, and

 Published online October 26, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00323-2

	Proposed responses
Clinical	
Excluding active tuberculosis, especially in HIV-positive patients	Use of clinical algorithms, more use of chest x-rays
Need for tuberculin or other testing [IGRA (interferon γ release assay)]	Develop new simple tests that are more predictive of subsequent active tuberculosis, improve worldwide production of tuberculin, treat high-risk patients without testing
Poor adherence and completion of preventive therapy	Use of short-course regimens and supervision of therapy
Drug toxicity	Encourage monthly monitoring and patient education
Perceived risk of acquiring drug resistance	Available evidence suggests this is not a problem
Health system	
Absence of consistent guidelines	Harmonised worldwide and national guidelines Development of preventive therapy instruments
Inadequately trained staff	Enhanced training for doctors, nurses, and other health workers
Stock-outs of drugs and diagnostics (tuberculin skin test or IGRA)	Strengthened supply chain
Poor surveillance and reporting	Better health information systems, increased monitoring and assessment
Inadequate funding	Expansion of vertical health programmes to address tuberculosis prevention (eg, HIV prevention of mother-to-child transmission), with benchmarks for disease control; more integration of tuberculosis control into primary health care
Policy and advocacy	
Absence of priority for prevention, with emphasis on proportion of active cases treated	Realignment of tuberculosis control programmes to incorporate prevention, with performance assessment linked to incidence
Inadequate investment in basic, clinical and implementation research and training	Increased funding for research
Absence of advocacy and demand from groups most at risk	Education and empowerment of at-risk group, including people with HIV and families

Table 1: **Barriers to implementation of tuberculosis preventive therapy and proposed responses**

programme effect make assessment of country-level efforts difficult. Further hampering use of preventive therapy is a very low level of community engagement and demand, in contrast with the demand for antiretroviral therapy and, increasingly, for treatment of hepatitis C virus infection. Finally, the poor prioritisation of research funding for new methods for tuberculosis control, which could include new vaccines to prevent infection and new diagnostics to predict risk of progression to disease, stifles innovation and restricts progress.

A further challenge in preventing tuberculosis is the high incidence of re-infection in HIV-infected individuals and other high-risk populations in sub-Saharan Africa, as well as other identified hotspots of uncontrolled transmission. The benefit of preventive therapy in these settings is less durable because the treatment effect seems to wane soon after discontinuation. This suggests that people treated for tuberculosis infection are either rapidly re-infected or persistent bacilli are not sterilised by isoniazid.[32,39] A cluster-randomised trial done in the high-burden setting of gold mines in South Africa, showed that mass screening and isoniazid preventive therapy was successful in preventing tuberculosis while individuals were receiving treatment, but had no durable effect in reducing overall tuberculosis incidence.[40] Similar limitation of benefit to the time during which individuals were taking preventive therapy was noted in studies in HIV-infected individuals in Botswana and Soweto, South Africa.[32,41] Thus, although short courses of preventive therapy can provide short-term to medium-term protection even in high-burden settings, long-term protection might only be conferred where transmission is better controlled through active case-finding and treatment. Further research is needed to understand population-level effects of preventive therapy in transmission hotspots and to inform efforts to control re-infection and subsequent disease.

Solutions to most of the technical challenges mentioned previously are available and can be implemented at present. For example, if tests for infection are not available or affordable, epidemiologically targeted preventive therapy can be offered as post-exposure treatment to the highest risk individuals without evidence of active tuberculosis, such as those with HIV, child contacts of an infected person,[42,43] or individuals with medical disorders that increase risk of tuberculosis. A symptom-screening algorithm with 80% sensitivity and a negative predictive value of 97% for diagnosing active tuberculosis in HIV-infected adults has been promulgated by WHO.[44] In children, WHO guidance encourages simple symptom-based screening because asymptomatic children are unlikely to have active tuberculosis or to acquire drug resistance if subclinical disease is missed.[45,46] The availability of cheap, rapid, and sensitive microbiological screening instruments or screening algorithms based on new tuberculosis infection diagnostics would complement efforts to scale up.

Adherence might be improved and hepatotoxicity reduced through the use of shorter rifamycin-based preventive therapy regimens rather than the use isoniazid for long durations (ie, 6, 9, 12, or 36 months). For individuals taking isoniazid, rates of drug-related liver injury can be kept low (<1–3%) with appropriate screening and monitoring, though isoniazid-induced hepatoxicity might still result in one death for every 25 000–40 000 patients treated.[40] In contrast, liver toxicity rates with rifamycin-based regimens are substantially lower, and adherence to these shorter course regimens is generally much better. Rifamycin-based regimen options include a weekly regimen of rifapentine plus isoniazid for 3 months, and daily regimens of isoniazid plus rifampicin or rifampicin alone for 3–4 months.[27,41,47–49] These regimens are all considered options in developed countries, and are likely to have a great effect on uptake as well as the workload and health workforce needed to give and monitor preventive treatment. Further improvements in the ease of giving and taking preventive therapy are anticipated, because a new fixed-dose combination tablet of rifapentine and isoniazid is expected to be marketed later this year, and a bold 4-week regimen of daily rifapentine and isoniazid is being assessed.[50,51] Unfortunately, in resource-constrained high tuberculosis burden countries, preventive therapy with 6–36 months of isoniazid is, uninspiringly, presented as the only option. This situation is perceived as a pragmatic choice, probably because most of the historical evidence for preventive therapy is with isoniazid, which is cheap and widely available. However, the adoption of shorter, easier to complete regimens would be particularly advantageous in settings of high tuberculosis burden and limited resources because this would enable many more people to complete preventive therapy in view of the low number of health-care staff available to give treatment and monitor adverse events. Although offering real hope in addressing the adherence challenge, to be successful, these biomedical advances will have to be supported by continuous qualitative work to explore individual and community understanding of latency, its relationship to disease, and the need for treating infections with an antibiotic to prevent active disease. Understanding of how to structure tuberculosis preventive therapy programmes from the perspective of the patient is needed to design relevant interventions to promote adherence and thus a more responsive preventive therapy programme.

Further barriers to implementation affect health systems and policies. Available guidelines do not provide sufficient guidance for national preventive therapy programmes to proceed. Firstly, leadership and the responsibility for prescribing and providing preventive therapy are unclear. Ownership could rest with tuberculosis programmes, HIV programmes, primary care clinics, the private sector, or some combination of these, but a plan that outlines responsibilities and a process for coordination of efforts is necessary no matter what the arrangement. Additionally, tuberculosis programmes would need to consider further devolution of responsibilities to procure and distribute drugs for preventive therapy.

Secondly, preventive therapy has to be implemented in clinical settings with heavy workloads and programme-specific delivery targets. Although tuberculosis programmes naturally have access to high-risk groups such as household contacts, the workload of dealing with active cases often overwhelms staff, who thus deprioritise preventive therapy. Within HIV programmes, clinicians have competing priorities, such as initiating antiretroviral therapy and managing infectious and non-infectious HIV-associated comorbidities. As a result, treatment of tuberculosis infection is often de-emphasised. Training and motivating health-care workers and building systems that can undertake the additional task of providing tuberculosis preventive therapy is an important but difficult challenge. Much innovation and evidence of successful strategies is needed to address this challenge. Answers might lie in some well known but underused approaches, such as task shifting to the lay cadres of the health workforce, decentralisation of centres testing for latent tuberculosis infection, delivery of treatment and monitoring of individuals on preventive therapy, and some less explored options, such as innovative approaches for simplifying testing for latent tuberculosis infection, which could include instruments for self-testing.

Thirdly, international consensus process and outcome indicators for preventive therapy programmes are not yet available, making it difficult to assess the successes and limitations of programmes. For example, accurate country-level assessments of uptake of preventive therapy in HIV-infected people who newly presented for care have proven elusive owing to concerns with the quality of monitoring and assessment. An analysis of the uptake of preventive therapy in 150 clinical sites in South Africa suggested an increase in the absolute numbers of individuals prescribed preventive therapy (from 3309 in 2010 to 49 130 in 2011) but a decrease in the proportion of patients receiving it (from 19% in 2010 to 11% in 2011).[52] Although encouraging, a reported surge in recipients is an insufficient indicator of successful implementation.[53] Indicators such as increases in coverage, completion rates, rates of adverse events, and active tuberculosis in people receiving preventive therapy are needed to show intervention fidelity. Monitoring of downward trends in the incidence of new infections and subsequent cases would provide evidence for interruption of transmission. The first Series paper[10] argues for an approach in which existing data collection systems are augmented with such new information and are increasingly used to inform success of local tuberculosis control interventions such as a preventive therapy programme.

