INT J TUBERC LUNG DIS 17(9):1125–1138

http://dx.doi.org/10.5588/ijtld.13.0117

STATE OF THE ART SERIES
Active case finding/screening
Series Editor: Martien Borgdorff *Guest Editor*: Knut Lönnroth
NUMBER 5 IN THE SERIES

Tuberculosis screening in high human immunodeficiency virus prevalence settings: turning promise into reality

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SUMMARY

Twenty years of sky-high tuberculosis (TB) incidence rates and high TB mortality in high human immunodeficiency virus (HIV) prevalence countries have so far not been matched by the same magnitude or breadth of responses as seen in malaria or HIV programmes. Instead, recommendations have been narrowly focused on people presenting to health facilities for investigation of TB symptoms, or for HIV testing and care. However, despite the recent major investment and scale-up of TB and HIV services, undiagnosed TB remains highly prevalent at community level, implying that diagnosis of TB remains slow and incomplete. This maintains high transmission rates and exposes people living with HIV to high rates of morbidity and mortality.

More intensive use of TB screening, with broader definitions of target populations, expanded indications for screening both inside and outside of health facilities, and appropriate selection of new diagnostic tools, offers the prospect of rapidly improving population-level control of TB. Diagnostic accuracy of suitable (high throughput) algorithms remains the major barrier to realising this goal.

In the present study, we review the evidence available to guide expanded TB screening in HIV-prevalent settings, ideally through combined TB-HIV interventions that provide screening for both TB and HIV, and maximise entry to HIV and TB care and prevention. Ideally, we would systematically test, treat and prevent TB and HIV comprehensively, offering both TB and HIV screening to all health facility attendees, TB households and all adults in the highest risk communities. However, we are still held back by inadequate diagnostics, financing and paucity of population-impact data. Relevant contemporary research showing the high need for potential gains, and pitfalls from expanded and intensified TB screening in high HIV prevalence settings are discussed in this review.

KEY WORDS: tuberculosis; screening; case finding; HIV; disease control; community; health facility; prevention

Previous articles in the series **Editorial:** Borgdorff M W, Yew W-W, Marks G. Active tuberculosis case finding: why, when and how? Int J Tuberc Lung Dis 2013; 17(3): 285. **No. 1:** Lönnroth K, Corbett E, Golub J, Godfrey-Faussett P, Uplekar M, Weil D, Raviglione M. Systematic screening for active tuberculosis: rationale, definitions and key considerations. Int J Tuberc Lung Dis 2013; 17(3): 289–298. **No. 2:** Kranzer K, Afnan-Holmes H, Tomlin K, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. Int J Tuberc Lung Dis 2013; 17(4): 432–446. **No. 3:** Zenner D, Southern J, van Hest R, deVries G, Stagg H R, Antoine D, Abubakar I. Active case finding for tuberculosis among high-risk groups in low-incidence countries. Int J Tuberc Lung Dis 2013; 17(5): 573–582. **No. 4:** Golub J E, Dowdy D W. Screening for active tuberculosis: methodological challenges in implementation and evaluation. Int J Tuberc Lung Dis 2013; 17(7): 856-865.

IN HIGH human immunodeficiency virus (HIV) prevalence settings, population-level tuberculosis (TB) incidence increased in parallel with adult HIV prevalence in the 1990s and remains extremely high, with over 1% of adults diagnosed with TB each year in many Southern African towns.[1] Outbreaks of multi- and extensively drug-resistant TB (XDR-TB) have been generated in HIV care clinics, and then spread into general communities.[2,3] Autopsy studies show that TB is the single biggest killer of people living with HIV (PLHIV), being the cause in 32% to 45% of HIV-related deaths[4] and with a high proportion of

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Article submitted 18 February 2013. Final version accepted 13 June 2013.

[A version in French of this article is available from the Editorial Office in Paris and from the Union website www.theunion.org]

fatal cases undiagnosed in life.[4,5] Of the estimated 430 000 TB-related deaths among PLHIV during 2011, 79% were in Africa. These stark facts demonstrate the urgent need to strengthen TB prevention and care services using all available approaches, including more ambitious TB screening strategies.

TB screening is the first step in both anti-tuberculosis treatment and TB prevention pathways, and has an integral place in routine HIV care and infection control. Key potential entry points for TB screening are illustrated in Figure 1. TB screening can be conducted at the clinic, facility or community level (Table 1),[6–12] and can be initiated by TB programmes, infection control services in general facilities or HIV testing and care services. Developing and scaling up effective TB screening strategies will ideally follow the same kind of combined approach that has proved effective for HIV testing and counselling (HTC). Diagnostic testing, provider-initiated HTC and promotion of client-initiated testing through 'know your status' campaigns in facility- and community-based testing services have led to remarkable progress in universal access to HIV testing and care, with both HIV and TB incidence rates falling regionally.[13] Early HIV detection and antiretroviral therapy (ART) are increasingly being recognised as critical for HIV prevention. Recommendations in the United States are moving towards annual HIV screening for all adults, while in Africa increasing emphasis is placed on home-based testing, due to much higher acceptability and uptake than other modalities.[14]

These ambitious targets and achievements contrast with a more conservative approach to TB screening. Although TB, like HIV, has characteristically prolonged infectiousness before diagnosis that plays a critical role in maintaining transmission in the community, there is no TB equivalent of the rapid diagnostic tests for HIV that provides highly sensitive and specific results within 20 minutes and cost less than US$1. New diagnostics for TB, increasing levels of political commitment to reducing HIV-related TB morbidity and mortality, and the optimism arising from the success of ART scale-up has heightened interest in TB screening, including 'active' and 'intensified' case-finding approaches in communities.

