Household contact investigation to improve tuberculosis control

New measures to contain the global tuberculosis epidemic are urgently needed, since efforts have not achieved the desired effect in high-prevalence settings.[1] The launch of the End TB Strategy in 2015, followed by the United Nations General Assembly high level meeting on tuberculosis in September, 2018, committed the global community to pursuing ambitious global tuberculosis reduction targets.[2] However, more than 3 million people with the disease remain undiagnosed each year, and major gaps in case detection must be bridged if substantial progress is to be made.[1] Traditional passive case-finding approaches, even when optimised, will not make a considerable difference.[3] Without a substantial expansion of current efforts to detect and prevent tuberculosis, very little progress can be expected.

Enhanced tuberculosis screening strategies, coupled with preventive therapy to reduce disease progression among infected individuals, are crucial to transforming the trajectory of the epidemic.[1,4] In particularly high-incidence areas, such strategies can be applied to the general population, as was done with great effect in studies done among the Inuit population in Alaska.[5] However, interventions can also focus on specific risk groups, where a combination of active case-finding and preventive therapy provide strong synergy—one intervention reducing tuberculosis prevalence and transmission, the other treating latent tuberculosis infection to reduce future incidence. This approach is routinely followed in low-burden settings, where close contacts of patients with pulmonary disease are routinely screened, and treated, for disease and infection.

Household contact investigation offers health practitioners the opportunity to detect and treat coprevalent disease in a high-risk population, while also identifying close contacts who may benefit from preventive therapy, particularly vulnerable young children at a high risk of tuberculosis-related mortality (table).[6] Detection of early tuberculosis disease in contacts will also benefit their communities, through a reduction in *Mycobacterium tuberculosis* transmission. These contacts are accessible by health services, with the index case being the point of entry into the household. Household contacts are also motivated to undertake screening, given the first-hand experience of tuberculosis disease in their family.

	Rationale	Likely benefits	Perceived challenges
General population			
Screening the entire community in a defined geographical area	Treatment of all incident cases reduces ongoing transmission; LTBI treatment reduces the pool of latent infection from which future cases might arise	Early treatment of prevalent tuberculosis cases might improve outcomes and reduce mortality; reduction in overall transmission within the community	Major logistical efforts required, with substantial expense to screen the population for tuberculosis and LTBI; reluctance of healthy people to comply with treatment, and difficulty ensuring adherence; risk of drug-related toxicity for community members, with difficulty in monitoring for adverse events at a population scale; the durability of effect is uncertain, with transmission to recommence if no intervention occurs in surrounding areas
High-risk populations			
Household contacts	A well defined high-risk population; readily accessible to the health system	Early disease diagnosis reduces transmission and mortality; a potential synergy between treatment support and household screening activities	Scarce human and financial resources in health systems; institutional barriers to scale-up contact screening and LTBI treatment; challenges monitoring for toxicity and treatment adherence with preventive therapy
People living with HIV	A well defined high-risk population; readily accessible to the health system, if already in HIV care	LTBI treatment reduces incident disease and mortality; early diagnosis prevents severe disease and mortality; regular health care contact facilitates screening; LTBI treatment and early diagnosis reduces transmission within HIV care facilities and the general community	Drug interactions between antiretroviral therapy and rifamycins might complicate use of short-course LTBI treatment; people living with HIV remain at an ongoing risk of tuberculosis, so preventive therapy on one occasion will not provide lasting protection; HIV-related stigma remains a major barrier in many settings, reducing early HIV diagnosis and health care access
Prisons and other institutional amplifiers	A well-defined high-risk population; readily accessible to the health system	Improved health outcomes for patients; reduction of transmission in prisons and after release from prison	Scarce health resources to support LTBI diagnosis and treatment in prisons; stigma of incarceration and reluctance to provide optimal medical care to prisoners; challenges ensuring continuity of care after discharge from prison

LTBI=latent tuberculosis infection.

Table: **The rationale for combined use of active case-finding and preventive therapy**

The global push to expand active tuberculosis case finding follows prevalence survey data, which demonstrate that up to half of people with confirmed pulmonary tuberculosis do not have typical symptoms, and might fail to present to clinical services of their own accord.[7] Consequently, many people with tuberculosis only seek care after developing advanced disease. This observation is consistent with a growing understanding of the natural history of tuberculosis, which spans a spectrum from asymptomatic infection through to infectious disease. Individuals with subclinical tuberculosis might have detectable, replicating bacteria that can be transmitted to others, but do not have sufficient subjective symptoms to seek care.[8] The initial success of passive case-finding programmes might have created selective pressure favouring the emergence of strains that induce subclinical disease states.