There is also a challenging shortage of advocacy and leadership to promote preventive therapy. Within Global

	Strategy	Proposed approaches
Reduce tuberculosis at the individual level		
Risk-stratified preventive therapy to latently infected or exposed individuals at risk of tuberculosis, or those who might transmit future disease to susceptible people	Treat proven tuberculin-positive infection (tuberculin skin test or interferon γ release assay positive*)	Always treat in people with HIV infection, other immune-compromised individuals, young children (<5 years of age), recent skin test converters, and individuals with abnormal chest x-rays consistent with untreated previous tuberculosis; consider treating in cigarette smokers or people with chronic lung disease, people with diabetes, malnourished individuals; recent immigrants from high-burden tuberculosis countries; health-care workers, and prisoners or residents of congregate living facilities (eg, long-term care)
	Treat probable *M tuberculosis* infection or re-infection (close contact with an infectious person)	Always treat in immune-compromised individuals (including people with HIV in a tuberculosis-endemic setting), young children (<5 years of age), and household contacts with widespread exposure (all ages)
Early diagnosis and prompt adequate treatment (also of drug-resistant tuberculosis)	Passive case-finding	Enhanced community awareness; universal access to care; well-functioning health systems; better diagnostic instruments
	Active case-finding	Routine screening and focus on high-risk groups such as close contacts to tuberculosis patients, mine workers, prisoners, and people with HIV or diabetes
Reduce tuberculosis at the community level		
Limit transmission	Community intervention	In addition to the individual approaches listed above, consider creative measures to identify transmission hot-spots and improve infection control
Increase resilience to disease	Reduce susceptibility	Ensure optimum HIV care and reduced HIV transmission, reduce cigarette smoking, indoor and outdoor air pollution, malnutrition, diabetes, alcohol, and substance misuse

*Acknowledging sensitivity and specificity limitations, not mandatory in people with HIV in a tuberculosis-endemic setting

Table 2: Treatment of *M tuberculosis* infection as part of a comprehensive approach to improve worldwide tuberculosis control

Fund programmes and grants, tuberculosis is enormously underemphasised, which reflects country-level and community-level absence of advocacy and demand. In contrast, widespread availability of antiretroviral therapy has been promoted by the powerful voice of affected communities coupled with visionary leaders who devised programmes like the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund for AIDS, TB and Malaria.[54] Building this support for tuberculosis preventive therapy will require education and engagement of both populations at risk and clinical and public health leaders.[55]

Proposed action plan

The abundance of existing evidence and knowledge about tuberculosis infection and preventive therapy provides a solid base for concerted worldwide action to incorporate treatment of tuberculosis infection into a comprehensive and epidemiologically sound strategy for tuberculosis elimination. Although the magnitude of the challenges implicated and the corresponding level of ambition needed are substantial, these efforts are necessary because case-finding and treatment approaches alone will not be sufficient, and both novel diagnostics to accurately identify incipient disease and effective vaccines to prevent infection or disease are distant goals. Additionally to biomedical interventions, political leadership and will are needed to modify the risk environment by addressing the social determinants of tuberculosis that perpetuate inequalities in health (see Ortblad et al, paper 4).[56,57] Finally, we need a worldwide interdisciplinary approach to accelerate research that furthers our understanding of the biology of tuberculosis infection, develops novel diagnostics and drug regimens for tuberculosis infection, strengthens health systems, and enhances sustainable large scale implementation of preventive therapy programmes. In this section we provide a roadmap to address identified key implementation barriers and immediately enhance implementation.

The clinical and technical approach

Tuberculosis preventive therapy should be implemented alongside tracing of case-contacts and other high-risk individuals, targeted active case-finding, and effective treatment of active disease (see Yuen et al, paper 2)[11] as a routine component of tuberculosis control programmes worldwide. Commitment to preventive therapy as a core element of control is needed at the global, national, provincial, and local levels. Additionally, preventive treatment for tuberculosis should be incorporated into other health programmes that provide treatment to populations at risk, such as HIV care, substance-misuse treatment, and occupational health clinics. We propose a single-bundle strategy of routine active case finding to identify people with active disease who should be promptly initiated on effective multidrug chemotherapeutic regimens and those without disease for risk-stratified treatment of *M tuberculosis* infection (table 1, table 2). Recognising the importance of expanding preventive interventions, in 2014, WHO revised guidelines for the diagnosis and treatment of tuberculosis infection.[55] The guidelines are mainly targeted at high-income or upper middle-income countries with an estimated tuberculosis incidence rate

of less than 100 per 100 000 population per year and have broadened the definitions of at-risk groups. Our proposed risk-stratified strategy aims to support these efforts and will ensure that preventive therapy is safely and efficiently provided to individuals at increased risk of disease in all settings, including high-burden countries.

In countries with uncontrolled *M tuberculosis* transmission, re-infection might limit the long-term benefit of short courses of preventive therapy, particularly within transmission hotspots. In particularly susceptible groups, such as people with HIV, miners, prisoners in areas with high transmission rates of tuberculosis, and other groups with a high risk of developing the disease owing to occupational (eg, health-care workers) or behavioural exposures (eg, drug-users), extended or periodic schedules of preventive therapy should be implemented. *M tuberculosis* transmission rates were astonishingly high in Alaska in the 1950s (>90% of children were infected by the age of 15 years) when the Bethel household isoniazid study took place, and rates of infection fell precipitously as a concerted programme of case finding, treatment, and preventive therapy was implemented.[58] This finding is strong evidence that preventive therapy plays an important part even in high-burden areas.

Health-systems, policy, and leadership

To deliver tuberculosis preventive therapy more broadly, engagement of other health programmes that provide care to high risk populations is essential. HIV programmes can easily provide preventive therapy to HIV-infected individuals, whereas maternal and child health programmes could actively support preventive therapy provision in young and susceptible children. As the link between diabetes and tuberculosis becomes better understood, diabetes clinics and primary health programmes caring for people with diabetes could consider tuberculosis prevention, diagnosis, and treatment. Occupational health programmes are responsible for providing treatment to workers at increased risk of tuberculosis, such as miners and health-care workers, but too often they neglect prevention. In many settings, primary health centres and private practitioners can deliver preventive therapy to people who would benefit, such as contacts of individuals infected with tuberculosis disease, people with diabetes or immunosuppression, and refugees or immigrants from high-burden tuberculosis areas. To identify and standardise functional monitoring and reporting pathways is essential to support preventive therapy implementation across providers, such as latent tuberculosis registries, because this is a key driver and the only proof of actual implementation.[59] In 2011 WHO launched a handbook for the programmatic management and implementation of drug-resistant tuberculosis activities and surveillance[60] A similar resource is urgently needed to decode existing preventive therapy guidelines and offer practical guidance to National HIV, tuberculosis, other programme managers, monitoring and assessment coordinators, and clinicians to accelerate preventive therapy implementation in partner countries.

Advocacy approach

Widening uptake of tuberculosis preventive therapy will need leadership and evidence-based advocacy by clinicians, public health officials, and communities at risk of infection. These stakeholders should demand that preventive therapy be provided at every opportunity and contact with the health system, as it is an essential part of the tuberculosis control package. For example, for some individuals, preventive therapy will be easier to give in antiretroviral therapy clinics and antenatal programmes than through tuberculosis clinics. Additionally, the absence of understanding of tuberculosis infection and the role of preventive therapy needs to be addressed in affected individuals, their health-providers, and their communities. This education could be the key to triggering bottom-up advocacy as is seen for HIV prevention and might increase the acceptability of treatment for an asymptomatic condition.

Projected population effect and cost

Good evidence exists of the population-level effect and cost-effectiveness of preventive therapy on tuberculosis dynamics in both low-income and high-income countries. One projection for India suggests that by increasing use of preventive therapy gradually by 2050, tuberculosis incidence could be reduced to one case per million people, and deaths could be reduced to fewer than ten cases per million people by 2035 (compared with a present estimated incidence of 1710 per million and estimated mortality of 190 per million population).[12] Another projection for the Republic of Kiribati (population of roughly 100 000 people, tuberculosis incidence of 487/100 000 people per year) suggested that a combination of active case finding and mass treatment with a full course of antituberculosis drugs given to the entire population from 2015 intermittently at 5-yearly rounds could eliminate tuberculosis from this Pacific island by 2030.[61] A systematic review by Chavan and collegues provides robust evidence of the effectiveness and cost effectiveness of preventive therapy in high-income countries. Remarkably, the analysis concluded that tuberculosis preventive therapy would be effective and cost effective even for adults up to aged 80 years old.[62]

Conclusions

After more than three decades of policy that focused only on the detection and treatment of active cases of tuberculosis, a better understanding of the epidemiology and population dynamics of the disease has emerged, and the essential role of controlling the seedbeds of disease (asymptomatic tuberculosis infections) is now understood. Evidence of the effectiveness of preventive therapy in high-risk individuals is abundant, and proof of

 Published online October 26, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00323-2

the population-level effect of preventive therapy exists in many settings across the globe. Implementation of tuberculosis preventive therapy will need addressing of clinical, administrative, structural, and economic barriers, and the engagement of several sectors, not just national tuberculosis programmes. With the advent of new treatments that shorten and simplify preventive therapy, the ability of health systems to reach and treat more high-risk individuals will be enhanced. As with malaria, HIV, and other infectious diseases of public health consequence, the key role of preventive therapy as part of a comprehensive control strategy for tuberculosis must be recognised and executed.

Contributors

REC and MXR conceived the idea for this Series paper. REC and MXR wrote the first draft of the paper, and all authors revised it for important intellectual content. All authors approved the final version submitted for publication.

Declaration of interests

We declare no competing interests. The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health.

Acknowledgments

We thank Ed Nardell for his review and the important comments he contributed during drafting, and Carly Rodriguez for coordination and research assistance in the preparation of this manuscript. MXR was supported by a University College London Excellence Fellowship and reports grants from the National Institute for Health Research University College London Hospitals Biomedical Research Centre. NAM reports grants from the US National Institutes of Health (R01 HD064354-03 and R01 DA030276-01A1) and the Medical Research Council Soweto Matlosana Center for HIV/AIDS and TB Research, and NAM and REC report grants from the US Centers for Disease Control and Prevention (2000-2009-32589). REC reports grants from the US National Institutes of Health (P30-AI-094189).

References

1 World Health Organization. Global strategy and targets for tuberculosis prevention, care and control after 2015. http://apps.who.int/gb/ebwha/pdf_files/EB134/B134_12-en.pdf?ua=1 (accessed July 25, 2015).

2 Barry CE 3rd, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nat Rev Microbiol* 2009; **7:** 845–55.

3 Ernst JD. The immunological life cycle of tuberculosis. *Nat Rev Immunol* 2012; **12:** 581–91.

4 Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. *N Engl J Med* 2015; **372:** 2127–35.

5 Ewer K, Millington KA, Deeks JJ, Alvarez L, Bryant G, Lalvani A. Dynamic antigen-specific T-cell responses after point-source exposure to Mycobacterium tuberculosis. *Am J Respir Crit Care Med* 2006; **174:** 831–39.