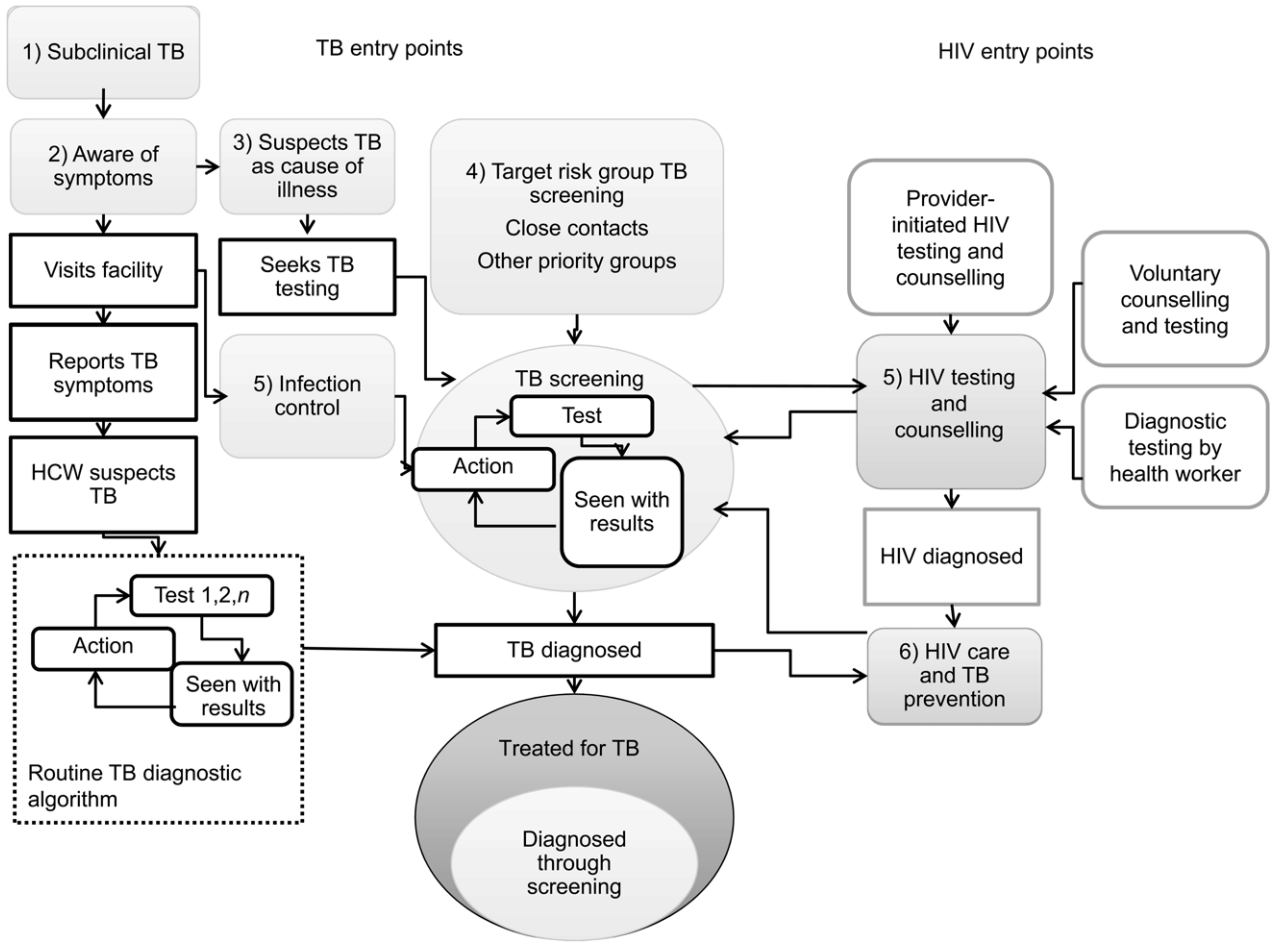

Figure 1 Patient flow and main entry points into TB screening. HIV entry points (5 and 6) are considered separately from other targeted risk groups, such as household contacts (4). TB screening can be directed against subclinical TB or at early stages of health seeking. TB = tuberculosis; HIV = human immunodeficiency virus; HCW = health care worker.

Table 1 Broad strategies and representative examples of different approaches to providing TB screening with integrated HIV testing and care

	Strategy	TB-HIV integration	Evidence of population-level impact on epidemiology
1 Household TB contact tracing	Visit and screen in households or invitation for facility-based screening	Provide early TB detection and TB preventive therapy following close contact Combine with HTC; ideally include home-based initiation of TB and HIV care	ZAMSTAR Reduced prevalence of TB from combined TB and HIV intervention (Ayles)[6] Requires rapid response
2 Screening and testing for TB in the general community	Outreach mobile services Door-to-door visits Community health worker visits: • As part of annual preventive screen • As part of multi-disease campaigns	Increase completeness of case detection and reduced delay in TB diagnosis Provide HIV testing: to all diagnosed with TB, with symptoms of TB, or as fully integrated TB-HIV screening Ideally include home-based initiation of TB and HIV care and prevention	DETECTB (increased case notifications and reduced undiagnosed TB; Corbett)[7] Reduced mortality from increased frequency of X-ray screening (Churchyard)[8]
3 Testing for HIV in the community, combined with TB screening	As for TB screening above	Provide TB screening during HTC Ideally initiate HIV and TB care and prevention	Home-based HIV testing reaches high coverage Few examples of fully integrated HIV and TB testing, and none assessed from TB control perspective
4 Facilitating access to TB diagnostic services	Sputum collection point Preparation and transportation of slides by CHWs	Avoid need to visit health facility for initial TB diagnosis	One important negative result (Ayles)[6] ZAMSTAR: increased case notifications in remote areas with poor access to health facilities
5 Raising awareness and community mobilisation	Advertising and media campaigns Engagement through existing community-based organisations	Reduce patient delays in health seeking Increase demand for services	One important negative result (Ayles)[6]
6 Facility-based screening for HIV and TB	Provider-initiated screening at every patient visit	Existing policy but poorly implemented	O'Grady showed 23% of unselected adult facility attendees had culture-positive TB[9]
7 Strengthen general facility-based services	Courteous services Efficient routine TB-HIV services Use of sensitive TB diagnostics High linkage and retention in care Infection control	Existing policy but poorly implemented	Churchyard showed no population impact from community-wide isoniazid without HTC despite individual benefit[10]
8 Strengthen HIV care services	Increase coverage of ART Early detection of HIV and treatment Increased use of isoniazid preventive therapy	Highly successful scale-up of HIV care services across Africa coinciding with declining TB incidence rates	Strong evidence of impact on individual, community and regional TB incidence from ART scale-up (Suthar)[11] Middelkoop showed evidence of community effect on undiagnosed TB[12]

TB = tuberculosis; HIV = human immunodeficiency virus; HTC = HIV testing and counseling; ZAMSTAR = Zambia South Africa TB and HIV Reduction; CHW = community health worker; ART = antiretroviral therapy.

SCREENING FOR TB AS PART OF THE RESPONSE TO TB-HIV IN HIGH HIV PREVALENCE SETTINGS

International policy

International policy is supporting more intensive use of TB screening, with updated recommendations for screening in PLHIV and close contacts of TB patients published by the World Health Organization (WHO) in 2012 and guidance encouraging broader consideration of screening in other priority groups, as well as operational research priorities.[15–17] More definitive TB screening guidelines will be published in 2013 following systematic reviews that have highlighted major evidence gaps but which also stress the need for caution.

Rationale and general principles

The main aims of TB screening are 1) to reduce individual morbidity and mortality through early diagnosis and treatment, 2) to reduce TB transmission by shortening the infectious period (Figure 2) and 3) to exclude TB to allow preventive treatment (such as isoniazid) to be started. In PLHIV, screening also reduces the risk of severe 'unmasking' of inflammatory reconstitution inflammatory syndrome (IRIS) when starting ART,[17,18] and may reduce early mortality in the critical ill. TB screening serves to raise awareness of TB symptoms and can have an important 'indirect' effect on subsequent health seeking, reducing subsequent patient delays in health seeking as well as providing direct access to diagnosis. This is especially pronounced in community-based interventions, and may have been a major contributor to the success of two recent interventions that reduced undiagnosed infectious TB at the population level.[6,7] Finally, TB screening has clear opportunities for linkage with HIV testing and care services, as discussed below.

