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The role of IGRA in the diagnosis of tuberculosis infection, differentiating from active tuberculosis, and decision making for initiating treatment or preventive therapy of tuberculosis infection

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ABSTRACT

Objectives: The World Health Organization estimated that a quarter of the global population is infected by Mycobacterium *tuberculosis* (Mtb). A better control of tuberculosis (TB) is based on the ability to detect Mtb infection, identifying the progressors to TB disease, undergoing to preventive therapy and implementing strategies to register the infections and treatment completion.
Design: we reviewed the literature regarding the tests available for TB infection diagnosis, the preventive therapies options and the cascade of care for controlling TB at a public health level.
Results: current tests for TB infection diagnosis as IFN-γ release assays or tuberculin skin tests are based on the detection of an immune response to Mtb in the absence of clinical disease. The main limit is their low accuracy to detect progressors to disease. New preventive treatments are available with short duration that are associated with better adherence. Options to register TB infections are presented.
Conclusions: Tests to diagnose TB infection are available but they lack accuracy to identify the progressors from infection to TB disease. Shorter preventive TB therapy are available but need to be implemented worldwide. A TB infection registry is crucial for improving the cascade of care leading to a better TB control.

Introduction

The World Health Organization (WHO) estimated that in 2020 around 10 million individuals had active tuberculosis (TB) including 1.1 million children leading to 1.5 million subjects dying from the disease, and that a quarter of the global population is infected by *Mycobacterium tuberculosis* (Mtb). (Global Tuberculosis Report 2021; Global tuberculosis report 2020.).

TB is an airborne-transmitted disease and Mtb is the causative agent. The bacilli are transmitted by inhaling droplet nuclei from contagious individuals by coughing (but also speaking, singing and sneezing) (Migliori et al., 2019). After Mtb exposure, an estimated 20–25% individuals are infected while in most subjects Mtb is cleared mainly by the innate response. Among the Mtb-infected subjects, 5% can develop active disease within 2 years and in the remaining 90-95% infection is controlled by the host immune response leading to a latent state; among these, TB may reactivate in 5-10% of the individuals during their life-time (WHO consolidated guidelines on tuberculosis, 2020; WHO. Global Tuberculosis Report 2021).

The infected subjects control Mtb replication through the immune response involving both the innate (mostly at the beginning) and adaptive immunity. TB infection has been traditionally indicated by the wording “latent tuberculosis infection” (LTBI). This phrasing defines a state of persistent immune response to stimulation by Mtb antigens detected by tests as the tuberculin skin test (TST) or an interferon (IFN)-γ release assay (IGRA) without clinically active TB disease (Getahun et al., 2015). Recently WHO adopted the term “TB infection” to better designate “a continuum process” in the natural history of TB, which follows inhalation of bacilli and may lead to clinically manifested TB disease (WHO con-

Abbreviations: IGRA, interferon gamma release assays; TST, tuberculin skin test.