6 Dowdy DW, Chaisson RE. The persistence of tuberculosis in the age of DOTS: reassessing the effect of case detection. *Bull World Health Organ* 2009; **87:** 296–304.

7 Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc* 1970; **26:** 28–106.

8 Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA* 1999; **282**: 677–86.

9 Gao L, Lu W, Bai L, et al. Latent tuberculosis infection in rural China: baseline results of a population-based, multicentre, prospective cohort study. *Lancet Infect Dis* 2015; **15:** 310–19.

10 Theron G, Jenkins HE, Cobelens F, et al. Data for action: collection and use of local data to end tuberculosis. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00321-9.

11 Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00322-0.

12 Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. *Annu Rev Public Health* 2013; **34:** 271–86.

13 Henderson DA. Principles and lessons from the smallpox eradication programme. *Bull World Health Org* 1987; **65:** 535–46.

14 Mackenzie CD, Homeida MM, Hopkins AD, Lawrence JC. Elimination of onchocerciasis from Africa: possible? *Trends Parasitol* 2012; **28:** 16–22.

15 Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; **12:** 45–55.

16 Lincoln EM. The effect of antimicrobial therapy on the prognosis of primary tuberculosis in children. *Am Rev Tuberc* 1954; **69:** 682–89.

17 Comstock GW, Baum C, Snider DE Jr. Isoniazid prophylaxis among Alaskan Eskimos: a final report of the bethel isoniazid studies. *Am Rev Respir Dis* 1979; **119:** 827–30.

18 Egmose T, Ang'awa JOW, Poti SJ. The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. *Bull World Health Org* 1965; **33:** 419–33.

19 Stop TB. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland: World Health Organization, 2011.

20 Mills HL, Cohen T, Colijn C. Modelling the performance of isoniazid preventive therapy for reducing tuberculosis in HIV endemic settings: the effects of network structure. *J R Soc Interface* 2011; **8:** 1510–20.

21 Dowdy DW, Golub JE, Saraceni V, Moulton LH, Cavalcante SC, Cohn S, et al. Impact of isoniazid preventive therapy for HIV-infected adults in Rio de Janeiro, Brazil: an epidemiological model. *J Acquir Immune Defic Syndr* 2014; **66:** 552–58.

22 Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a US Public Health Service cooperative surveillance study. *Am Rev Respir Dis* 1978; **117:** 991–1001.

23 Comstock GW. Prevention of tuberculosis among tuberculin reactors: maximizing benefits, minimizing risks. *JAMA* 1986; **256:** 2729–30.

24 Tsevat J, Taylor WC, Wong JB, Pauker SG. Isoniazid for the tuberculin reactor: take it or leave it. *Am Rev Respir Dis* 1988; **137:** 215–20.

25 Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2010; **20**: CD000171.

26 Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. *Am J Respir Crit Care Med* 2000; **161:** S221–47.

27 Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev* 2000; **2:** CD001363.

28 Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS* 2007; **21:** 1441–8.

29 Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet* 2014; **384:** 682–90.

30 TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373:** 808–22.

31 Ayieko J, Abuogi L, Simchowitz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. *BMC Infect Dis* 2014; **14:** 91.

32 Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **377:** 1588–98.

33 Cavalcante SC, Durovni B, Barnes GL, et al. Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2010; **14:** 203–09.

34 Durovni B, Saraceni V, Moulton LH, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. *Lancet Infect Dis* 2013; **13:** 852–58.

35 Golub JE, Cohn S, Saraceni V, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. *Clin Infect Dis* 2015; **60:** 639–45.

36 Chee CB, Teleman MD, Boudville IC, Do SE, Wang YT. Treatment of latent TB infection for close contacts as a complementary TB control strategy in Singapore. *Int J Tuberc Lung Dis* 2004; **8:** 226–31.

37 Cegielski JP, Griffith DE, McGaha PK, et al. Eliminating tuberculosis one neighborhood at a time. *Am J Public Health* 2013; **103**: 1292–300.

38 Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis* 2006; **12:** 744–51.

39 Dickinson JM, Mitchison DA. Experimental models to explain the high sterilizing activity of rifampin in the chemotherapy of tuberculosis. *Am Rev Respir Dis* 1981; **123:** 367–71.

40 Churchyard GJ, Fielding KL, Lewis JJ, et al. A trial of mass isoniazid preventive therapy for tuberculosis control. *N Engl J Med* 2014; **370:** 301–10.

41 Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med* 2011; **365:** 11–20.

42 Triasih R, Robertson CF, Duke T, Graham SM. A prospective evaluation of the symptom-based screening approach to the management of children who are contacts of tuberculosis cases. *Clin Infect Dis* 2015; **60:** 12–18.

43 Mandalakas AM, Kirchner HL, Lombard C, et al. Well-quantified tuberculosis exposure is a reliable surrogate measure of tuberculosis infection.*Int J Tuberc Lung Dis* 2012 Aug; **16:** 1033–9

44 Getahun H KW, Heilig CM, Corbett EL, et al. Development of a standardized screening rule of tuberculosis in people living with HIV in resource-constrained settings: Individual participant data meta-analysis of observational studies. *PLoS Med* 2011; **8:** 1–13.

45 WHO. Guidance for National Tuberculosis Programmes on the management of tuberculosis in children - second edition. Geneva, Switzerland: Stop TB Partnership Childhood TB Subgroup, World Health Organization, 2014.

46 Kruk A, Gie RP, Schaaf HS, Marais BJ. Symptom-based screening of child tuberculosis contacts: improved feasibility in resource-limited settings. *Pediatrics* 2008; **121:** e1646–52.

47 Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011; **365:** 2155–66.

48 Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr* 2015; **169:** 247–55.

49 Centers for Disease C, Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. *MMWR Morb Mortal Wkly Rep* 2011; **60:** 1650–53.

50 Zhang T, Zhang M, Rosenthal IM, Grosset JH, Nuermberger EL. Short-course therapy with daily rifapentine in a murine model of latent tuberculosis infection. *Am J Respir Crit Care Med* 2009; **180:** 1151–57.

51 Podany AT, Bao Y, Chaisson RE, et al. Efavirenz pharmacokinetics in HIV-infected persons receiving rifapentine and isoniazid for tuberculosis prevention. *Clin Infect Dis* 2015; published online June 16. DOI:10.1093/cid/civ464.

52 Bristow CC, Larson E, Vilakazi-Nhlapo AK, Wilson M, Klausner JD. Scale-up of isoniazid preventive therapy in PEPFAR-assisted clinical sites in South Africa. *Int J Tuberc Lung Dis* 2012; **16:** 1020–22.

53 Martinson NA, McLeod KE, Milovanovic M, Msandiwa R, Lebina L. Implementation of isoniazid preventive therapy for HIV-infected adults: overstatement of district reports. *Int J Tuberc Lung Dis* 2014; **18:** 1005.

54 Keshavjee S, Beauvais SG. Let's learn from HIV activists how to achieve zero tuberculosis deaths. *Huffington Post*. http://www.huffingtonpost.com/salmaan-keshavjee/tb-hiv-patients-awareness_b_1700450.html (accessed Sept 19, 2015).

55 WHO. Guidelines on the management of latent tuberculosis infection. Geneva, Switzerland: World Health Organization, 2015.

56 Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00324-4.

57 Raviglione M, Krech R. Tuberculosis: still a social disease. *Int J Tuberc Lung Dis* 2011; **15** (suppl 2)**:** S6–8.

58 Kaplan GJ, Fraser RI, Comstock GW. Tuberculosis in Alaska, 1970: the continued decline of the tuberculosis epidemic. *Am Rev Respir Dis* 1972; **105:** 920–26.

59 van Soelen N, du Preez K, van Wyk SS,et al. Does an isoniazid prophylaxis register improve tuberculosis contact management in South African children? *PLoS One* 2013; **8:** e80803.

60 WHO. Guidelines for the programmatic management of drug-resistant tuberculosis 2011 update. Geneva, Switzerland: World Health Organization, 2011.

61 Hill PC, Dye C, Viney K, et al. Mass treatment to eliminate tuberculosis from an island population. *Int J Tuberc Lung Dis* 2014; **18:** 899–904.

62 Chavan S, Newlands D, Smith C. A systematic review of economic evaluations of chemoprophylaxis for tuberculosis. *J Trop Med* 2011; **2011:** 130976.

How to eliminate tuberculosis 4

Stopping tuberculosis: a biosocial model for sustainable development

Katrina F Ortblad, Joshua A Salomon, Till Bärnighausen, Rifat Atun

Tuberculosis transmission and progression are largely driven by social factors such as poor living conditions and poor nutrition. Increased standards of living and social approaches helped to decrease the burden of tuberculosis before the introduction of chemotherapy in the 1940s. Since then, management of tuberculosis has been largely biomedical. More funding for tuberculosis since 2000, coinciding with the Millennium Development Goals, has yielded progress in tuberculosis mortality but smaller reductions in incidence, which continues to pose a risk to sustainable development, especially in poor and susceptible populations. These at-risk populations need accelerated progress to end tuberculosis as resolved by the World Health Assembly in 2015. Effectively addressing the worldwide tuberculosis burden will need not only enhancement of biomedical approaches but also rebuilding of the social approaches of the past. To combine a biosocial approach, underpinned by social, economic, and environmental actions, with new treatments, new diagnostics, and universal health coverage, will need multisectoral coordination and action involving the health and other governmental sectors, as well as participation of the civil society, and especially the poor and susceptible populations. A biosocial approach to stopping tuberculosis will not only target morbidity and mortality from disease but would also contribute substantially to poverty alleviation and sustainable development that promises to meet the needs of the present, especially the poor, and provide them and subsequent generations an opportunity for a better future.