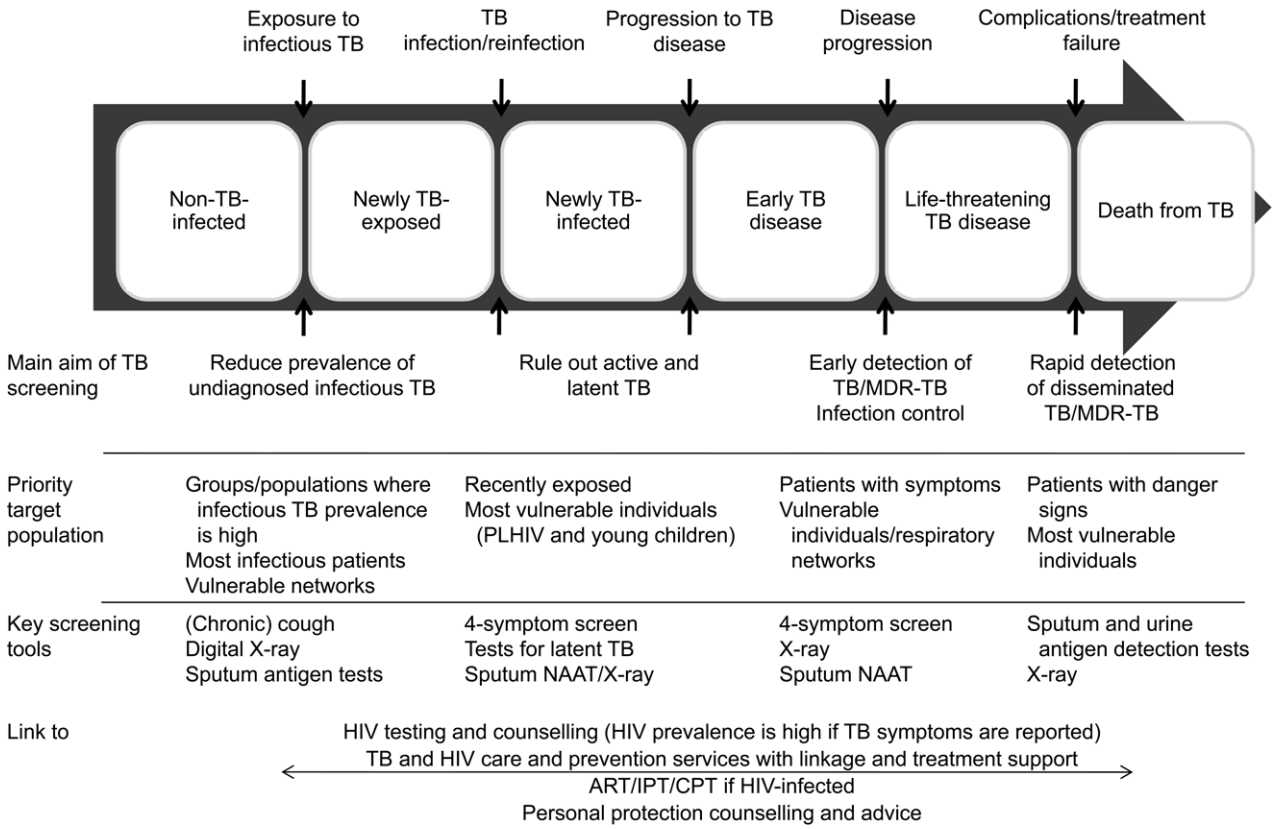

Figure 2 TB progression along an individual patient pathway. Depending on the nature of TB screening, individuals can be targeted at any point along their disease progression. This will influence the choice of diagnostic tools and the principal aim of screening. TB = tuberculosis; MDR-TB = multidrug-resistant TB; PLHIV = people living with HIV; NAAT = nucleic acid amplification test; HIV = human immunodeficiency virus; ART = antiretroviral therapy; IPT = isoniazid preventive therapy; CPT = cotrimoxazole preventive therapy.

Epidemiology of undiagnosed tuberculosis disease

The target of TB screening is undiagnosed infectious TB, which is still highly prevalent, as summarised in Table 2.[7,9,10,12,19–31] Variation between countries is marked and predates the HIV epidemic.[1,32,33] Lengthy delays in diagnosis and missed diagnosis are still reported by many HIV-positive and HIV-negative TB patients, despite major investment in strengthening health systems and TB services during the last decade.[17,18,34,35]

Patient delays in seeking care can also be prolonged, particularly among HIV-negative TB patients, for whom recent estimates suggest a mean duration of smear positivity before diagnosis of >1 year in Africa and even longer in many parts of Asia. In contrast, HIV-related TB progresses more rapidly, with a relatively brief duration of infectiousness (mean of a few weeks to months).[20,25,26] A substantial percentage of the total burden of undiagnosed smear-positive TB in the general community, the main driver of TB transmission, is thus HIV-negative individuals, even in very high HIV prevalence settings (Table 2 and Figure 3[36]). HIV-related TB, however, dominates the epidemiology of undiagnosed disease in facilities (Table 2).

Undiagnosed infectious TB in HIV-negative individuals is an important control target because of its disproportionate contribution to community transmission, and also due to the high responsiveness to interventions. For example, in Zimbabwe, the prevalence of culture-positive TB fell by 61% in HIV-negative individuals but only 25% in HIV-positive individuals (overall decline 41%) during a 2.5 year intervention based on 6-monthly periodic TB screening in the community targeting individuals with chronic cough and using smear microscopy for diagnosis.[7] By the end of the intervention, most undiagnosed infectious TB was HIV-related (Table 2: study 5), illustrating the need for combined approaches to prevent prolonged transmission from HIV-negative patients and reducing the high incidence of new TB disease among PLWHA.[7]

Whom to target?

Subgroups in whom undiagnosed TB prevalence is consistently ⩾1% (number needed to screen [NNTS] of <100 to detect one case of TB if using perfect screening tools), and people being considered for isoniazid preventive therapy (IPT) are the natural focus of screening efforts.[16] These include patients

Table 2 Prevalence of undiagnosed culture-positive TB in facility- and community-level studies from high HIV prevalence settings