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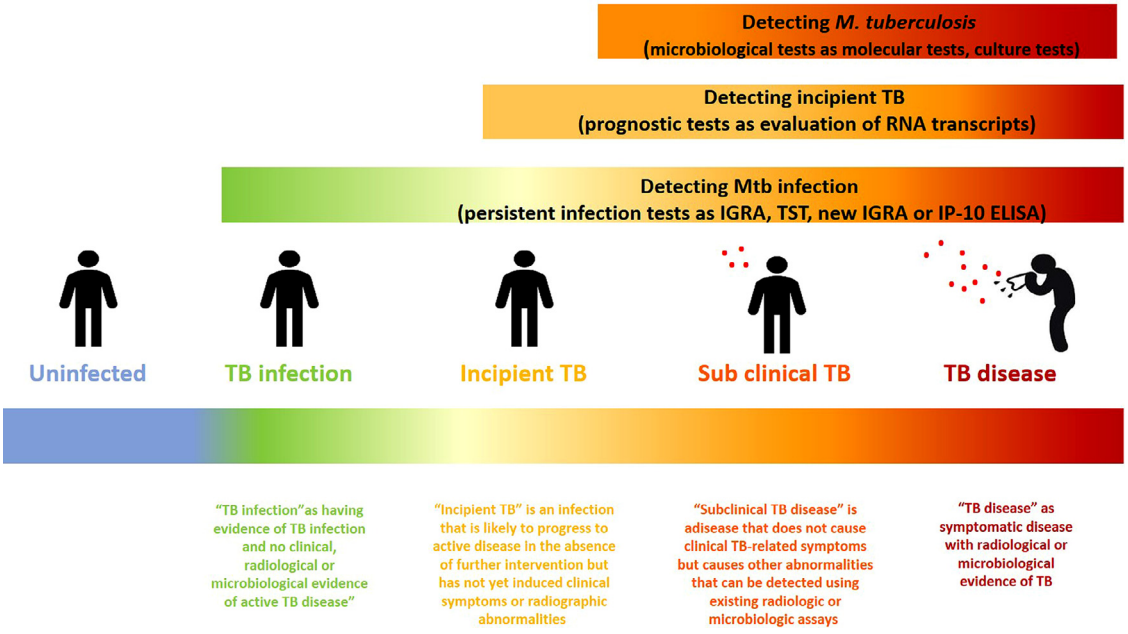

Figure 1. The "continuum process" leading from TB infection to disease. Mtb infection is characterized by a dynamic equilibrium between the host and the microbe, which may result in different conditions spanning from: TB infection, with no overt signs or symptoms of disease; incipient TB, there is an increase in viable bacteria in the involved tissues due to the partial failure of the host to contain Mtb, but no signs or symptoms of disease; sub-clinical TB, with increase in bacterial burden and damage of the involved tissue detectable by radiological tests; TB disease, with classical signs and symptoms of disease. TB: tuberculosis; TST: tuberculin skin test; IP: IFN-γ inducible protein; IGRA: IFN-γ release assays.

solidated guidelines on tuberculosis, 2020; WHO. Global Tuberculosis Report 2021).

The "continuum process" is characterized by a dynamic equilibrium between Mtb and the host, with the bacilli switching between different metabolic states (dormancy, intermittent replication, active replication) and the host able to contain Mtb replication through an efficient immune system (Drain et al., 2018). Recently, in an effort to better describe the process (and providing a tailored clinical approach) two additional clinical stages have been proposed to describe this bi-directional flow in the process going from TB infection to TB diseases: incipient and subclinical TB (Drain et al., 2018; Esmail et al., 2020) (Figure 1). Incipient TB, which lies between TB infection and subclinical TB, features the initial stage when the of host immune response struggles to contain Mtb replication and viable bacilli increase in number in granulomas. Most of what we know on incipient TB comes from experimental studies in non-human primates, and we lack validated tools to diagnose incipient TB in humans (Cadena et al., 2017; Drain et al., 2018). At this stage, the extent of tissue damage is limited and the patient is probably not infectious. Subclinical TB is defined as "disease", due to the increased number of viable Mtb in "unresolved" enlarged granulomas causing different abnormalities detectable by radiological images without showing clinical TB-related symptoms. (Esmail et al., 2020; Mendelsohn et al., 2021; Scriba et al., 2021) At the subclinical TB stage, Mtb can be detected with sufficiently sensitive tests (culture or molecular tests) and therefore at this stage the patient is potentially infectious although symptoms may not be present or, if present, not recognized by the patient. (Scriba et al., 2021)

TST and IGRA: benefits and limits

TB infection is a paucibacillary state where the small amounts of bacilli in infected individuals have immunogenic antigens that stimulate host responses that can serve as a surrogate for detection of the bacillus itself.

Tuberculin skin test (TST) based on the intradermal injection of purified protein derivative (PPD), a crude mixture of antigens, many of which are shared by Mtb and other mycobacteria, including Bacille Calmette-Guérin (BCG). TST response is evaluated by measuring the transverse diameter of skin induration. The cross-reactivity of the antigens included in the PPD compound with several mycobacteria is responsible for the suboptimal specificity of the test for Mtb infection. (Delogu and Goletti, 2014; Goletti et al., 2014; Petruccioli et al., 2016) Details on test characteristics and accuracy of TST and IGRA are summarised in table 1.