Published **Online**
October 26, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00324-4

See **Online/Comments**
http://dx.doi.org/10.1016/S0140-6736(15)00401-8,
http://dx.doi.org/10.1016/S0140-6736(15)00320-7, and
http://dx.doi.org/10.1016/S0140-6736(15)00319-0

This is the fourth in a **Series** of four papers about how to eliminate tuberculosis

Department of Global Health and Population, Harvard T H Chan School of Public Health, Harvard University, Boston, MA, USA (K F Ortblad MPH, J A Salomon PhD, T Bärnighausen MD, Prof R Atun FRCP)**; and Wellcome Trust Africa Centre for Health and Population Studies, Mtubatuba, South Africa** (T Bärnighausen)

Correspondence to:
Prof Rifat Atun, Department of Global Health and Population, Harvard T H Chan School of Public Health, Harvard University, Boston, MA 02115, USA
ratun@hsph.harvard.edu

Introduction

Tuberculosis has been called the perfect expression of an imperfect civilisation.[1] Despite scientific and social advances a high burden of tuberculosis persists worldwide, particularly affecting poor and susceptible populations.[1]

Tuberculosis transmission and progression are largely driven by social factors such as poor living conditions and poor nutrition.[2] However, with the discovery of anti-tuberculous medicines in the 1940s, the approaches in fighting tuberculosis have been largely biomedical.[3,4] The burden of tuberculosis declined rapidly in the early 1950s, coinciding with the use of anti-tuberculous medicines, but progress since the 1960s has been slow and uneven, with declines in many settings occurring well before the introduction of chemotherapy (figure 1), probably attributable at least in part to improved standards of living.[2,5,6]

In the late 1980s and early 1990s, when the HIV epidemic was emerging, funding was reduced for tuberculosis treatment programmes in many industrialised countries, and the Soviet Union was breaking up,[7–9] tuberculosis incidence and mortality rose to become the sixth leading cause of death worldwide, and the eighth leading cause of disease burden worldwide in 1990.[10,11] In 1993, WHO declared tuberculosis a global health emergency, and in 1994, adopted a new approach to address tuberculosis called DOTS—originally an acronym for directly observed therapy, short course, but later used to identify the entire WHO-endorsed strategy including political commitment, drug supply chain management, and monitoring and assessment in addition to treatment using standard regimens.[12] However, worldwide tuberculosis incidence and mortality remained high throughout the 1990s. In 2000, the Millennium Development Goal 6: "combat HIV/AIDS, malaria and other diseases",[13] and the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002 helped to mobilise new funding to fight the tuberculosis epidemic.[13] However, rates of tuberculosis

Key messages

- Tuberculosis has its roots in underdevelopment, poverty, and social exclusion, but worldwide efforts to address tuberculosis during the past several decades have emphasised biomedical solutions.
- Progress against tuberculosis has been slow because of gaps in coverage of tuberculosis programmes and unmitigated risk factors for tuberculosis transmission and progression in low-income and middle-income countries, including overcrowding, indoor air pollution, malnutrition, diabetes mellitus, and tobacco and alcohol use.
- Social solutions for fighting tuberculosis, such as improved nutrition and improved housing conditions, were evidently major drivers of reductions in the burden of tuberculosis in the pre-chemotherapy era.
- The fight against tuberculosis should strengthen current biomedical solutions through new treatments, diagnostics, and service delivery models—and introduce approaches to combat the social drivers of the epidemic.
- Stopping tuberculosis needs a biosocial solution—one that integrates the social and biomedical approaches for sustainable development.

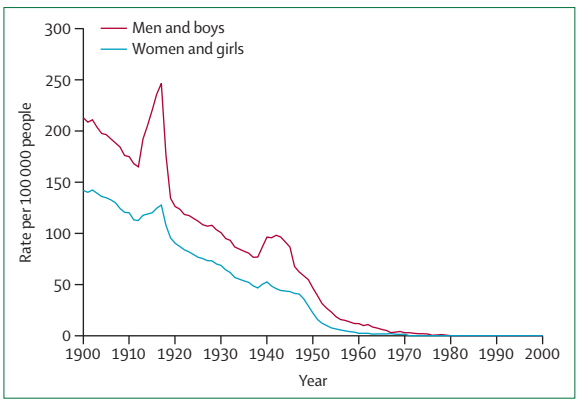

Figure 1: **Age-standardised tuberculosis deaths by sex, 1901–2000**
Data from England and Wales office of national statistics

Panel: Social reforms in 1934 for improving health and well being of workers and reducing the burden of tuberculosis in Chile

During the 1930s, Chile had the highest tuberculosis mortality burden of any country globally. Chile—fully aware of the social determinants for tuberculosis—devised a 14-point social reform to address the epidemic by reducing the country's underlying social inequalities and improving the living standards of the growing working class.[27]

This social reform shifted the focus of the tuberculosis response from the individual patient (eg, sanatoria and surgical interventions) to the larger social context. Despite initial successes in decreasing deaths from tuberculosis in Chile through the 1940s, social reform was quickly replaced by biomedical solutions after the introduction of chemotherapy in the 1950s.[27]

Chile's 14-point social reform to address the tuberculosis epidemic:

- Increase wages.
- Decrease the length of the average working day
- Eliminate overtime
- Regulate the working conditions of night workers
- Construct sound, affordable housing for workers
- Improve unsafe working environments in factories
- Enact legislation to protect worker's health and provide protection for those that are sick or injured
- Make unemployment insurance compulsory
- Carry out anti-alcohol campaigns
- Carry out anti-venereal disease campaigns
- Protect abandoned infants and children
- Promote sports. Construct stadiums, parks, and gardens
- Clean up all public places in which there are regular assemblages of people: theatres, churches, etc
- Reform Law 4054 (a law that addressed illness, disability, ageing, and death)

incidence worldwide decreased more slowly than those for both HIV and malaria; estimates of the pace of decline in tuberculosis incidence since 2000 range from less than 1% per year to around 1·5% per year with variations by country and region.[5]

Tuberculosis has its roots in underdevelopment, poverty, and social exclusion.[2] Slow progress in the fight against tuberculosis since the 1990s is due in part to gaps in coverage of DOTS programmes,[14] but more importantly because of the failure to address the social drivers of the epidemic such as crowded living conditions among increasingly urbanised populations,[15] indoor air pollution,[16,17] malnutrition,[18] diabetes mellitus,[19] tobacco,[20] alcohol,[21,22] and factors such as stigma and social isolation.[2,23] Despite tuberculosis having strong social determinants, efforts during the past several decades have focused almost exclusively on biomedical solutions. DOTS and the more recent WHO Stop TB Strategy largely emphasise delivery of tuberculosis services; supply interventions (eg, human resources, new diagnostics, and treatment for service provision) that are focused on test and treat strategies, and have paid insufficient heed to patient characteristics, the nature of their demands, and the broader context in which tuberculosis programmes are implemented.[3,4,24]

Sustainable development aims to meet "the needs of the present without compromising the ability of future generations to meet their own needs".[25,26] In practice, this statement means meeting basic needs (eg, food, shelter, and sanitation), while providing those in need with opportunities for a better quality of life through social, economic, and environmental action. Sustainable development promises to meet the needs of the poor and provide them an opportunity for a better future. The long history of tuberculosis and society's organised response to it can be instructive; social approaches to fighting tuberculosis, such as improved nutrition and social conditions, evidently contributed to reducing the burden of tuberculosis in the pre-chemotherapy era.[6]

The time has come to reconsider the fight against tuberculosis as a development imperative: a response that combines social approaches from the past with enhanced biomedical approaches that not only target morbidity and mortality from disease but also contribute to poverty alleviation and sustainable development.

The social approach of the past

Before the introduction of chemotherapy in the 1950s, solutions for tuberculosis were largely based on improving living standards or providing infected individuals with space, clean air, sunlight, rest, and proper nutrition, typically in sanatoria, which kept infected individuals isolated from the general public.[1] However, this method of treatment was expensive and largely inaccessible to poor populations that had disproportionally high rates of tuberculosis, prompting countries like Chile to introduce social approaches to managing tuberculosis (panel).

As working conditions in factories improved and public health interventions improving overall sanitation were implemented, the burden of tuberculosis began to decline in the rich and the poor.[1,6] Economic prosperity enabled people to feed themselves properly and live in more spacious housing. McKeown,[6] who recognised the effect of improved standards of living on tuberculosis by analysing historic death records in England and Wales, argued that an improved diet was the greatest contributor to the tuberculosis decline.

The era of biomedical interventions

After the discovery of streptomycin in 1944, various anti-tuberculosis drugs emerged in the 1950s, leading to an era of combination therapy for treating active tuberculosis. However, the risk factors for infection largely remained the same. From 1960 to 1999 the world population grew at an unprecedented rate, increasing from 3 billion to 6 billion.[28] Globalisation and new technologies increased the movement and spread of people, products, and information. Urbanisation accelerated, as people moved from rural areas to crowded cities in search of employment, but found all too often cramped living quarters, low wages, and poor working conditions, and struggled to afford adequate nutrition. In low-income and middle-income countries, absence of universal health coverage meant that many individuals seeking tuberculosis care could not afford health services.[29]

The biomedical approach to management of tuberculosis likewise evolved over time. In 1994, WHO launched DOTS, emphasising standardised case management of tuberculosis—to replace earlier approaches that involved many different medicines for lengthy periods. DOTS-Plus followed in 1999, with the addition of culture-based diagnosis, drug susceptibility tests, and treatment with second-line drugs to DOTS to address the emerging burden of multidrug-resistant (MDR) tuberculosis.[30,31] Persistent challenges in fighting tuberculosis prompted the launch of the Stop TB Strategy in 2006, which emphasised DOTS expansion, laboratory strengthening, tuberculosis with HIV, MDR tuberculosis, and the development of new methods.[24,32]

Although DOTS has undoubtedly contributed to the fight against tuberculosis since the 1990s, the biomedical approach has mainly emphasised supply-side interventions that rely heavily on functioning health systems. Yet tuberculosis remains deeply rooted in poverty and poor living conditions. Therein lies the difficulty: a biomedical approach to fighting tuberculosis addresses only part of the issue. A biosocial model that combines biomedical and social approaches is crucial and well overdue to win the battle against tuberculosis.