Randomised trial data from Vietnam[9] indicate that active case-finding among household contacts more than doubles case detection over a 2-year period, compared with standard passive case finding. The notification rate of bacteriologically confirmed tuberculosis was increased six times. A substantial proportion of cases were only detected after baseline screening, indicating that a single screening intervention, without the provision of preventive therapy to non-diseased infected contacts, will miss the opportunity to prevent a substantial proportion of incident disease. However, in endemic settings, a high proportion of household contacts who develop tuberculosis might not have contracted their infection from the identified index case, emphasising the potential benefit of expanded screening beyond the immediate household.

Infected household contacts benefit from preventive therapy, with randomised trials showing a 60–90% decrease in incident tuberculosis in the period after exposure.[10] Rifamycin-based regimens (12 weekly doses of isoniazid or rifapentine or 4 months of daily rifampicin) have equivalent effectiveness to traditional 6–9-month isoniazid monotherapy regimens with less toxicity and a reduced duration of therapy.[11] Given the benefits of these regimens, recent WHO guidelines recommend preventive therapy for many high-risk populations with documented infection, such as household contacts (including older adults), people living with HIV, and immunosuppressed individuals.[12] These recommendations were based upon perceived individual benefit, recognising that around 10% of infected contacts will develop the disease at some time in their lives.

However, few high-prevalence countries have successfully scaled-up preventive therapy for high-risk populations. The gap between the WHO recommendations to implement preventive regimens, and current practice remains wide. Resource limitations and a dearth of appreciation of the benefits of preventive therapy and of access to tuberculin skin testing are some of the barriers to the programmatic expansion of preventive therapy. This relates in part to scarce resources, with some programmes struggling to deliver routine care for tuberculosis disease, and deficient in public health financing to support screening of high-risk populations. However, a growing body of evidence indicates that contact investigation and preventive therapy is likely to be cost-effective in most settings.[13]

Modelling studies suggest that household contact investigation alone is likely to have a relatively modest effect upon the population-wide epidemiology.[14] More ambitious screening strategies might be required to alter the trajectory of the tuberculosis epidemic. Community-wide screening for active disease in high-prevalence settings remains a promising strategy to reduce disease prevalence in a short period, despite mixed evidence of effectiveness.[15,16] Even more ambitious programmes to screen for and treat latent tuberculosis infection in the general community could have an even larger effect upon disease incidence.

In conclusion, strong evidence now exists to support the scale-up of active case-finding for tuberculosis, and treatment of latent tuberculosis infection, among household contacts in high-burden settings. Further research will be essential in bridging the current policy-practice gaps, optimising the reach of these interventions, and evaluating the effectiveness of widespread active case-finding and prevention in the greater community.

Greg J Fox, Peter J Dodd, Ben J Marais
Centre for Research Excellence in Tuberculosis and the Marie Bashir Institute for Infectious Diseases and Biosecurity, The University of Sydney, Sydney NSW 2006, Australia (GJF, BJM); and School of Health and Related Research, University of Sheffield, Sheffield, UK (PJD).
greg.fox@sydney.edu.au

We declare no competing interests.

1 WHO. 2018 global tuberculosis report. Geneva: World Health Organization, 2018.

2 Marais B, Zumla A. Advancing global tuberculosis control after the UNGA-HLM. *Lancet* 2018; **392:** 1096–97.

3 Dowdy DW, Basu S, Andrews JR. Is passive diagnosis enough? The impact of subclinical disease on diagnostic strategies for tuberculosis. *Am J Respir Crit Care Med* 2013; **187:** 543–51.

4 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; **386:** 2344–53.

5 Comstock GW, Ferebee SH, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. *Am Rev Respir Dis* 1967; **95:** 935–43.

6 Dodd P, Yuen CM, Becerra MC, et al. Potential effect of household contact management on childhood tuberculosis: a mathematical modelling study . *Lancet Glob Health* 2018; **6:** e1329–38.

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

8 Drain PK, Bajema KL, Dowdy D, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clin Microbiol Rev;* 2018; **31:** e00021-18.

9 Fox GJ, Nhung NV, Sy DN, et al. Household-contact investigation for the detection of tuberculosis in Vietnam. *N Engl J Med* 2018; **378:** 221–29.

10 Lobue P, Menzies D. Treatment of latent tuberculosis infection: an update. *Respirology* 2010; **15:** 603–22.

11 Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med* 2018; **379:** 440–53.

12 WHO. Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. Geneva: World Health Organization, 2018.

13 Johnson KT, Churchyard GJ, Sohn H, Dowdy DW. Cost-effectiveness of preventive therapy for tuberculosis with isoniazid and rifapentine versus isoniazid alone in high-burden settings. *Clin Infect Dis* 2018; **67:** 1072–78.

14 Kasaie P, Andrews JR, Kelton WD, Dowdy DW. Timing of tuberculosis transmission and the impact of household contact tracing: an agent-based simulation model. *Am J Respir Crit Care Med* 2014; **189:** 845–52.

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

16 Corbett EL, Bandason T, Duong T, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet* 2010; **376:** 1244–53.