The development of more specific tests to diagnose TB infection than the TST started with the identification of a specific region of the Mtb DNA, region of difference 1 (RD1), which is absent in Mycobacterium bovis bacille Calmette–Guérin (BCG), but present in the strains of Mtb complex. (Andersen et al., 2000) This region encodes ESAT-6 and CFP-10 which are Mtb-specific and highly immunogenic, as shown by the evidence that peripheral blood mononuclear cells (PBMCs) or whole blood stimulated with ESAT-6 and CFP-10 peptides or recombinant proteins induced IFN-γ secretion. This Mtb-induced IFN-γ response was shown to correlate with the grade of exposure to a TB index case more than TST. (Barcellini et al., 2016; Ewer et al., 2003) The first IGRAs commercially available were the QuantiFERON-TB Gold In-Tube (a whole blood IGRA) and the T-SPOT TB assay (a PBMC-based IGRA) based on enzyme-linked immunosorbent assay (ELISA) or ELISPOT read-out, respectively. (Petruccioli et al., 2016)

Newer whole blood assays are now available (Table 1) based on tubes containing peptides or recombinant proteins of Mtb with IFN-γ read-out different from ELISA, as for the Liason QuantiFERON Plus or the AdvenSureI3 TB-IGRA (LG Chem, Republic of Korea) based on the detection of IFN-γ by the chemiluminescence, or tests still based on ELISA as: Standard E TB-Feron (SD Biosensor, Republic of Korea), AdvanSure TB-IGRA ELISA (LG Chem, Republic of Korea) and LIOFeron TB/LTBI (LIONEX Diagnostics & Therapeutics GmbH, Braunschweig, Germany) (Fukushima et al., 2022; Hamada et al., 2021; Migliori et al., 2021; Miotto et al., 2022;

Table 1
Characteristics and accuracy of routine-, new- and experimental-tests for tuberculosis infection detection.

	Routine tests		New routine tests			Experimental tests		
	TST	QuantiFERON Plus and T-SPOT.TB	Skin testing with RD1-encoded antigens	IGRA RD1- or PPD-antigens based tests		Transcriptomic signature in whole blood	PET/CTSCAN	Microbiological tests for TB infection
Read-out	Intradermal induration in mm	ELISA, ELISPOT	Intradermal induration in mm	ELISA, Chemiluminescence	Lateral flow, ELFA systems, other technologies	RNA transcripts	Images	Mtb DNA
Immuno-factor detected	NA	IFN-γ		IFN-γ or IP-10	IFN-γ or IP-10	NA	NA	NA
			• Diaskin test, • EC-skinTest • c-Tb	• Standard E TB-Feron, • AdvanSure TB-IGRA ELISA, LIOFeron TB/LTBI, • IP-10 IGRA ELISA, • LIAISON QuantiFERON-TB Gold Plus	• QIAreach QuantiFERON-TB • ichroma IGRA-TB, • STANDARD F TB-Feron FIA, • Erythra TB-test*, • IP-10 IGRA LF • VIDAS TB-IGRA • AdvanSure I3 TB-IGRA, • GBTsol Latent TB Test Kit			
Accuracy for active TB from LTBI discrimination	No	No	No	No	No	Possible	Possible	Unlikely
Accuracy to detect those at high risk of developing active TB	Low	Low	Low	Low	Low	Possible	Possible	Possible
Negativization of the response after preventive therapy	Usually no	Usually no	Unlikely	Unikely	Unlikely	Possible	Possible	Possible
Large scale tests for screening	Yes	Possible in higher resource settings	Yes	Possible in higher resource settings	Likely in both, higher and low resource settings	Possible if operationalized for field use	No	Possible if operationalized for field use
Cost	Low	Medium/High	Low	Medium/High	Medium	Potentially medium if operationalized for field use	High	Potentially medium/high if operationalized for field use
Laboratory facilities needed	No	Yes	No	Yes	yes	Yes	NA	Yes
Imaging facilities needed	NA	NA	NA	NA	NA	NA	Yes	NA