Rediscovering and enhancing the social approach

Tuberculosis is both a cause and result of poverty,[23] driven by social exclusion, including malnutrition, overcrowding, and indoor air pollution.[2,17] Tuberculosis risk is higher in individuals facing other illnesses such as HIV and diabetes, and those participating in behaviours that put their health at risk, such as smoking and excessive use of alcohol.[2] The risk factors associated with poverty not only increase susceptibility to active tuberculosis, but are also associated with greater difficulty in accessing care in health systems because of financial and geographical constraints, and provider prejudices.[30] Limited access to the health system delays diagnosis and treatment of tuberculosis, leading to longer periods of infectiousness and greater mortality risk (figure 2).

Tuberculosis is a driver of poverty. The disease leads to days off work and out of pocket health expenditures. Around 60% of the financial burden of tuberculosis comes from income loss when people are on treatment, and tuberculosis patients and their families spend an average of over half their yearly income on tuberculosis treatment.[30] The high cost of tuberculosis treatment makes it difficult for infected individuals to afford the full regimen of 6 or more months of therapy, impeding adherence and treatment success.[31] The result is a vicious tuberculosis–poverty cycle that cannot be broken by biomedical interventions alone (figure 2).

Our analysis strongly suggests substantial association between level of development (sanitation, improved water, access to electricity, urbanicity, malnutrition, and education), poverty, health system access, and tuberculosis (table). Social interventions aimed at addressing tuberculosis must therefore address these pathways specifically and collectively in the tuberculosis–poverty cycle (figure 2). Social interventions can effectively combine with biomedical approaches that incorporate new technologies and solutions. Interventions in nutrition, urban planning and built environment, working conditions, addiction recovery, and psychological services hold much promise.

Social protection for tuberculosis risk

Social protection and health interventions have been combined to effectively address infectious diseases, as well as maternal and child health.[33] Social protection spending that allocates resources to elderly and susceptible populations, unemployment protection, and housing, is strongly associated with lower tuberculosis case notifications, incidence, and mortality rates. A study of 21 European countries showed between 1995 and 2012, each increase in social protection spending of US$100 per

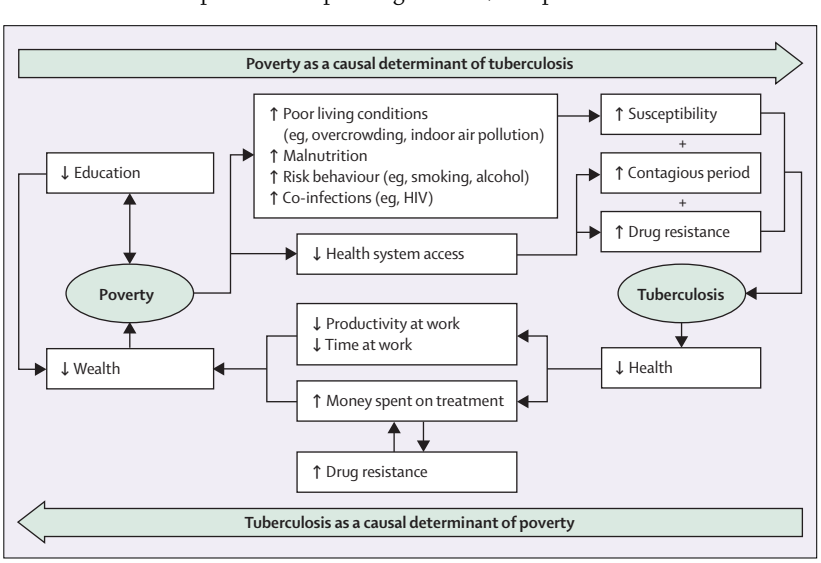

Figure 2: **The cycle of poverty and tuberculosis**

	Country-years of data	Tuberculosis case notification coefficient	p value
Access to sanitation (% population)	3754	−2·858	0·000
Improved water source access (% population)	3828	−1·373	0·000
Access to electricity (% population)	166	−1·993	0·000
Urban population (% population)	5638	−1·611	0·000
Malnutrition, height for age (% of children under 5 years)	2532	1·630	0·000
Primary school enrolment (% gross)	4676	−0·114	0·259
Out of pocket health expenditure (% of total expenditure)	3103	0·095	0·522
DPT immunisation coverage (% children 12–23 months old)	5214	−0·340	0·000
Poverty headcount, US$1·25 per day (% population)	1063	0·995	0·000
Poverty headcount, US$2·00 per day (% population)	1063	1·233	0·000
Income share held by highest 10%	1074	1·536	0·006

Country-years of data refers to the sum of the number of countries, multiplied by the number of years of data used for each country in the analysis. The tuberculosis case notification coefficient refers to the association between the case notification rate, the dependent variable in the regression analysis, and the WDI for poverty and deprivation used in the analysis as an explanatory variable. To explore the relation between poverty indicators and tuberculosis outcome in the tuberculosis–poverty cycle (figure 2) we used WHO tuberculosis case notifications (corrected for under-reporting using case detection rates estimated from country workshops) and World Bank WDIs. The WDI variables included in our analysis were intended to capture living conditions (eg, sanitation, improved water source access, access to electricity), nutrition, education, out of pocket health expenditure, and health system access (measured by DPT immunisation). We also included the World Bank's composite poverty indicators as a measure of income inequality. The analysis consisted of 11 separate mixed-effect regressions with random effect on country. Each regression quantified the association between the tuberculosis case notification rates with one of the WDI variables. Country random effects were included to control for dependence of reported observations over time within the same country, and calendar year was included as an additional independent variable to control for share of secular trends in tuberculosis case notification rates across countries. The regression results support the associations outlined in the tuberculosis–poverty cycle; all the regression coefficients are significant ($p<0·05$) with the exception of education and health-care expenditure, and all coefficients have the expected sign. Improved living conditions, health system access, and education have a negative relationship with tuberculosis case notification rates, and increased malnutrition, health expenditure, poverty, and inequality have a positive relationship with tuberculosis case notification rates. DPT=diphtheria, pertussis, and tetanus. WDI=World Development Indicator.

Table: **Tuberculosis case notification rates and World Development Indicators of poverty and deprivation**

person was associated with a 1·5% decrease in the number of tuberculosis case notifications, 1·7% decrease in estimated tuberculosis incidence, 2·7% decrease in the rate of non-HIV-related tuberculosis mortality, and 3·2% decrease in the rate of all-cause mortality.[34] In Peru, education, community mobilisation, psychosocial support, and poverty reduction programmes improved tuberculosis screening from 82% to 96% and treatment completion from 91% to 97%.[35]

Cash transfer schemes, both direct and indirect, and microfinance can help beneficiaries utilise health services and improve their health outcomes.[36] Increasing socioeconomic position, food security, and health-care access—all major protective factors for tuberculosis—can reduce the burden of both poverty and tuberculosis.[37,38] Direct cash transfer can increase tuberculosis treatment completion rates and decrease default rates; a study from China[38] showed that individuals that received cash transfers had 8% higher treatment completion rates and 21% lower default rates compared with controls.

Enhancing nutritional value

The association between nutrition and tuberculosis is well established.[18,39–42] Malnutrition and micronutrient deficiencies increase the risk of active tuberculosis, which in turn worsens malnutrition. Rapid urbanisation in low-income and middle-income countries is contributing to the nutritional transition that increases prevalence of diabetes, which amplifies tuberculosis risk and worsens outcomes in those infected with tuberculosis.[29]

In view of the connection between nutrition and tuberculosis, interventions such as nutritional counselling, food parcels, or high-energy oral nutritional supplements might enhance management of tuberculosis.[43] Micronutrient supplementation (eg, vitamin A-fortified sweet potatoes) or food aid for susceptible or transient populations are population-level interventions that would help improve nutritional status and probably reduce risk of tuberculosis.[41,44–46]

Sustainable agricultural interventions include individual agricultural support and incentives for the growth of diversified crops that are more economically viable in the long term than cash crops (which generate money more quickly) or use of high-yield seeds that are more robust to droughts, and are additional strategies that might shape agricultural practice in low-income and middle-income countries in a way that has a positive effect on tuberculosis and other health outcomes.[47]

Improving the built environment

Tuberculosis is spread via aerosol droplets from a patient with active disease. Overcrowding, indoor air pollution, and poor ventilation in homes, hospitals, and public transportation assist with the spread of the infection.[15,29,48] In low-income and middle-income countries, migration from rural to urban areas has led to an estimated 1 billion people living in overpopulated slum communities with poor infrastructure. From 1950 to 2014 the urban population grew from 746 million to 3·9 billion worldwide and by 2050 the UN projects that 66% of the world's population will live in urban areas[49,50] with implications for the struggle against tuberculosis. Rapid urbanisation calls for better built environment and improved housing design in urban areas,[51] the development of policies controlling urbanisation, urban regeneration and slum upgrading programmes, and design of public spaces and transportation systems to

reduce transmission risk at home or work, while commuting, and in public places.[52] Innovative technologies that improve local exhaust, general ventilation, room filtration, and ultraviolet air disinfection can promote natural ventilation and reduce transmission risk.[53] A study in rural South Africa[54] suggests that the risk of tuberculosis transmission decreased from 55·4% to 9·6% by opening windows and doors to increase airflow. Improving the built environment has benefits beyond direct health effects. Better roads, for example, improve access to schools, health services, and food markets, all of which can greatly reduce the burden of tuberculosis.[23]

