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EDITORIAL COMMENTARY

Ending Tuberculosis in Older People: New Strategies for an Age-old Disease

Tom Wingfield[1,2]

[1]Departments of Clinical Sciences and International Public Health, Liverpool School of Tropical Medicine, Liverpool, L3 5QA, United Kingdom; and [2]World Health Organization Collaborating Centre in Tuberculosis and Social Medicine, Department of Global Public Health, Karolinska Institutet, Norrbackagatan 4, 171 76 Stockholm, Sweden

(See the Major Article by Hu et al. on pages 1468–75.)

Between 2015 and 2050, the number of people in the world aged 60 years or over is expected to double to 2.1 billion, of whom 80% will be living in low- and middle-income countries [1]. This global increase in the older population masks gross life-course inequalities, both within and across countries, not only in life expectancy but also in the number of healthy life-years lost, including to disease and disability [2]. In 2020, to reduce these inequalities and improve the health and well-being of older people, their families and communities, the United Nations General Assembly declared 2021–2030 the Decade of Healthy Aging.

Tuberculosis (TB) is an age-old disease typified by inequity that has been overlooked in such healthy aging strategies, despite a pronounced impact on older people [3]. Although over recent decades, the human immunodeficiency virus (HIV) epidemic skewed TB notification rates toward younger people, especially in sub-Saharan Africa, the proportion of older people among all those newly diagnosed with TB globally is increasing and will likely continue to do so in line with life expectancy. Older people remain one of the largest reservoirs of TB infection worldwide. [3] In low TB burden settings, this is predominantly due to distant exposure in early life whereas in high TB burden settings it may be more likely to relate to recent exposure [4]. Most TB deaths and more than a quarter of TB-related disability adjusted life-years (DALYs) globally occur in people older than 50 years [4], with countries in the Southeast Asia and Western Pacific regions being particularly affected [4, 5]. In China, a country of 1.4 billion people, national TB prevalence surveys have demonstrated that older people, especially older men, have the highest prevalence of TB of all age groups [6].

In this issue of *Clinical Infectious Diseases*, Hu et al describe the implementation and evaluation of a mass tuberculosis screening intervention among the elderly (60 years or over) in China. The screening was implemented in Lanxi County, an area in which more than 1 in 4 people notified with TB are elderly. The intervention consisted of chest radiographs with focused clinical and sociodemographic questionnaires and clinical examination and was integrated with an existing national program called the "Basic Public Health Service Project" (BPHSP), in which individuals aged 60 years or over or with diabetes are provided healthcare examinations at no individual cost.

Chest radiographic images were uploaded to 2 platforms, 1 where images were read by a specialist radiologist, and another where images were read by the BPHSP attending physician. A multidisciplinary team discussed discrepant reports and agreed a final report by consensus. No computer assisted digital (CAD) or other artificial intelligence tools were used to interpret images. People with chest radiographs showing signs of TB, including cavities, tuberculoma, miliary changes, infiltrates, and/or pleural effusions or thickening, went on to have a computed tomography of the thorax and sputum smear examination. If either CT or sputum smear was positive, an Xpert molecular test and mycobacterial culture was performed at the local hospital. Concurrent to the intervention, the team collected data on older people in Lanxi County diagnosed through passive case finding (PCF).

The mass screening intervention reached nearly one third (32%) of the total population of older people in Lanxi county. Of 49 399 individuals screened, 599 (1.2%) had an abnormal chest radiograph, of whom 115 were subsequently diagnosed with TB. Case detection was 44% higher (233 cases per 100 000 people screened vs 168 cases among 103 979 person-years, prevalence to notification ratio [PNR] 1.44, 95% confidence interval [CI]: 1.14–1.84) in the mass screening population versus PCF population with a number needed to screen of 430 (95% CI: 357–526). The difference in case detection was highest among males (PNR 1.77, 95% CI: 1.09–2.89) and 60- to 69-year-olds (PNR 1.77, 95% CI: 1.09–2.89), but there was no difference in case detection between people with and without diabetes (PNR 1.04, 95% CI: .56–2.05).

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Correspondence: T. Wingfield, Departments of Clinical Sciences and International Public Health, Liverpool School of Tropical Medicine, Pembroke place, Liverpool, L3 5QA, UK. (tom.wingfield@lstmed.ac.uk / @drtomwingfield).

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Of the people with TB identified through mass screening, half (50%) were asymptomatic, and more than one quarter (26%) were not microbiologically confirmed by smear, Xpert, or mycobacterial culture. Symptom duration prior to diagnosis was shorter in the mass screening versus PCF group, although this was largely driven by the number of asymptomatic cases. In adjusted multivariable logistic regression, people with TB identified by mass screening were more likely than people identified by PCF to be current smokers (adjusted odds ratio [aOR] 2.43, 95% CI: 1.15–5.17), have diabetes (aOR 4.72, 95% CI: 2.17–10.91), and have only basic "Urban residents" medical insurance (aOR 4.52, 95% CI: 1.35–21.28).