Abbreviations: TB: tuberculosis; LTBI: latent tuberculosis infection; IFN-g: interferon; IP-10: IFN-g inducible protein; LF: lateral flow; ELFA: enzyme-linked fluorescence assay; ELISA: enzyme-linked immunosorbent assay; TST: tuberculin skin test; ELISA:; IGRA: IFN-γ release assays; ELISPOT: enzyme-Linked immunoSPOT; NA: not available; *based on purified protein derivative (PPD).

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Petruccioli et al., 2021) or tests based on the lateral flow chromatography technology including QuantiFERON-TB (Qiagen, The Netherland), the ichroma IGRA-TB (Boditech Med Inc., Republic of Korea), the STANDARD TB-Feron FIA (SD Biosensor, Republic of Korea) and the Erythra TB-KIT (Erythra Inc, Stanford, CA, USA). Other assays are the VIDAS TB-IGRA (Biomerieux, Marcy l'Etoile, France) which is a fully automated test and GBTsol Latent TB Test Kit (Glory Biotechnologies Corp., Republic of Korea) which detects antigen-specific cells through a microfilter separation of whole blood. Interestingly, a whole blood test based on the detection of IFN-γ-induced protein-10 (IP-10) by ELISA (rBiopharm, Darmstadt, Germany) is now available. The chemokine IP-10 is present at higher levels compared to IFN-γ and is associated with TB. (Goletti et al., 2010). Among the tests reported, Erythra TB-KIT is the only test based on purified protein derivative (PPD) stimulation.

Regarding the advantages and disadvantages: TST platform may offer the advantages over IGRAs because it is less expensive, not needing a laboratory setting and easier to be used for large screening settings. On the other side, compared to TST, IGRAs or the assay based on IP-10 detection have several advantages: these tests do not need a second visit for reading; have a lower number of false-negative results in immunosuppressed individuals; are specific for Mtb infection and therefore they are scored negative in BCG-vaccinated subjects or individuals with nontuberculous mycobacteria infection (with the exception of *M. kansasii, M. szulgai, M. marinum, and M. riyadhense* that contain ESAT-6 ref). (van Ingen et al., 2009)

The main objective to diagnose TB infection is to prevent active TB development. However, several studies have shown that TST and IGRA have a low ability to predict active TB development, as also recently shown in a prospective study done in TB contacts and recent immigrants in a low TB-incidence setting. The positive predictive value (PPV) of the QuantiFERON-TB Gold In-Tube was 3.3%, while the reported PPV of T-SPOT TB was 4.2% and that of TST (a 15 mm cut-off was used to define positivity) was 3.5%.(Abubakar et al., 2018) Therefore, based on this evidence, currently, we treat a large number of subjects scored IGRA or TST positive to prevent one individual from developing TB disease. (Esmail et al., 2020; Petruccioli et al., 2016; Scriba et al., 2021) Therefore, there is an urgent need to develop a new generation of assays that predict with higher accuracy those that will progress to disease and focus the diagnostic effort on this target population.

Children TB

Immune-based TB tests are also used for TB infection screening in children (Martinez et al, 2020; Carvalho et al, 2018). To note that children TB diagnosis is challenging and IGRAs and TST are also used as supporting adjunctive diagnostic tools in those with suspected TB disease (Lewinsohn et al, 2017) especially in extra-pulmonary TB (Basu Roy et al, 2020). The immature immune system of young children may be associated to higher proportion of IGRAs indeterminate scores [on average in 1 out 25 tests performed (Meier et al, 2019) or false negative results (Martinez et al, 2020)]. More accurate diagnostic tools are needed.