Reducing occupational risk

Factory workers and labourers working in extractive industries such as mining are populations at greater risk for contracting tuberculosis.[55–57] In South Africa, the incidence of tuberculosis in miners is ten times higher than the general population and miners have 3·6 times greater odds of dying from tuberculosis compared with other workers in the region.[58,59] Miners, who are in poorly paid and demanding jobs, typically work and live in congregate settings with poor ventilation and indoor air pollution. Factory workers and labourers are often migrants, spreading the infection from work to their home towns. Good employment practices (including appropriate wages, reasonable hours, health insurance, and protection from injury), decent conditions at the workplace, and living accommodations aimed at the "Declaration on Tuberculosis in the Mining Sector" by the 15 heads of state belonging to the Southern African Development Community, can greatly reduce risk of tuberculosis in working populations, especially those working in extractive industries.[60]

Improving mental health

Mental illness often prevents individuals from properly caring for themselves, contributing to malnutrition and a weakened immune system, and increasing the risk of developing active tuberculosis infection.[61] Additionally, mental illness hampers adherence to medical care, which reduces the effectiveness of tuberculosis treatment. Mental illness carries stigma and is strongly associated with homelessness,[62] making it difficult for individuals to secure employment. The relation between mental health and tuberculosis likewise works in reverse—mental illness develops or is worsened by social isolation during treatment or can emerge as a side-effect of some treatment drug regimens, all compounded by the stigma for mental illness and tuberculosis alike.[61] Psychological services and housing assistance for tuberculosis patients can help improve health outcomes and provide these individuals with an opportunity to plan for their future.[63] Individuals with mental health disorders are at greater risk for addictive disorders, particularly alcohol misuse.[64] Alcohol use is a risk factor for the development of active tuberculosis; people who drink more than 40 g of alcohol a day are around three times more likely to develop tuberculosis compared with those who do not.[65]

Enhancing the biomedical approach

Although many of the technological components of the approach to preventing, diagnosing, and treating tuberculosis are decades old, there is renewed interest in developing new diagnostics, drugs, and treatment regimens.[66] As potential new products are developed, it remains essential to consider whether innovations in delivery of existing interventions can greatly reduce the burden of tuberculosis.

Developing effective vaccines

Limitations in available tuberculosis vaccines and treatment regimens have been well characterised.[67–73] The BCG vaccine was developed in the 1920s and estimates of its effectiveness have ranged from 80% protection to no benefit,[74,75] with particular concerns about duration of protection and therefore subsequent population-level effects in terms of preventing active tuberculosis in adolescents and adults. Although there continues to be high interest in developing new tuberculosis vaccines, development of a novel tuberculosis vaccine with high efficacy and persistent protection remains an elusive goal.[67–70]

Developing new treatment approaches

For individuals with latent *Mycobacterium tuberculosis* infection, preventive treatment can be effective in reducing the likelihood of progression to active disease.[76] Commonly recommended preventive therapy regimens have durations up to 9 months, but more recent studies have reported that shorter regimens can provide similar efficacy.[69,70] For active cases of tuberculosis, standard first-line treatment regimens continue to be based on drugs that were discovered 50 to 60 years ago, and there are various challenges associated with these therapies, including long treatment durations, toxic effects, interactions with antiretroviral drugs, and drug resistance in some settings.[71] Several new options are in various stages of development, with the potential to shorten regimens, yield high efficacy against MDR tuberculosis, and provide effectiveness against both latent and active tuberculosis.[72,73]

Improving tuberculosis detection

A rapid and accurate point-of-care diagnostic test for tuberculosis is still absent, therefore detection of tuberculosis is highly reliant on individuals accessing the health system.[77] Tuberculosis prevalence surveys[78] have shown that more than 50% of those with bacteriologically confirmed tuberculosis do not report the symptoms that often trigger disease investigation (eg, cough lasting

2–3 weeks). WHO reports that in 2013 more than 3 million tuberculosis cases worldwide were undiagnosed or were not notified. Case detection in many settings continues to rely largely on sputum smear microscopy, which has low sensitivity, especially in HIV-infected patients, and can cause delays in initiating treatment or loss to follow-up because immediate results are not available. However, alternative choices are becoming available, with potential to offer substantial improvements in test characteristics.[79] An important advance in tuberculosis diagnosis was the introduction of the Xpert MTB/RIF test, with greater sensitivity than sputum smear microscopy, leading to 45% increase in case detection in patients infected with HIV.[80,81] The experience with implementing Xpert substantiated the benefits of better case detection with new diagnostics, and highlighted the challenges in introducing new technologies in weak health systems with poor service coverage and access.[82]

Treatment with mobile telephone and health information technologies

Mobile telephone messaging is effectively used for managing self-management of long-term illnesses.[83] SMS text messaging improves treatment adherence and success of tuberculosis treatment.[84] A study done in South Africa[84] reported that tuberculosis cure rates were 2·3 times higher in patients that received SMS reminders for treatment compared with another group receiving standard DOTS treatment, whereas a study in Kenya[84] reported clinical attendance on scheduled days was 1·56 times higher in tuberculosis patients that received SMS reminders compared with those who did not. Electronic health records, including open source systems, mobile telephones, or personal digital assistants could be used to track and monitor patients with tuberculosis to improve health outcomes, as has been shown in Africa (Kenya, Rwanda, South Africa), Latin America (Peru), and Asia (Philippines).[85,86]

Combining biomedical and biosocial approaches

The enhanced social and biomedical approaches to tuberculosis care are not mutually exclusive, but can work together to address tuberculosis, especially in hard to reach and at-risk populations, and promote sustainable development. Although addressing the social determinants through a biosocial approach helps to reduce tuberculosis burden and improve outcomes, an enhanced biomedical approach could help reduce poverty and improve life chances of affected individuals and families, thereby improving their social determinants of health.

Tuberculosis places a disproportional burden on particular at-risk groups such as migrants and refugees,[46] individuals living in densely populated urban areas or living in areas of conflict and crisis,[15,29,45,48,52] children, and individuals with HIV/AIDS or diabetes. Understanding the context and developing context-specific solutions is important, as tuberculosis propagates through a series of local outbreaks, and the local conditions affect the success of tuberculosis programmes.[7,9,87]

Societal upheavals can displace large populations to new environments that lack food, adequate housing, and medical care, and increase the risk of mental illness, all of which are risk factors for tuberculosis. In the USA, the percentage of tuberculosis cases occurring in foreign-born people is over 60%.[88] As a result of the Ebola crisis, several tuberculosis programmes in Liberia, Guinea, and Sierra Leone were repurposed to address Ebola, leaving new and existing patients without treatment.[89]

The health, social, and economic effect of tuberculosis on children is significant; almost 1 million children have tuberculosis and 10 million children have been orphaned by tuberculosis. Children with tuberculosis are often in the hospital for extended periods of time, resulting in high treatment costs or parental lost time from work.[90,91] Individuals with HIV/AIDS or diabetes have suppressed immune systems that make them more susceptible to the development of active tuberculosis. A biosocial approach to tuberculosis needs to be uniquely tailored to address at-risk populations and ensure context specificity, taking into account cultural nuances and pervasive stigma.

Discussion

Sustainable development is predicated on meeting basic needs, eg, food, shelter, and sanitation, through social, economic, and environmental actions that are crucial for better quality of life and in the fight against tuberculosis.[25,26] A biosocial approach that expands the biomedical model and combines it with social, economic, and environmental actions is essential for the fight against tuberculosis.

Biomedical approaches alone have not achieved substantial decreases in tuberculosis burden. Although expanding universal health coverage will improve access to essential health services and protect from catastrophic health expenditures, it alone will not be sufficient to stop tuberculosis, as social determinants greatly affect the burden of tuberculosis, the fight against tuberculosis and the tuberculosis–poverty cycle. Evidence from Vietnam, Morocco, Pakistan, Sri Lanka, Myanmar, and India suggest that the benefits of improved diagnostics and treatment is offset by susceptibility to tuberculosis in at-risk populations.[92–94]

Although the thrust of this Series paper is on biosocial approaches, we also argue for enhancing biomedical approaches by strengthening health systems and scaling up innovations in tuberculosis detection and treatment. Combining biomedical and biosocial approaches will allow cooperation in detection and treatment of tuberculosis, and address comorbidities (such as HIV and diabetes) and risks through social protection and

improvements in nutrition, the built environment, occupational safety, and mental health.

Tuberculosis both causes and results from weak or failing health, education, and economic systems and development. Tuberculosis takes a heavy toll, not only on health and social services, but also on entire regions participating in the global economy, as tuberculosis predominantly affects the most economically active age group. An ailing workforce reduces productivity, lowers revenue, and weakens economies. By trapping people in a cycle of poverty and disease, tuberculosis slows national development and reduces competitiveness.[95] Combined biomedical and biosocial approaches are essential to mitigate the adverse effects of tuberculosis on individuals, households, and economies.

Implementing a biosocial approach to stop tuberculosis will be challenging, as the risk factors for tuberculosis will rise in the future. The number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030,[96] an estimated 70% of the world population could be living in urban areas by 2050,[97] the number of people living in slum dwellings will more than double to 2 billion in 2030 from 924 million in 2001, and worldwide migration will increase, with adverse risks for development.[98]

A proposed biosocial approach will align the tuberculosis response with sustainable development goals, extending the responsibility for national tuberculosis strategies beyond the health sector. Successful implementation of a biosocial model will need shared vision and collaboration across government sectors, professional groups, and civil society to mount integrated multisectoral action. Leadership and political commitment at the highest level of government is essential to include ministries of finance, development, housing, labour, education, and health to comprehensively address the social, environmental, nutritional, and occupational risk factors for tuberculosis and monitor progress.[60] Just as food security is often used to assess the success of the nutritional effect of poverty reduction strategies,[99] tuberculosis indicators could be used to monitor the effect of poverty reduction, urban planning, and development strategies on health. Accountability for the tuberculosis response across sectors could be further amplified through targets that relate to sectoral contributions to the tuberculosis response, such as the proportion of well aerated houses in public housing projects.

International institutions, such as the WHO, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Stop TB Partnership, UNAIDS, UNICEF, and the World Bank, have an important part to play, as they have done with the HIV response, to support country-led initiatives aimed at introducing the biosocial approach.