Author, year, reference	Country	Setting	Population	Pre/post intervention	Culture method	Participants *n*	Culture+ *n*	Culture+ TB %	HIV prevalence % positive*	Infectious TB in HIV− participants* Smear+ %	Infectious TB in HIV− participants* Culture+ %
General population											
Den Boon, 2006[19]	South Africa	Urban	General	NA	LJ	2608	26	1.0	ND	ND	ND
Wood, 2007[20†]	South Africa	Urban	General	Pre	MGIT	762	12	1.6	22.8	16.7	25.0
Middelkoop, 2010[12†]	South Africa	Urban	General	Post	MGIT	1259	8	0.6	25.0	NS	50.0
Corbett, 2009[21‡]	Zimbabwe	Urban	General	Pre	LJ	10092	66	0.7	21.1	51.3	46.00
Corbett, 2010[7‡]	Zimbabwe	Urban	General	Post	LJ	11018	46	0.4	18.7	39.1	35.1
Ayles, 2009[22]	Zimbabwe	Urban + rural	General	NA	MGIT	8044	79	1.0	28.8	59.10	45.6
van't Hoog, 2011[23]	Kenya	Rural	General	NA	LJ+MGIT	20710	123	0.6	16.8	NS	NS
Shapiro, 2012[24§]	South Africa	Urban	General	NA	MGIT	983	4	0.4	20.6	100.0	100.0
Special populations											
Corbett, 2004[25]	South Africa	Mines	Miners	NA	LJ	1773	45	2.6	26.1	77.8	62.2
Corbett, 2007[26¶]	Zimbabwe	Urban	Workplace	Post	LJ	4668	15	0.3	22.0	66.7	66.7
Churchyard, 2012[10#]	South Africa	Mines	Miners	Post	MGIT	12606	285	2.3	ND	ND	ND
Shapiro, 2012[24]	South Africa	Urban	TB household	NA	MGIT	2166	169	7.8	21.0	NS	NS
Facility-based											
O'Grady, 2012[9]	Zambia	Urban	Medical admissions	NA	MGIT	881	201	22.8	65	NS	16.2
Hoffman, 2013[27]	South Africa	17 urban clinics	Antenatal clinic HIV+	NA	MGIT	1403	35	2.5	100	NA	NA
HIV care clinics											
Shah, 2009[28]	Ethiopia	Urban	Voluntary counselling and testing clinic	NA	LJ	427	27	6.3	100	NA	NA
Lawn, 2009[29]	South Africa	Urban	ART clinic	NA	MGIT	235	58	25.7	100	NA	NA
Cain, 2010[30]	South East Asia	Urban	HIV clinic	NA	LJ+MGIT	1724	267	15.5	100	NA	NA
Bassett, 2010[31]	South Africa	Urban	HIV clinic	NA	MGIT	825	157	19.0	100	NA	NA

*HIV prevalence refers to % positive in those consenting to be tested. ND = HIV testing not done as part of prevalence survey.
†Repeated prevalence surveys in the same South African township before and after scale-up of facility-based HIV testing and care services, including ART clinic and TB screening as part of infection control and HIV care.
‡Before-and-after prevalence surveys in population provided with six rounds of periodic TB screening in the community.
§Surveys for undiagnosed TB in household contacts and controls from the same South African community.
¶Prevalence surveys following 2 years of promoting HIV testing and provision of easy access to culture-based TB diagnosis and radiological diagnosis of patients with suspected smear-negative TB through workplace-based primary care clinics.
#Survey for undiagnosed TB in goldminers following a randomised trial of community-wide isoniazid preventive therapy. Results include both arms.
TB = tuberculosis; HIV = human immunodeficiency virus; + = positive; − = negative; NA = not applicable; LJ = Löwenstein-Jensen; ND = not done; MGIT = Mycobacterial Growth Indicator Tube; NS = not stated.

attending HTC clinics or HIV care clinics,[18,37–39] unselected medical admissions and out-patient attendees,[9,38] household contacts of TB patients,[21,40] prisoners,[38] silica-exposed mineworkers,[10] unselected adults in some communities,[12,19,21–23,26] and adult residents volunteering symptoms of TB during surveys or outreach TB screening. Prevalence in adults in the general community and other risk groups, including diabetics, is highly variable and needs local situational analysis to guide planning.[7,34,41–43]

Household contacts, PLHIV and facility attendees stand out as having much higher prevalence rates than other risk groups (Table 2 and [38]), indicating an urgent need for effective TB screening using accurate diagnostic tools to provide individual benefit. However, undiagnosed TB in these subgroups is more of a

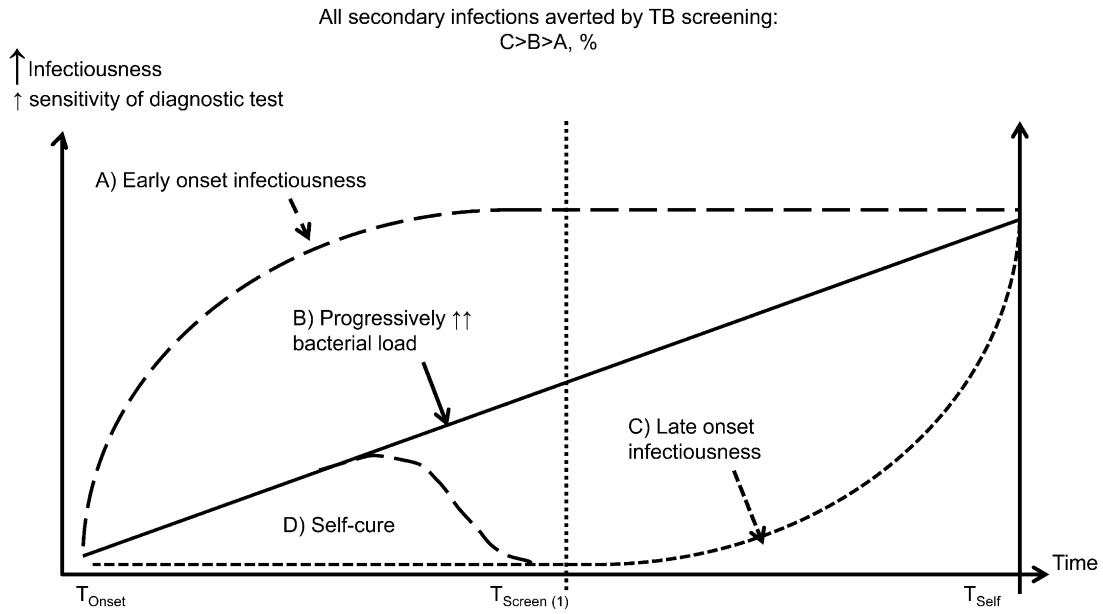

Figure 3 Possible patterns of disease progression and onset of infectiousness. TB screening gains in terms of secondary infections averted and ease of diagnosis (sensitivity of diagnostic tools) will depend on the pattern of onset of infectiousness relative to symptoms, and how the screen is targeted. Screening may detect patients who are in the process of self cure following transient culture positivity. Adapted from Dowdy et al.[36] TB = tuberculosis.

symptom than the main contributor to TB transmission in communities.[35,44]

OPTIMAL SCREENING STRATEGIES FOR DIFFERENT PRIORITY GROUPS

TB screening has a number of different goals and entry points (Figures 1 and 2) affecting where, how and how often screening should be carried out. For instance, prevention of mortality is the overriding goal when screening acutely ill in-patients, and ideally requires diagnostics able to rapidly detect disseminated HIV-related TB (Figure 2). At the other extreme, interventions aimed at reducing transmission in the general community need to detect infectious participants affordably and efficiently (Figure 2). Critical decisions include which algorithm to use, and whether or not to screen for subclinical TB. Following the general principals of screening, sensitive screening tests should be confirmed by a highly specific test.[45] As no current TB screening algorithm is ideal, compromises have to be made.[46,47] In practice, TB screening usually starts with either symptoms or X-ray,[48] although there is increasing use of Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) as both initial and confirmatory test.[9,49–51]

The performance of all tests tends to be less good due to lower sensitivity when used for screening than for patient-initiated diagnostic testing, as the spectrum of undiagnosed disease detected is shifted towards earlier, paucibacillary cases (Figures 2 and 3): this includes culture, smear microscopy and Xpert.[30,41,49,50,52–54] There is considerable incremental yield from combining different tests, or repeating the same test on different specimens.[30,53,55] All tests also have relatively low positive predictive value when used for screening, due to the lower prevalence of true disease.