Experimental tests for identifying progressor to TB disease

Recently, blood gene expression signatures of the host have been identified in both HIV-uninfected and -infected individuals as associated with a higher risk to develop active TB. (Mendelsohn et al., 2021; Scriba et al., 2021) These signatures can predict short-term progression to active disease and positron emission tomography-computed tomography images confirmed intrathoracic lesions with increased uptake of radiolabelled glucose in the absence of specific symptoms or chest radiography images indicative of TB disease. (Esmail et al., 2020, 2016) The best therapy for the individuals that are "transcript signature positive" is unknown now, since preventive therapy failed to prevent disease development. (Scriba et al., 2021)

Another approach is to detect *Mtb* DNA based on a bacteriophage-based technology, as shown in 3/18 asymptomatic TB contacts living in a different low-incidence setting (United Kingdom), of whom 2 went on to develop active TB after 7 months. (Verma et al., 2020) This approach proposes to detect the pathogen (Mtb) more than the immune response as a tool to identify those with TB infection more likely to progress to active disease.

Other approaches to detect Mtb DNA in whole blood by a digital PCR have been recently described in a population of HIV-infected and uninfected subjects in Ethiopia. Preventive therapy to HIV-infected participants reduced the prevalence of PCR-detected *Mtb* from 95% at baseline to 54% post-treatment (Belay et al., 2021). Experimental in vitro tests based on the detection of IFN-γ to heparin-binding hemagglutinin antigen (HBHA) have been shown interesting results as associated with *Mtb* containments and as tools to monitor active TB clinical states in children (Sali et al, 2018) confirming results from the adults (Delogu et al., 2011; Hedid et al., 2020; Chiacchio et al, 2017; Tang et al, 2021). Further studies to evaluate the ability of these approaches to predict TB development are needed (Table 1).

Recommended regimens for preventive therapy

WHO revised (WHO consolidated guidelines on tuberculosis, 2020; WHO. Global Tuberculosis Report 2021) the available evidence and indicated the following population groups as at high risk for progression to TB disease or at high rates of TB infection as: HIV-infected individuals as adults, adolescents, and children; household or close contacts of patients with bacteriologically confirmed pulmonary TB (all ages, but especially young children <5 years of age); candidates to either tumour necrosis factor(TNF)-α inhibitors, or dialysis, or organ or haematological transplant; subjects with silicosis; prisoners, healthcare workers having frequent unprotected contact with TB patients, migrants from countries with high TB burden, homeless people and people who abuse drugs.

Additional groups at risk are those with diabetes, alcohol abusers, tobacco smokers and those underweight; however, systematic TB infection testing and preventive therapy is not recommended unless they also belong to the risk groups described above.

Treatment is an essential component to the programmatic management of TB infection, designed to prevent the progression of TB infection to clinically active TB disease. Currently recommended treatment regimen are selected on the basis of evidence around efficacy, tolerability, acceptability, costs, feasibility under program conditions, and risk of fostering drug resistance during treatment. Safety is obviously pivotal, as all treated patients are healthy, and only a small proportion would develop active TB even in the absence of treatment. For example, pyrazinamide containing regimens were excluded from the WHO recommended options based on the evidence of fatal cases in a survey of state and city TB programs and other health-care settings in the United States. (McElroy et al., 2005)

Isoniazid has been the mainstay of TB infection treatment for a long time, with efficacy ranging from 60 to 90% (Horsburgh and Rubin, 2011) (Table 2). More recently, research around preventive therapy developed around two main axes: developing regimens that are less toxic than isoniazid and that are shorter, to increase

Table 2
Preventive therapy options available.