Prior to delivering the mass screening intervention, the team implemented a countywide health information campaign about the TB screening with the aim of increasing rates of participation. Although vital to provide evidence-based information, dispel myths and misconception, and improve willingness to seek care [4], the design of the education campaign and its constituent elements were not described in the article. Moreover, no costing or cost-effectiveness analyses were reported with which to guide policy makers and implementers, no data was shown to facilitate comparison of PCF rates prior to and during the intervention, and the impact of the intervention (or multiple rounds of the mass screening) on TB prevalence remains unknown.

Despite the elderly being recognized by the World Health Organization (WHO) as a priority group for TB screening, especially in Southeast Asia and Western Pacific Regions [7], there are few studies on Active Case Finding (ACF) or mass screening in the elderly with which to compare Hu et al's results. A pilot ACF project in Sichuan province screened 17 000 older people during an annual check-up using a symptom and risk factor screening followed by chest radiograph and found few TB cases with an estimated detection rate of 146 per 100 000 cases [8]. A cross-sectional survey in 10 provinces of China among people over 65 years being screened for TB showed underweight, diabetes, and previous TB as risk factors for TB; identified a dose-response relationship between TB risk, increasing age and decreasing body mass index; and suggested ACF strategies should target older people with these risk factors [9].

Hu et al's article is timely and useful to consider within the context of the distinct, intersecting biosocial determinants and health system factors influencing TB in older people (Table 1), which represent a challenge to successful TB elimination strategies for this vulnerable age group.

First, TB transmission to or between older people is complex and setting-dependent. For older people in TB-endemic low- and middle-income countries with large informal economies, social determinants including poverty, overcrowding related to congregate settings or multi-generational households, poor housing conditions, and limited access to healthcare, social protection or pensions, may foment conditions for TB transmission and infection, and impact negatively on healthcare access. It is notable in Hu et al's findings that people identified with TB by mass screening were more likely to have only basic health insurance than people identified through PCF.

Second, rates of TB infection increase with age, but tuberculin skin-testing is hampered by lower sensitivity in older age groups, TB infection screening among the elderly is inconsistently implemented, and TB preventive therapy is underused in older people [4]. This, coupled with physiological processes including immune senescence and "inflammaging" [10], lack of efficacy of Bacillus Calmette–Guérin (BCG), higher rates of immunosuppressive and immunomodulatory therapy use, and comorbidities including diabetes, undernutrition, and chronic lung and/or kidney disease [11], increase the likelihood of progression of TB infection to disease among older people. In endemic areas, integrating TB screening with existing screening programs, such as for diabetes, would be of benefit.

Third, identifying TB disease in older people is challenging, meaning that diagnosis can be delayed or missed [12]. Older people with TB are more likely to present with no, few, or atypical TB symptoms, and to under-recognize or under-report their symptoms (including dyspnea). Microbiological confirmation of TB diagnosis is not straightforward in elderly populations. Older people may be less able to produce sputum and have higher likelihood of smear- or Xpert-negative disease, or extrapulmonary TB. Hu et al found a sizeable proportion of people with TB, diagnosed through both mass screening and PCF, were not microbiologically confirmed. Chest radiograph findings are distinct in this age group compared to younger adults, with lower rates of cavitation but higher rates of pleural effusion, pleural thickening, infiltrates, nodules, and mass-like lesions. Clinicians may attribute signs and symptoms to alternative diagnoses such as chronic lung disease and bronchogenic carcinoma, which have increasing prevalence with increasing age. Hu et al rightly note the low specificity of human-read chest radiographs and the potential for misclassification or overdiagnosis—such issues with radiographic interpretation have also been recognized in other countries in the region [13]. Although computer-aided detection (CAD) systems in chest radiography may lead to improvements in both sensitivity and specificity to diagnose TB, artificial intelligence algorithms will require age-adjustment to increase their utility in ACF programmes focused on older people.

Fourth, although outside of the scope of the article by Hu et al, treating older adults with TB comes with multiple nuances that, if not appreciated, can hamper rates of TB treatment success. TB care for older people should be holistic, including assessment and management of frailty and nutritional status, and ideally involve specialist gerontology multidisciplinary team input. Underweight

Table 1. Determinants of and Potential Solutions to TB Exposure, Infection, Disease, and Adverse Treatment Outcomes and Sequelae Among Older People

