

Tuberculosis active case-finding: looking for cases in all the right places?



WHO estimated that in 2019, 2.9 million people with active, presumably contagious tuberculosis were not diagnosed and probably not treated.¹ This estimate is corroborated by national tuberculosis prevalence surveys done within the past two decades in Africa and Asia that revealed substantial gaps in tuberculosis detection.² Finding the so-called missing millions through active tuberculosis case-finding has been advocated because of the potential benefits to individuals through access to treatment that would reduce morbidity and prevent mortality, and to populations by reducing transmission and preventing secondary cases.^{3,4} However, the benefits of active case-finding for populations or individuals remain controversial,^{3,4} particularly because WHO recommended discontinuation of population-wide active case-finding activities in 1974,⁵ due to declining yield and evidence that most smear-positive cases had rapid clinical progression and were detected passively rather than through periodic active case-finding.^{3,6}

In *The Lancet Public Health*, Rachael Burke and colleagues⁷ report findings of a systematic review summarising the evidence for population-level effectiveness of active case-finding for tuberculosis. The authors appraised 36 studies published between Jan 1, 1980, and April 13, 2020, of adult populations from 16 countries that were exposed to different active case-finding interventions. Studies of health-care workers or household contacts were excluded. Three outcomes were evaluated: case notification rates (which were expected to increase³), prevalence of active tuberculosis, and tuberculosis infection among young children as an indicator of transmission (both expected to decrease in the long term).³

Case notification rates were assessed in 28 studies, of which six were randomised trials. Most reported higher notification rates in the intervention group than the control group. However, enthusiasm generated by this finding should be tempered by the fact that this is the minimum expected result, because active case-finding aims to diagnose tuberculosis that has been missed by routine practice,³ and the included studies had several important methodological limitations. Most importantly, the duration of this benefit was not reported, meaning that the increase could have been temporary, and could

have simply reflected the greater sensitivity of the tests used in many studies compared with those used in routine services (eg, culture or GeneXpert vs acid-fast bacillus smear). The harms resulting from false positive results were not assessed in this systematic review. Study-level heterogeneity related to differences in populations, interventions, and screening methods precluded pooling results and, finally, only four studies were judged to be at low risk of bias.

Tuberculosis prevalence was evaluated in six uncontrolled before-after studies, in one before-after analysis of a cluster-randomised trial (DETECTB⁸), and in two cluster-randomised controlled trials (ACT3 and ZAMSTAR^{9,10}). Prevalence decreased in five of the seven before-after analyses but all of these studies were judged to be at high risk of bias due to confounding by concomitant interventions, and trends. The two controlled trials were judged to be at low risk of bias but the findings were contradictory; active case-finding resulted in significantly lower tuberculosis prevalence in the ACT3 study but not in the ZAMSTAR study. The likely epidemiological effect is even less clear. Most studies have reported that people detected through active case-finding will be less likely to have positive results on acid-fast bacillus sputum smear, or cavitation on chest x-ray.⁴ Proponents of active case-finding interpret this as evidence of earlier detection but studies from the pre-antibiotic era, as reviewed by Rieder,⁶ suggest that this reflects longer survival of people with less extensive tuberculosis. We suggest that mass active case-finding does not detect individuals at an earlier stage of disease, but rather an entirely different group of people with relatively stable disease who survive for many years; if they are less contagious, active case-finding will have little effect on transmission.⁶

Tuberculosis infection in young children was measured in only two studies, ZAMSTAR and ACT3. Neither found any impact of active case-finding on this important measure, as an indicator of recent transmission.

In summary, this systematic review suggests that active case-finding interventions might increase case notification rates for an unknown duration, and it provides inconsistent evidence that active case-finding can reduce prevalence in populations. Two well designed trials suggest

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that active case-finding has no impact on community transmission. A further major knowledge gap is the costs of the active case-finding interventions, which were not reported in any of the primary studies. The interventions described in these studies were often complex, and likely to be costly, raising questions about their cost-effectiveness and affordability.

How can we find the missing millions? First, within local health systems with reinforced capacity to diagnose and treat active tuberculosis. One consistent finding of national tuberculosis surveys in the past two decades is that many people with undiagnosed active tuberculosis had previously sought medical attention but had not been diagnosed, or had not sought medical attention due to geographical or financial barriers.² Second, we suggest expansion of active case-finding interventions in household contacts, as recommended by WHO in 2013.¹¹ A systematic review of studies in low-income and middle-income countries reported prevalence among household (or close) contacts of active tuberculosis of 4.5% (95% CI 4.3–4.8) and of latent tuberculosis of 51.4% (50.6–52.2).¹¹ Moreover, household contacts are easily identified at the time of diagnosis of the index case, and are more likely to have early disease that will progress rapidly. However, the population impact of large-scale active case-finding programmes among household or other close contacts has not been established. Hence, we suggest further studies to define the long-term benefits, risks, and costs of such a programme.

We declare no competing interests.

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Edgar Ortiz-Brizuela, *Dick Menzies
dick.menzies@mcgill.ca

Montreal Chest Institute and McGill International TB Centre (EO-B, DM), Department of Epidemiology, Biostatistics and Occupational Health (DM), and Department of Medicine (DM), McGill University, Montreal, QC H4A 3J5, Canada; Department of Medicine, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico (EO-B)

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For the 2013 WHO report on active case-finding see <https://www.ncbi.nlm.nih.gov/books/NBK294083>