In addition to government and international organisations, the private sector, non-governmental organisations, and civil society will be instrumental in targeting social, economic, and environmental tuberculosis risks. For instance, companies employing workers who face high tuberculosis risks either because of the nature of the occupation or socioeconomic characteristics (eg, low wage or seasonal workers),[23,55–57] can contribute to biosocial approach through targeted prevention programmes. Similarly, labour unions and professional organisations, for example those in the mining, health-care, and building industries, could contribute to the fight against tuberculosis—for example, by making sure their members are aware of approaches that reduce tuberculosis transmission risks through better design and building of public housing, schools, social spaces, and hospitals.

Introduction and scaling up of innovations for tuberculosis prevention, detection, and treatment, although crucial, might be hindered because of low rewards for innovators and commercial investors,[100] inability of governments to invest in new health technologies while coverage of other cost-effective health interventions are low, and the difficulty for patients (who are typically the economically worst-off populations), to pay for novel tuberculosis interventions. Innovative approaches are needed to motivate the private and public sectors to invest in tuberculosis related research and development. Innovative financing that has been used to fund product development partnerships, provide advance market commitments, establish patent pools for new medicines, and encourage rapid uptake of new diagnostics, treatments, and care models to address health priority interventions would be instructive to create incentives for innovations to address tuberculosis.[101] However, an important lesson from large-scale implementation of Xpert in South Africa, is that technological innovations can fail to achieve their potential effect because of health system barriers to implementation, such as access to services, paucity of human resources, or inappropriate infrastructure.[81]

We have to learn from the past to create effective solutions for the future. Before the introduction of chemotherapy, the burden of tuberculosis was already decreasing as a result of social interventions and rising standards of living. Although biomedical interventions have helped to augment this decline, the improvements have been slow, and tuberculosis remains a major challenge worldwide. Stopping tuberculosis will need a renewed focus on multisectoral action to forge a biosocial response. The sustainable development agenda provides the opportunity to harness social, economic, and environmental actions to stop tuberculosis that has proven so difficult to defeat with biomedical approaches alone.

Contributors

RA conceived the idea for this manuscript. KFO and RA wrote the first draft and all authors revised it for important intellectual content. All authors approved the final version as submitted for publication.

Declaration of interests

The authors declare no conflicts of interest. Role of funding: TB was supported by the Wellcome Trust and the US National Institutes of Health (1P01AG041710–01). KFO, JAS, and RA have no external funding sources to disclose in relation to this Series paper. The funders had no

roles in the conception, preparation, review, approval, or submission of this manuscript.

Acknowledgments
We acknowledge Janice Hu for her contributions to draft revisions.

References

1 Dormandy T. The white death. New York: New York University Press, 2000.
2 Dye C, Lönnroth K, Jaramillo E, Williams BG, Raviglione M. Trends in tuberculosis incidence and their determinants in 134 countries. *Bull World Health Organ* 2009; **87:** 683–91.
3 World Health Organization. The five elements of DOTS. http://www.who.int/tb/dots/whatisdots/en/ (accessed June 3, 2015).
4 World Health Organization. The Stop TB Strategy. http://www.who.int/tb/strategy/stop_tb_strategy/en/ (accessed June 3, 2015).
5 Murray CJL, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384:** 1005–70.
6 McKeown T, Record RG. Reasons for the Decline of Mortality in England and Wales during the Nineteenth Century. *Popil Stud* 1962; **16:** 94–122.
7 Atun RA, Samyshkin YA, Drobniewski F, et al. Barriers to sustainable tuberculosis control in the Russian Federation health system. *Bull World Health Organ* 2005; **83:** 217–23.
8 Atun RA, Samyshkin Y, Drobniewski F, et al. Costs and outcomes of tuberculosis control in the Russian Federation: retrospective cohort analysis. *Health Policy Plan* 2006; **21:** 353–64.
9 Coker RJ, Atun RA, McKee M. Health-care system frailties and public health control of communicable disease on the European Union's new eastern border. *Lancet* 2004; **363:** 1389–92.
10 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2095–128.
11 Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2197–223.
12 World Health Organization. WHO declares tuberculosis a global emergency. 1993.
13 United Nations. The Millennium Development Goals Report 2012. http://www.un.org/millenniumgoals/pdf/MDG%20Report%202012.pdf (accessed June 3, 2015).
14 Dye C, Watt CJ, Bleed DM, Williams BG. What is the limit to case detection under the DOTS strategy for tuberculosis control? *Tuberculosis (Edinb)* 2003; **83:** 35–43.
15 Lienhardt C. From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis. *Epidemiol Rev* 2001; **23:** 288–301.
16 Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med* 2007; **4:** e20.
17 Lin HH, Suk CW, Lo HL, Huang RY, Enarson DA, Chiang CY. Indoor air pollution from solid fuel and tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2014; **18:** 613–21.
18 Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. *Int J Tuberc Lung Dis* 2004; **8:** 286–98.
19 Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis* 2009; **9:** 737–46.
20 Slama K, Chiang CY, Enarson DA, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2007; **11:** 1049–61.
21 Rehm J, Samokhvalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. *BMC Public Health* 2009; **9:** 450.
22 Coker R, McKee M, Atun R, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. *BMJ* 2006; **332:** 85–87.
23 Hargreaves JR, Boccia D, Evans CA, Adato M, Petticrew M, Porter JD. The social determinants of tuberculosis: from evidence to action. *Am J Public Health* 2011; **101:** 654–62.
24 World Health Organization. Stop TB Partnership: Operational Strategy 2013-2015. http://www.stoptb.org/assets/documents/about/OperationalStrategy2013-2015.pdf (accessed June 3, 2015).
25 United Nations. Our Common Future: The World Commission on Environment and Development. 1987. http://www.un-documents.net/ocf-02.htm (accessed June 3, 2015).
26 United Nations. Report of the United Nations Conference on Sustainable Development; Rio de Janeiro, Brazil; 20–22 June 2012. A/Conf.216/16. United Nations; New York, 2012. http://www.uncsd2012.org/content/documents/814UNCSD%20REPORT%20final%20revs.pdf (accessed July 23, 2015).
27 Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: systematic review. *BMJ* 2008; **336:** 484–87.
28 Lam D. How the world survived the population bomb: lessons from 50 years of extraordinary demographic history. *Demography* 2011; **48:** 1231–62.
29 McMichael AJ. The urban environment and health in a world of increasing globalization: issues for developing countries. *Bull World Health Organ* 2000; **78:** 1117–26.
30 Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. *Eur Respir J* 2014; **43:** 1763–75.
31 Dheda K, Gumbo T, Gandhi NR, et al. Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis. *Lancet Respir Med* 2014; **2:** 321–38.
32 World Health Organization. The Global Plan to Stop TB, 2011–2015. http://www.stoptb.org/assets/documents/global/plan/tb_globalplantostoptb2011-2015.pdf (accessed June 3, 2015).
33 de Andrade LOM, Pellegrini Filho A, Solar O, et al. Social determinants of health, universal health coverage, and sustainable development: case studies from Latin American countries. *Lancet* 2015; **385:** 1343–51.
34 Reeves A, Basu S, McKee M, Stuckler D, Sandgren A, Semenza J. Social protection and tuberculosis control in 21 European countries, 1995–2012: a cross-national statistical modelling analysis. *Lancet Infect Dis* 2014; **14:** 1105–12.
35 Rocha C, Montoya R, Zevallos K, et al. The Innovative Socio-economic Interventions Against Tuberculosis (ISIAT) project: an operational assessment. *Int J Tuberc Lung Dis* 2011; **15** (suppl 2)**:** S50–57.
36 Atun R, de Andrade LO, Almeida G, et al. Health-system reform and universal health coverage in Latin America. *Lancet* 2015; **385:** 1230–47.
37 Boccia D, Hargreaves J, Lönnroth K, et al. Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications. *Int J Tuberc Lung Dis* 2011; **15** (suppl 2)**:** S37–49.
38 Wei X, Zou G, Yin J, et al. Providing financial incentives to rural-to-urban tuberculosis migrants in Shanghai: an intervention study. *Infect Dis Poverty* 2012; **1:** 9.
39 Ramakrishnan CV, Rajendran K, Jacob PG, Fox W, Radhakrishna S. The role of diet in the treatment of pulmonary tuberculosis. An evaluation in a controlled chemotherapy study in home and sanatorium patients in South India. *Bull World Health Organ* 1961; **25:** 339–59.
40 Coker RJ, Dimitrova B, Drobniewski F, et al. Health system frailties in tuberculosis service provision in Russia: an analysis through the lens of formal nutritional support. *Public Health* 2005; **119:** 837–43.
41 Wilkinson RJ, Llewelyn M, Toossi Z, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. *Lancet* 2000; **355:** 618–21.
42 Podewils LJ, Holtz T, Riekstina V, et al. Impact of malnutrition on clinical presentation, clinical course, and mortality in MDR-TB patients. *Epidemiol Infect* 2011; **139:** 113–20.
43 Sinclair D, Abba K, Grobler K, Sudarsanam T. Nutritional supplements for people being treated for active tuberculosis. The Cochrane Collaboration, 2011. http://fr.cmamforum.org/Pool/Resources/Nutr-supplements-and-active-TB-Cochrane-review-2011.pdf (accessed June 3, 2015).
44 Shah R. USAID Frontiers in Development. USAID, 2012. http://www.usaid.gov/sites/default/files/documents/1868/USAID_eBook.pdf (accessed June 3, 2015).

45 Rodger AJ, Toole M, Lalnuntluangi B, Muana V, Deutschmann P. DOTS-based tuberculosis treatment and control during civil conflict and an HIV epidemic, Churachandpur District, India. *Bull World Health Organ* 2002; **80:** 451–56.

46 Minetti A, Camelique O, Hsa Thaw K, et al. Tuberculosis treatment in a refugee and migrant population: 20 years of experience on the Thai-Burmese border. *Int J Tuberc Lung Dis* 2010; **14:** 1589–95.