Symptom screening

TB symptoms are the most common first step in TB screening, and may currently be the only feasible option in many settings. However, undiagnosed TB can occur without any reported TB symptoms and, irrespective of HIV status, less than half of culture-positive participants have the 'hallmark' symptom of prolonged cough.[18] In a meta-analysis of data from 8148 PLHIV screened using culture, prolonged cough was reported by 1530 (20.0%) participants and identified 260 (52.5%) culture-positive participants, while one or more of the four symptoms (cough, fever, night sweats or weight loss) was reported by 3563 (46.6%) participants, including 418 (84.4%) with confirmed TB.[18]

Subclinical tuberculosis

Subclinical TB (culture-positive TB with none of the above four symptoms) is consistently identified whenever screening is carried out. In very high transmission settings, including household contacts and newly diagnosed patients attending HIV care clinics, numbers of patients with subclinical culture-positive disease can exceed symptomatic cases, and reach very high rates (up to 15%).[18,31,50,56] However, the consequences of missing subclinical TB disease need to be weighed against the expense and consequences of

more systematic screening of all suspects. For example, adding extra steps in an already tortuous patient pathway could increase loss to care.

Individual consequences of missing subclinical active TB include IRIS, which is rarely fatal, although extremely unpleasant and disruptive to HIV care.[57,58] Inappropriate isoniazid monotherapy may even be lifesaving in HIV-positive patients with difficult-to-diagnose TB,[59] and there is no clear evidence of increasing drug resistance.[60,61] The extent to which subclinical TB contributes to overall TB transmission is unclear,[36] and will depend on how infectiousness relates to symptoms (Figure 3). Local TB epidemiology can be dominated by stable, minimally symptomatic but highly infectious 'super-spreaders',[62] but this does not appear to be a common phenotype,[26] and pronounced reductions in undiagnosed TB at the population level can be achieved without systematic screening for subclinical TB.[7,11,12]

Radiological screening

Chest radiography (CXR) provides the opportunity for high-volume TB screening, and is increasingly feasible due to digital technology. Computer-aided diagnostics,[63] validated reading and scoring systems,[64] remote reading and lay readers[65,66] are all under active investigation. CXR is already part of the adult and paediatric TB diagnostic algorithms, and combines high sensitivity with reasonably high specificity.[65,67,68] Immediate decisions on the need for confirmatory testing and follow-up can be made by trained readers,[64,66] as exemplified by outreach interventions among hard-to-reach risk groups in Europe.[65,69] HIV immunosuppression affects radiological manifestations of TB; low sensitivity has been reported in clinic-based screening,[30,70] but not in community-based studies.[48] Two studies from Botswana reported a low-to-modest yield and high incremental cost of adding CXR to clinic-based symptom screening.[71–73] The main barriers to use are the high capital costs, radiation hazard and lack of skill base in Africa.

New tuberculosis diagnostics for tuberculosis screening

Xpert and urinary lipoarabamannan (LAM) antigen detection are both new diagnostics being used for TB screening, mainly in the context of HIV care. The development and roll-out of the Xpert platform is a major breakthrough for the diagnosis and management of HIV-related TB and multidrug-resistant TB (MDR-TB) that was endorsed by the WHO in 2010.[74] It has increased sensitivity compared to smear microscopy, and has led to a clinically important decrease in time to diagnosis and treatment initiation in self-presenting patients with suspected TB. The sensitivity of Xpert compared to culture is highest in hospital in-patients with TB symptoms (82–91%).[75]

Data on the use of Xpert as a TB screening tool in high HIV prevalence populations are currently limited to four studies (Table 3);[9,49–51] however, these numbers are likely to increase rapidly. Excluding one very small study of five culture-positive cases, the sensitivity of Xpert compared to culture was lower when used for diagnostic testing (range 58.3–88.2%), but much more sensitive than smear microscopy (sensitivity range 17.6–52.8%). Use of Xpert for routine diagnostic testing is likely to be cost-effective in many settings;[76,77] however, affordability, limited throughput capacity and substantially lower sensitivity than culture and CXR may restrict the widespread adoption of this test for screening to specified high TB prevalence groups, such as PLHIV, facility attendees and close contacts, and to confirmatory testing after CXR or symptom screen. More research is needed to define sensitivity, specificity and feasibility in these groups.

LAM is a *Mycobacterium tuberculosis* cell-wall polysaccharide that can be detected in the urine of TB patients, and is now available as a point-of-care lateral flow assay.[29] It is a useful screening test in PLHIV with advanced immunosuppression, diagnosing disseminated disease that tends to smear-negative. Its low sensitivity and suboptimal specificity limit the value of the test in patients with CD4 count of >200 cells/mm.[29] LAM has marked prognostic significance predictive of high mortality, and a number of clinical trials are ongoing in South Africa and Uganda.

MANAGEMENT OF HIV AND TUBERCULOSIS IN SCREENING PARTICIPANTS

Integrating TB screening with HIV testing and care

TB screening during HIV care (Figure 1) is a high priority from multiple different perspectives, and the

Table 3 Use of Xpert® MTB/RIF for screening

Study	Country	Screening population	HIV prevalence % positive	HIV prevalence *n*	Culture-positive *n*	Sensitivity of smear microscopy % (95%CI)	Sensitivity of Xpert® MTB/RIF % (95%CI)
Lawn, 2012[52]	South Africa	ART clinic	100	515	81	22.2 (13.3–33.6)	58.3 (46.1–69.8)
O'Grady, 2012[9]	Zambia	Medical admissions able to produce sputum	65	881	201	52.8 (45.1–60.4): HIV+ 48.6 (33.0–64.4): HIV−	88.2 (81.9–92.6): HIV− 74.3 (56.4–87.0): HIV−
Dorman, 2012[49]	South Africa	Prevalence survey	ND	6893	187	17.6 (12.5–23.9): HIV+	62.6 (55.2–69.5)
Ntinginya 2012[51]	Tanzania	Household contacts	ND	219	5	60.0 (14.7–94.7): HIV−	100 (47.8–100)

HIV = human immunodeficiency virus; ART = antiretroviral therapy; ND = not done.

subject of recent comprehensive and systematic reviews.[18,75] Screening newly diagnosed PLHIV targets a patient group with a high prevalence of undiagnosed TB disease, indications for IPT, high vulnerability to rapidly progressive TB with a fatal outcome and collective vulnerability to nosocomial transmission through a shared respiratory contact network at the HIV care clinic. Intensive TB screening with Xpert MTB/RIF and culture can increase pre-ART identification of TB patients dramatically,[30,31,39,50,78] leading to a low incidence of TB in the subsequent 12 months. Tests with pronounced prognostic significance include detectable bacilli or antigen in urine or blood which identify individuals with high risk of early death.[39,55]