	TB Exposure	TB Infection, TB Infection Screening, and TB Preventive Therapy	TB Disease, TB Disease Screening and Diagnosis	TB Treatment And Care, TB Outcomes and Sequelae
Individual biological and/or clinical determinant	• Distant exposure to (commonly) drug-sensitive TB in low TB burden settings • Recent exposure to TB in high-burden settings with rates of drug-resistant TB reflecting background community rates	• Immune senescence, "inflammaging" • Lack of BCG efficacy • Underweight/undernutrition • Comorbidities including diabetes, CLD, and chronic kidney disease • Reduced sensitivity of tuberculin skin testing among older people	As per TB infection plus delayed diagnosis due to: • Asymptomatic, pauci-symptomatic • Atypical or masked symptoms • Unable to produce sputum • Lack of microbiological confirmation • Distinct chest radiographic findings (eg, less cavitation, more pleural involvement) • Low specificity of human-read chest radiographs • Alternative or dual diagnoses (ie, lung cancer or CLD)	• Adverse effects of medications • Polypharmacy and drug-drug interactions • Altered absorption and pharmacokinetic/pharmacodynamic drug properties, including due to changes in muscle mass and gastrointestinal disorders • Pre-existing lung disease, decreased lung function secondary to aging, potential altered risk of post-TB lung disease or disability compared to younger people
Individual social determinant	• Multi-generational households • Congregate settings including residential and care homes • Use of public transport	• Food insecurity or reduced dietary intake • Reduced health knowledge and awareness	• Smoking history, and smoke and air pollution exposure indoors, outdoors, and through occupation • Food insecurity or reduced dietary intake • Reduced health knowledge and awareness • Lack of access to social protection or pension schemes	• Variations in social networks and availability of treatment support to facilitate treatment adherence and accompany to clinic or for directly-observed therapy where needed • Difficulties with adherence due to memory, visual, or hearing impairment
Health system factors	• More frequent and/or prolonged contact with health system at all levels, including in the community and during home visits • Nosocomial TB transmission	• Limited access to healthcare • Difficulties navigating healthcare due to disabilities including visual and hearing impairment • Lack of health insurance or only basic health insurance • Lack of specific TB infection screening and TB preventive therapy guidance for elderly • Inconsistent implementation of TB preventive therapy	• Limited access to healthcare • Difficulties navigating healthcare due to disabilities including visual and hearing impairment • Lack of health insurance or only basic insurance • Lack of specific TB disease and symptom screening for elderly	• Lack of specific guidance on TB treatment and care for elderly • Limited guidance on integrated management of TB and comorbidities or multimorbidity, or palliative care options where appropriate • Lack of health insurance or only basic insurance
Potential solutions	• Awareness and knowledge raising campaigns through outreach and/or media suitable for elderly people and/or through involvement of social care staff or relatives/friends • TB surveillance data disaggregated by age • Modelling of intersecting age, social determinants, and comorbidities to predict and respond to TB epidemic in older people both nationally and subnationally	• Implementation and evaluation of interferon gamma release assays and newer TB infection screening tools (ie, C-Tb) among older people • Implementation and evaluation of safe and effective shorter TB preventive therapy regimens among older people, including consideration of mitigation and management of side effects and drug-drug interactions • Improved access to health insurance and simplified processes for use of health insurance, taking into account visual or hearing impairment • Evaluation of newer TB vaccines among older people	• Mass TB disease screening including through outreach and/or integrated with existing screening and health checks for older people and/or those with comorbidities or multimorbidity • Active case finding strategies tailored to reach underserved older people including in the community and social care settings • Improvement in CAD AI algorithms to identify TB and other diagnoses among older people with and without symptoms	• Improve access to health insurance, social protection, and pension schemes • Integrated care pathways for older people with TB and comorbidities or multimorbidity, with consideration of assessment and management of frailty and disability, and involvement of gerontologist or other healthcare professional with expertise in medicine for the elderly where possible • Adherence support mechanisms adapted to older people with due consideration of memory, visual and hearing impairment, and use of appropriate media/tools (i.e mobile phone interventions may not be appropriate vs setting alarms or landline prompts)

Abbreviations: AI, artificial intelligence; BCG, Bacillus Calmette–Guérin; CAD, computer assisted digital tool; CLD, chronic lung disease; C-Tb, skin test for TB (Statens Serum Institute, Copenhagen, Denmark); TB, tuberculosis.

and undernutrition, comorbidity and multimorbidity, and polypharmacy may negatively affect absorption and metabolism of TB drugs, exacerbate adverse drug effects, and increase the risk of drug-drug interactions. Alongside other factors such as memory impairment or dementia, these issues can collectively contribute to non-adherence and adverse TB treatment

outcomes including TB treatment failure, post-TB sequelae, and TB-related mortality, and require careful consideration and management. This is also of importance given newer technologies to support adherence such as video-observed therapy (VOT) may have reduced effectiveness due to limited smartphone literacy and/or visual and hearing impairment in this age group.

Ending TB among elderly individuals, especially in countries with aging populations like China, is a complex challenge influenced by age-specific biosocial factors. A multisectoral response is required to overcome this challenge, including through awareness raising and targeted or mass screening approaches as implemented by Hu et al, and also through development of tailored, integrated, and holistic TB prevention and care strategies for this underserved group.

Notes

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