47 Masters WA, Webb P, Griffiths JK, Deckelbaum RJ. Agriculture, nutrition, and health in global development: typology and metrics for integrated interventions and research. *Ann N Y Acad Sci* 2014; **1331:** 258–69.

48 Hasan R. Drug resistant tuberculosis: Challenges of urbanization. *Int J Mycobacteriology* 2014; **3:** 79–81.

49 Cordaid. UN-Habitat: number of slum dwellers grows to 863 million. 2014. https://www.cordaid.org/en/news/un-habitat-number-slum-dwellers-grows-863-million/ (accessed June 3, 2015).

50 United Nations Department of Economic and Social Affairs. World Urbanization Prospects, 2014 Revision. 2014. http://esa.un.org/unpd/wup/Highlights/WUP2014-Highlights.pdf (accessed June 3, 2015).

51 Wagstaff K. Architecture latest tool in fight against malaria, tuberculosis in slums. *The Utopianist*, 2011. http://utopianist.com/2011/04/non-profit-hopes-to-fight-malaria-tuberculosis-in-slums-with-architecture/ (accessed June 3, 2015).

52 Northridge ME, Sclar E. A joint urban planning and public health framework: contributions to health impact assessment. *Am J Public Health* 2003; **93:** 118–21.

53 Nardell EA. Fans, filters, or rays? Pros and cons of the current environmental tuberculosis control technologies. *Infect Control Hosp Epidemiol* 1993; **14:** 681–85.

54 Lygizos M, Shenoi SV, Brooks RP, et al. Natural ventilation reduces high TB transmission risk in traditional homes in rural KwaZulu-Natal, South Africa. *BMC Infect Dis* 2013; **13:** 300.

55 Zafar Ullah AN, Huque R, Husain A, Akter S, Akter H, Newell JN. Tuberculosis in the workplace: developing partnerships with the garment industries in Bangladesh. *Int J Tuberc Lung Dis* 2012; **16:** 1637–42.

56 Hanifa Y, Grant AD, Lewis J, Corbett EL, Fielding K, Churchyard G. Prevalence of latent tuberculosis infection among gold miners in South Africa. *Int J Tuberc Lung Dis* 2009; **13:** 39–46.

57 Stuckler D, Basu S, McKee M, Lurie M. Mining and risk of tuberculosis in sub-Saharan Africa. *Am J Public Health* 2011; **101:** 524–30.

58 Reid PJ, Sluis-Cremer GK. Mortality of white South African gold miners. *Occup Environ Med* 1996; **53:** 11–16.

59 Government of South Africa. Tuberculosis Strategic Plan for South Africa, 2007–2011. http://www.tbonline.info/archive/document/7/ (accessed June 3, 2015).

60 Southern African Development Community. Declaration on Tuberculosis in the Mining Sector. 2012. http://www.stoptb.org/assets/documents/news/Declaration%20on%20Tuberculosis%20in%20the%20Mining%20Sector2012English.pdf (accessed July 23, 2015).

61 Doherty AM, Kelly J, McDonald C, O'Dywer AM, Keane J, Cooney J. A review of the interplay between tuberculosis and mental health. *Gen Hosp Psychiatry* 2013; **35:** 398–406.

62 Fischer PJ, Breakey WR. Homelessness and mental health: an overview. *Int J Ment Health* 1985; **14:** 6–41.

63 Pachi A, Bratis D, Moussas G, Tselebis A. Psychiatric morbidity and other factors affecting treatment adherence in pulmonary tuberculosis patients. *Tuberc Res Treat* 2013; **2013:** e489865.

64 Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990; **264:** 2511–18.

65 Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis—a systematic review. *BMC Public Health* 2008; **8:** 289.

66 Yasinskaya Y, Plikaytis B, Sizemore C, Sacks L. Advancing the development of diagnostic tests and biomarkers for tuberculosis. *Int J Tuberc Lung Dis* 2011; **15:** 985–87.

67 Weiner J 3rd, Kaufmann SHE. Recent advances towards tuberculosis control: vaccines and biomarkers. *J Intern Med* 2014; **275:** 467–80.

68 da Costa C, Walker B, Bonavia A. Tuberculosis vaccines—state of the art, and novel approaches to vaccine development. *Int J Infect Dis* 2015; **32:** 5–12.

69 Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med* 2011; **365:** 11–20.

70 Villarino ME, Scott NA, Weis SE, et al, and the International Maternal Pediatric and Adolescents AIDS Clinical Trials Group, and the Tuberculosis Trials Consortium. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr* 2015; **169:** 247–55.

71 Zumla AI, Gillespie SH, Hoelscher M, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *Lancet Infect Dis* 2014; **14:** 327–40.

72 Zumla A, Nahid P, Cole ST. Advances in the development of new tuberculosis drugs and treatment regimens. *Nat Rev Drug Discov* 2013; **12:** 388–404.

73 Lienhardt C, Vernon A, Raviglione MC. New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes. *Curr Opin Pulm Med* 2010; **16:** 186–93.

74 Kernodle DS. Decrease in the effectiveness of Bacille Calmette-Guérin vaccine against pulmonary tuberculosis: a consequence of increased immune suppression by microbial antioxidants, not overattenuation. *Clin Infect Dis* 2010; **51:** 177–84.

75 Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guérin vaccination against tuberculosis. *Health Technol Assess* 2013; **17:** 1–372, v–vi.

76 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00323-2.

77 McNerney R, Maeurer M, Abubakar I, et al. Tuberculosis diagnostics and biomarkers: needs, challenges, recent advances, and opportunities. *J Infect Dis* 2012; **205** (suppl 2)**:** S147–58.

78 World Health Organization. Systematic screening for active tuberculosis; Principles and reccomendations. 2013. http://www.who.int/tb/publications/Final_TB_Screening_guidelines.pdf (accessed June 3, 2015).

79 Pai M, Schito M. Tuberculosis diagnostics in 2015: landscape, priorities, needs, and prospects. *J Infect Dis* 2015; **211** (suppl 2)**:** S21–28.

80 Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010; **363:** 1005–15.

81 Lawn SD, Kerkhoff AD, Vogt M, Ghebrekristos Y, Whitelaw A, Wood R. Characteristics and early outcomes of patients with Xpert MTB/RIF-negative pulmonary tuberculosis diagnosed during screening before antiretroviral therapy. *Clin Infect Dis* 2012; **54:** 1071–79.

82 Creswell J, Codlin AJ, Andre E, et al. Results from early programmatic implementation of Xpert MTB/RIF testing in nine countries. *BMC Infect Dis* 2014; **14:** 2.

83 De Jongh T, Gurol-Urganci I, Vlasta Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging telemedicine for facilitating self management of long-term illnesses. *Cochrane Database Syst Rev* 2012; **12:** CD007459.

84 Nglazi MD, Bekker LG, Wood R, Hussey GD, Wiysonge CS. Mobile phone text messaging for promoting adherence to anti-tuberculosis treatment: a systematic review. *BMC Infect Dis* 2013; **13:** 566.

85 Fraser HS, Allen C, Bailey C, Douglas G, Shin S, Blaya J. Information systems for patient follow-up and chronic management of HIV and tuberculosis: a life-saving technology in resource-poor areas. *J Med Internet Res* 2007; **9:** e29.

86 Fraser H, Choi SS, Galipot M, Jazayeri D, Mangubat N. Successful transfer of a Web-based TB medical record from Peru to the Philippines. *AMIA Annu Symp Proc* 2006; **2006:** 924.

87 Atun R, Olynik I. Resistance to implementing policy change: the case of Ukraine. *Bull World Health Organ* 2008; **86:** 147–54.

88 CDC. Executive Commentary—Reported Tuberculosis in the United States. 2011. http://www.cdc.gov/tb/statistics/reports/2011/executivecommentary.htm (accessed June 3, 2015).

89 Edelstein M, Angelides P, Heymann DL. Ebola: the challenging road to recovery. *Lancet* 2015; **385:** 2234–35.

90 Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet* 2014; **383:** 1572–79.

91 World Health Organization. No more crying, no more dying: towards zero TB deaths in children. 2012. http://www.who.int/tb/ChildhoodTB_report_singles.pdf (accessed July 22, 2015).

92 Walley JD, Khan MA, Newell JN, Khan MH. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. *Lancet* 2001; **357:** 664–69.

93 Vree M, Bui DD, Dinh NS, Nguyen VC, Borgdorff MW, Cobelens FG. Tuberculosis trends, Vietnam. *Emerg Infect Dis* 2007; **13:** 796–97.

94 Dye C, Ottmani S, Laasri L, Bencheikh N. The decline of tuberculosis epidemics under chemotherapy: a case study in Morocco. *Int J Tuberc Lung Dis* 2007; **11:** 1225–31.

95 World Health Organization. Tuberculosis and sustainable development. WHO/CDS/STB/2000.4. http://apps.who.int/iris/bitstream/10665/66239/1/WHO_CDS_STB_2000.4.pdf?ua=1 (accessed July 22, 2015).

96 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27:** 1047–53.

97 UN-Habitat. State of the World's Cities 2012/2013, Prosperity of Cities. 2013. https://sustainabledevelopment.un.org/content/documents/745habitat.pdf (accessed July 23, 2015).

98 UN-Habitat. The challenge of slums—global report on human settlements. 2003. http://www.unhabitat.org/pmss/getElectronicVersion.aspx?nr=1156&alt=1%E2%80%8E (accessed July 23, 2015).

99 McMichael P, Schneider M. Food security politics and the Millennium Development Goals. *Third World Q* 2011; **32:** 119–39.

100 Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and a public-health policy failure. *Lancet* 2002; **359:** 2188–94.

101 Atun R, Knaul FM, Akachi Y, Frenk J. Innovative financing for health: what is truly innovative? *Lancet* 2012; **380:** 2044–49.