How best to integrate HIV testing and care into TB screening interventions delivered outside of HIV programmes is less well defined. At a minimum, it is essential to confirm positive TB screening results and ensure that patients are promptly linked into TB care, with diagnostic HIV testing offered to all TB patients and participants with TB symptoms. As routine programmes lose about 15% of their newly diagnosed smear-positive TB patients and over 70% of newly diagnosed HIV-positive patients before any treatment is provided, care needs to be taken to avoid loss to follow-up between diagnosis and treatment. Loss to follow-up can be much higher when the diagnosis is made outside the routine setting, undermining the effectiveness of TB-HIV screening.[41]

ART is by far the most effective method of preventing HIV-related TB, with a 65% reduction in incidence, rising to 84% if the CD4 count is <200 cells/mm.[11,79] Irrespective of their final diagnosis, people identified as having symptoms of TB have a high probability of being HIV-infected,[22,80] being unaware of their HIV status, being eligible for ART[80] and having a high risk of death if their HIV is not promptly diagnosed and treated.[80–83] Indeed, in settings with generalised HIV epidemics, the NNTS to identify one patient with undiagnosed HIV is far lower than the NNTS to identify one patient with undiagnosed TB.

More completely integrated TB-HIV interventions include HIV treatment-as-prevention (TasP) strategies providing home-based HTC with TB screening and immediate ART and IPT for HIV-positive individuals,[84] and combined TB and household-based HIV and TB prevention.[6] ART for TasP has extremely high potential as a TB control strategy, with declining national and regional TB incidence apparent already just from routine ART scale-up.[84] Eight different trials of ART for HIV prevention that include TB outcomes are currently underway or planned.[85]

Follow-up of suspected tuberculosis

Once TB is suspected, no diagnostic test is able to both rule-in *and* rule-out TB accurately.[30,86] As such, it is vital to ensure continuity of care by promptly diagnosing and treating HIV infection, and by providing participants with follow-up management until TB is confirmed or excluded.[80] As symptoms develop within a short time in patients with confirmed 'subclinical' TB, repeated assessment after a short interval can distinguish progressive TB disease from false-positive screening results.[56]

In Harare, Zimbabwe, only 20% of smear-negative 'TB suspects' identified in the community attended free follow-up care services.[87] Participants who attended follow-up had a high prevalence of undiagnosed HIV infection, a high rate of smear-negative TB diagnosis, and high mortality at 12 months during a period of very limited access to ART.[80]

TUBERCULOSIS SCREENING USING DIFFERENT TUBERCULOSIS ENTRY POINTS

Community-based screening for tuberculosis regardless of symptoms (entry points 1 to 3)

Community-based TB screening has not been included in international recommendations for TB control for several decades.[88] Before the mid-1970s, radiological screening was widely implemented, but without clear demonstration of its impact on TB epidemiology or individual benefit.[44,88] Mobile radiography is still used in some European towns to screen high-risk groups such as the homeless and drug users, with acceptable NNTS and cost-effectiveness.[65,69]

The South African mining industry has used annual screening since the 1930s. The onset of the HIV epidemic was associated with decreasing proportions of TB in miners diagnosed using annual CXR screening.[67] TB found using screening had lower case fatality rates: an individually randomised trial of 6-monthly vs. the standard of care 12-monthly CXR screening of 2634 gold miners led to a 52% reduction in the risk of death during the first 2 months of anti-tuberculosis treatment in the more intensively screened arm.[8] Radiography in miners has much lower sensitivity for culture-confirmed TB (~25%) than screening-naïve populations (>90%), potentially reflecting 'screening escape'.[89]

CXR screening is highly efficient, and should be investigated in very high transmission settings, for example, combined with other intensified TB-HIV activities in South African townships where the adult prevalence of culture-positive TB is up to 4% (NNTS ~25), and for outreach screening in prisons. Another obvious application would be in facility-based screening (Figure 1).

Outreach tuberculosis screening in general communities (entry points 2 and 3)

Outreach interventions in general communities also show promise. Here the aim is to provide access to diagnosis of symptomatic TB in the community. Studies in Zimbabwe and South Africa have shown high uptake, with 2–5% smear positivity prevalence in

participants.[7,41] Epidemiological impact was assessed in a cluster randomised trial, with 46 neighbourhoods in Harare, Zimbabwe (DETECTB) randomised to six rounds of 6-monthly active case finding using door-to-door enquiry for chronic cough in the household or mobile van with loudspeakers.[7] Participants provided sputum for smear microscopy results. Smear-positive TB case notification rates increased substantially in both arms, with the mobile van arm diagnosing the most smear-positive TB. There was a substantial and highly significant reduction in population-level culture-positive TB (before:after adjusted reduction of 41% over 2.5 years, from 7.9 per 1000 adult residents). An estimated 15–25% of undiagnosed smear-positive residents were diagnosed at each intervention round,[7,21] despite the intrinsic limitations of using a low sensitivity screening algorithm (chronic cough and microscopy[7]).

In contrast, a large cluster multifactorial randomised trial of 24 communities in Zambia and South Africa provided with 3 years of 1) enhanced case finding (ECF) in the community, and 2) household intervention,[22,43] did not show any epidemiological benefit from the ECF intervention despite considerable participation. DETECTB and ZAMSTAR (Zambia South Africa TB and HIV Reduction) ECF were complex interventions with several differences: there was less focus on direct sputum collection in ZAMSTAR-ECF, and DETECTB included dedicated follow-up clinics for smear-negative patients and active tracing of smear-positive patients.

TB REACH, a case-finding initiative funded by the Canadian International Development Agency and coordinated by the WHO, is also providing numerous examples of highly successful TB screening interventions,[15,90–93] including a number of interventions using Xpert supported by UNITAID. So far the emphasis has been on increasing case detection, rather than follow-up, to show declining TB incidence trends.

Combined TB-HIV household contact tracing interventions (entry point 4)

Household contacts of TB patients are at high risk for undiagnosed TB,[40,94] with two recent meta-analyses reporting a median yield of undiagnosed TB of 3.1% and 4.5%.[40,94] Pronounced heterogeneity by region and screening algorithms was noted, with one recent study showing very high rates of subclinical culture-positive disease (Shapiro in Table 2).[24]

According to conventional wisdom, intensive household contact tracing has limited potential to affect TB epidemiology, although of high individual benefit, as only about 10% of TB patients report household TB exposure.[35] However, this has been challenged by a recent study (ZAMSTAR) that showed significant (22%) reduction in undiagnosed culture-positive TB in the general community through a cluster randomised trial that combined TB screening, HIV testing and prevention counselling in Zambia and South Africa ('ZAMSTAR' Household Arm[6]). The intervention was intensive, with three separate visits over the course of 12 months. Fitting of mathematical models to trial data suggests diffusion of indirect benefits beyond households directly covered by the intervention.[43] The major challenge of timely contact screening is the need for efficient communications, transportation and a means of interacting with the community.

Broader facility-based tuberculosis screening (entry point 5)

Relatively few studies have assessed systematic screening of general out-patient clinic or primary care clinic attendees for TB in HIV-prevalent settings;[9] however, there are many reasons for prioritising intensified screening for this entry point: first, it is a natural extension of TB screening provided in HIV care settings, as general clinic attendees have high HIV prevalence and high rates of undiagnosed TB.[9] Second, it is an opportunity to strengthen provider-initiated HTC,[95] and numerous studies have shown poor identification and management of people with TB symptoms in routine systems. Finally, screening all facility attendees for cough is already part of infection control policy.[96] A recent intervention in the low HIV prevalence country of Pakistan greatly increased case notification rates using lay volunteers to provide out-patient screening, based around a mobile phone system for communication and payment of incentives.[97]

Facility-based interventions have the potential for population-level impact if they are implemented well enough. The first clear example of this was from Cape Town, South Africa, where a substantial fall in undiagnosed TB was reported for a community served by an unusually strong TB-HIV health clinic.[12]

COSTS, COST-EFFECTIVENESS AND MATHEMATICAL MODELLING OF TUBERCULOSIS SCREENING INTERVENTIONS

An increasing number of studies are estimating full screening costs and the cost-effectiveness of TB screening. Costs per participant found to have TB are higher for TB screening than for patient-initiated diagnosis: for example, US$1117 per patient[41] in a South African community-based TB screening intervention and approximately US$809 under the various interventions funded through the TB REACH initiative.[15] However, these estimates do not include costs averted, for example, from managing patients found at an earlier stage of disease, nor from episodes of disease and death averted. Costs incurred through false-positive diagnoses also need to be included. Even relatively small per-patient costs will require substantial additional funding to be affordable by national TB control programmes in low-income

countries.[98] Effective targeting to high TB prevalence risk groups and populations will be critical for maximising cost-effectiveness.[44]

KNOWLEDGE GAPS AND RESEARCH PRIORITIES IN TUBERCULOSIS SCREENING

Major gaps in our knowledge remain. For community-based interventions, these gaps lie in some critical areas.[44] It is still unclear to what extent TB screening can contribute to reduced TB transmission, and, if so, how intensively, how often and for how long TB screening interventions have to be delivered before appreciable gains are seen.[36,99,100] The nature and impact of critical health system constraints is also poorly d efined, as are individual risks and benefits from TB s screening, both for PLHIV and for HIV-negative participants.

Addressing our current knowledge gaps requires operational and public health research with appropriate impact evaluation,[101–103] and linked mathematical and economic modelling. Understanding the impact of screening on 'patient-important outcomes' such as survival and well-being, and population-level epidemiological impact are critical in guiding choices and investment.[44,46,104] Mathematical modelling can identify and clarify important key principles, identify misconceptions, constraints and theoretical limitations, as well as being a tool to guide realistic study design, cost-effectiveness and provide fuller analysis and projection of real-life data.[36,84,99,100,105]

Among our most pressing needs are new diagnostics: a highly sensitive, portable, low-cost, point-of-care diagnostic able to 'rule out' TB effectively would revolutionise TB screening at all levels of the health system and community and allow rapid scale-up of HIV testing. Furthermore, tools to enable efficient population-level impact evaluation, such as robust and low-cost tests for *recent* TB infection able to evaluate transmission rates in communities and quantify facility-level infection control are desperately needed (Table 4).[7,22,30,31,39,43,58,78,101,103,106]

Table 4 Approaches to impact evaluation for TB screening interventions (adapted from[102])

Impact being evaluated	Study designs	Expected outputs and examples
Any high-risk group		
Comparison of performance characteristics between different tests and algorithms	Cross-sectional studies evaluating new TB diagnostics	Estimates sensitivity and specificity; can inform on robustness of new diagnostic systems in resource-poor settings[30,31,78] Provides number-needed-to-screen per TB patient diagnosed in different populations
HIV care clinics and household contacts		
Direct cohort follow-up to evaluate patient-important outcomes following screening	Cohort studies comparing outcomes according to whether or not/how screened Appropriate comparator populations provided by randomisation (e.g., step-wedge), or historical or non-randomly selected comparison cohorts	Outcomes post-screening can include numbers diagnosed with TB at and after screen, vital status, retention in care, time to TB treatment[58] Cost effectiveness and consequences of false-negative and false-positive screening results can also be assessed
Well-defined high TB incidence populations		
Time trends in TB case notification rates compared to non-intervention comparator populations	Time trend analysis for: a) initial peak in case notifications attributable to screening, and 'additionality' compared to comparator and historic trends b) post-peak accelerated rate of decline in new cases	Need accurate routine case notification system; can be confounded by other changes in routine TB diagnosis/reporting Requires disaggregation of routine case notification data to subdistrict level (unless intervention is district-wide)
Time trends in deaths from diagnosed/undiagnosed TB	Aiming for reduced diagnosed +/− undiagnosed TB deaths ideally routine as well as intervention participants	Need complete TB registration and outcome data for diagnosed TB deaths Accurate capture of undiagnosed TB deaths requires autopsy
Prevalence surveys for undiagnosed TB in the general population	Repeated before-after, or cluster-randomised cross-sectional outcomes Requires very large sample sizes and consistent survey methods	Change/difference in undiagnosed TB provides outcome (less is always better). Several recent examples[7,22,39,43,107] Before:after change does not prove causality; aim for major change in short time period to provide strongest evidence[104]
TB transmission rates	Before-after estimates, or cluster randomised cohort or cross-sectional outcomes; requires large sample sizes and consistent methods	Evidence of impact on TB transmission is an ideal outcome, but difficult to measure and so not often evaluated in high TB incidence settings; results affected by HIV status One recent example used an incidence cohort design in schoolchildren[22,43]
TB prevalence in HIV-infected patients	Assessed through repeated before-after design, regular surveillance with time trends, or cluster-randomised cross-sectional outcomes New clinic attendees, or routine post-mortem	A key indicator of population-level TB control, and also the main target of prevention for TB-HIV interventions Occurs at high prevalence and clearly linked to TB transmission

TB = tuberculosis; HIV = human immunodeficiency virus.

Without a TB equivalent for HIV-incidence assays, large cohorts, repeated cross-sectional measurements or analysis of time trends in TB incidence are required to measure trends in TB control (Table 4). These are not only expensive, but also often fail to deliver clear answers due to the logistical difficulties of this kind of indirect evaluation. Demonstration projects providing high-intensity, high-coverage combined TB-HIV screening interventions could provide relatively rapid insight into which approaches to TB screening are most effective in very high TB incidence settings. Both facility- and community-based interventions need to be investigated for their acceptability and potential impact on the population, including settings with high MDR-TB rates.[84,107] Intervention design should resist the temptation to over-emphasise sustainability and test low-intensity complex interventions without first establishing effectiveness.

Without clear evidence to guide policy and practice, resources may be wasted on ineffective interventions, and, conversely, the value of effective interventions may be grossly under-estimated. The need to establish effectiveness is most pressing for community-wide interventions, where costs and potential harms, but also potential benefits, are at their highest, and where contemporary examples with impact evaluation have given conflicting results.[7,43]

Important operational questions include linkage and retention in TB-HIV care when screening individuals not already in chronic care services. Health systems research priorities include the feasibility of provider-initiated TB and HIV screening at the facility level, and models of delivering interventions through community-directed approaches.[96,108,109]

CONCLUSIONS

In high HIV prevalence settings with high rates of morbidity and mortality from TB, the evidence for pursuing much bolder TB screening policy and practice is compelling, despite high cost and many remaining unknowns. Facility-based TB screening and screening of household contacts should be greatly intensified, while developing evidence around community-based interventions. As with HIV testing, a combination approach adapted to the local epidemiology will be needed. Gains from each TB infection averted are unusually high in the highly vulnerable HIV-infected members of the community, and the costs of TB screening are small compared to expenditure on HIV care.

Effective intervention with the limited diagnostics available today will have to start without clear evidence, but with investment in research to support impact evaluation, ideally at individual, clinic, facility and population level. More innovative approaches to defining and responding to needs include, for example, combined surveillance-response strategies used for targeting efforts against other major infectious diseases.[110] Geospatial and molecular epidemiology could allow us to capitalise on existing epidemiological, demographic, health service resource usage data.[111]

Combined TB and HIV interventions are essential if any gains made through TB screening are to be maintained in high HIV prevalence settings, and they require joint planning, implementation and financing from the early stages of planning. Effective linkage to treatment and prevention of both TB and HIV needs to be the focus of special attention for both TB and HIV screening. We cannot continue to tolerate high rates of undiagnosed TB in communities and health facilities, but need to act in proportion to the threat to health and wellbeing: the magnitude and consequences of XDR-TB and MDR-TB epidemics in South Africa provide a graphic illustration of the huge cost of failure to implement effective TB and HIV screening and care.

Acknowledgements

ELC and PM are funded by the Wellcome Trust (Grant nos. WT091769 and WT089673, respectively).

Conflict of interest: none declared.

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RÉSUMÉ

En 20 années de taux d'incidence très élevés de la tuberculose (TB) et de forte mortalité TB dans les pays à haute prévalence de l'infection par le virus de l'immunodéficience humaine (VIH), les initiatives contre la TB sont très loin de correspondre à l'ampleur des réponses observées dans les programmes de malaria ou de VIH. En effet, les recommandations ont été focalisées de façon très étroite sur les personnes consultant les services de santé pour l'investigation des symptômes de TB ou les fréquentant pour des tests et des soins VIH. Toutefois, en dépit de l'investissement majeur récent et étendu des services TB et VIH, la TB non-diagnostiquée reste hautement prévalente au niveau de la collectivité, ce qui signifie que le diagnostic de la TB reste lent et incomplet. Ceci maintient des taux élevés de transmission et expose les personnes atteintes par le VIH à des taux élevés de morbidité et de mortalité.

Une utilisation plus intensive du dépistage de la TB avec des définitions plus larges des populations visées, des indications élargies du screening à la fois à l'intérieur et à l'extérieur des services de santé et une sélection appropriée de nouveaux outils de diagnostic offrent la perspective d'une amélioration rapide de la lutte antituberculeuse au niveau de la population. La précision du diagnostic des algorithmes adaptés (à débit élevé) reste une barrière majeure à l'égard de la réalisation de cet objectif.

Nous faisons ici la revue des évidences disponibles pour orienter une extension du dépistage de la TB dans les contextes où le VIH est prévalent, idéalement par des interventions combinées TB-VIH qui assurent le dépistage à la fois de la TB et du VIH et qui maximisent l'accès aux soins et à la prévention de la TB et du VIH. Idéalement, nous devrions tester, traiter et prévenir la TB et la VIH de façon systématique et complète en offrant le dépistage à la fois de la TB et du VIH à tous les sujets fréquentant les services de santé, aux ménages TB et à tous les adultes dans les collectivités où le risque est le plus élevé. Toutefois, nous sommes toujours freinés par les techniques inadéquates en matière de diagnostic, par le financement et par la médiocrité de l'impact sur la population. Les recherches contemporaines pertinentes montrant l'importante nécessité, les avantages potentiels et les dangers d'un dépistage élargi et intensifié de la TB dans les contextes à prévalence élevée de VIH font l'objet des discussions de cette revue.

RESUMEN

En 20 años de tasas de incidencia de tuberculosis (TB) exorbitantes y una gran mortalidad por esta causa en los países con alta prevalencia de infección por el virus de la inmunodeficiencia humana (VIH), las iniciativas emprendidas están muy lejos de corresponder en magnitud ni amplitud a las respuestas que se observan en los programas contra la malaria o la infección por el VIH. Por el contrario, las recomendaciones se han centrado en las personas que acuden a los centros de atención de salud por síntomas indicativos de TB o en busca de pruebas diagnósticas o atención de la infección por el VIH. Sin embargo, pese al reciente aumento de la inversión y a la ampliación de escala de los servicios que se ocupan de estas enfermedades, los casos de TB que se pasan por alto en la comunidad siguen siendo muy frecuentes, lo cual indica que el diagnóstico es aun demasiado lento e insuficiente. Esta situación favorece la persistencia de altos índices de transmisión y expone a las personas infectadas por el VIH a altas tasas de morbilidad y mortalidad.

Una intensificación de la detección sistemática de la TB con definiciones más amplias de las poblaciones destinatarias, indicaciones extendidas de ejecución en los centros sanitarios y por fuera de los mismos y una selección apropiada de nuevos instrumentos diagnósticos ofrece una perspectiva de mejoramiento rápido del control de la TB en la población. El principal freno al logro de esta meta sigue siendo la precisión diagnóstica de algoritmos adaptados (con alta productividad).

En el presente artículo se analizan los datos científicos existentes, con el propósito de orientar la ampliación de la detección sistemática de la TB en los entornos con alta prevalencia de infección por el VIH, idealmente mediante intervenciones combinadas contra la TB y el VIH que ofrezcan la detección de ambas enfermedades y fomenten al máximo la utilización de los servicios de atención y prevención. Lo ideal sería practicar las pruebas diagnósticas, tratar y prevenir la TB y la infección por el VIH de manera exhaustiva, por conducto de una oferta de detección conjunta, a todos los usuarios de los establecimientos de atención sanitaria en las comunidades que presentan el mayor riesgo de transmisión. Sin embargo, el progreso se ve obstaculizado por medios diagnósticos inadecuados, un financiamiento insuficiente y la escasez de datos sobre la repercusión en las poblaciones. En el presente análisis se examinan las investigaciones recientes pertinentes que han puesto de manifiesto la gran necesidad de evaluar de las posibles ventajas y los inconvenientes de la ampliación y la intensificación de la detección de la TB en los entornos con alta prevalencia de infección por el VIH.