Regimen	Dose by age and weight band					
6 or 9 months of daily isoniazid monotherapy (6H, 9H)[a]	Age 10 years & older: 5 mg/kg/day Age < 10 years: 10 mg/kg/day (range, 7–15 mg)					
Four months of daily rifampicin (4R)	Age 10 years & older: 10 mg/kg/day Age < 10 years: 15 mg/kg/day (range, 10–20 mg)					
Three months of daily rifampicin plus isoniazid (3HR)	Isoniazid: Age 10 years & older: 5 mg/kg/day Age < 10 years: 10 mg/kg/day (range, 7–15 mg) Rifampicin: Age 10 years & older: 10 mg/kg/day Age < 10 years: 15 mg/kg/day (range, 10–20 mg)					
Three months of rifapentine plus high dose isoniazid weekly (12 doses) (3HP)	Age 2–14 years[d]					
	Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	> 34 kg
	Isoniazid 100 mg[b]	3	5	6	7	7
	Rifapentine 150 mg	2	3	4	5	5
	Isoniazid + rifapentine FDC (150 mg/150 mg)[c]	2	3	4	5	5
	Age > 14 years[d]					
	Medicine, formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	> 70 kg
	Isoniazid 300 mg	3	3	3	3	3
	Rifapentine 150 mg	6	6	6	6	6
	Isoniazid + rifapentine FDC (300 mg/300 mg)[c]	3	3	3	3	3
One month of rifapentine plus isoniazid daily (28 doses) (1HP)	Age ≥ 13 years (regardless of weight band) Isoniazid 300 mg/day Rifapentine 600 mg/day					
Six months of levofloxacin daily (preventive treatment of MDR-TB)	Age > 14 years, by body weight: < 46 kg, 750 mg/day; > 45 kg, 1g/day Age < 15 years[e] (range approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day; 10–15 kg: 200–300mg/day; 16–23 kg: 300–400mg/day; 24–34 kg: 500–750mg/day					

Abbreviations: H: isoniazid; P: rifapentine; R: rifampicine; 6H: 6 months isoniazie; 1HP: 1 month isoniazid and rifapentine; 3HR: 3 months isoniazid and rifampicine.

[a] A triple pill combination containing isoniazid 300 mg + pyridoxine 25 mg + sulfamethoxazole 800 mg + trimethoprim 160 mg (scored) is the preferred alternative regimen for PLHIV being considered for isoniazid monotherapy (1 pill daily for adults, half pill for children 5 years and older of age and quarter for children < 5 years of age).

[b] 300 mg formulation can be used to reduce the pill burden.

[c] Expected to become available in a near future.

[d] Dosage may differ among adults and children in overlapping weight-bands.

[e] Levofloxacin 100 mg dispersible tablets available for children.

the probability of completing treatment. A network meta-analysis published in 2017 evaluated the comparative efficacy and harms of TB infection treatment regimens aimed at preventing active TB among adults and children. It included 61 studies and showed evidence for the efficacy and safety of 6-months isoniazid monotherapy, rifampicin monotherapy for 4 months, and combination therapies with 3 months of isoniazid and rifampicin. (Zenner et al., 2017) A comparison of regimens for efficacy and hepatotoxicity showed that rifampicin for 4 months had lower liver-related serious adverse events compared to both 6 months of isoniazid and 3 months of rifampicin and isoniazid. A couple of years later a multicenter, randomized clinical trial run for about a decade, demonstrated the equivalence, in terms of efficacy, of daily rifampin for 4 months compared to a 9-month regimen of isoniazid. (Menzies et al., 2008)

Significant progresses, in the field of TB preventive therapy, were achieved by introducing rifapentine regimens in clinical practice. A once-weekly regimen had similar efficacy compared to a 9-month regimen of daily isoniazid and was associated with higher treatment-completion rates and less hepatotoxicity both in adults (Sterling et al., 2011) and children (Villarino et al., 2015). Importantly, these results were confirmed, in terms of better completion rate, in the U.S. TB Control Programs after its implementation in routine practice (Sandul et al., 2017). Moreover, while in initial equivalence studies rifapentine and isoniazid were administered by directly observed therapy, the same results were obtained by self-administration of the drugs (Belknap et al., 2017). Finally, an ultrashort regimen, consisting of 1 month of daily isoniazid 300 mg and rifapentine 300–600 mg was non-inferior to 9 months of isoniazid for TB prevention in persons living with HIV infection (Swindells et al., 2019) (Table 2). Importantly, the percentage of patients who completed treatment was significantly higher in the 1-month group. This very promising regimen requires validation to define efficacy and tolerability in different populations, as shown in a recent study showing that 1HP was safely and feasibly implemented in children and adolescents in a programmatic setting in a low-resource setting in south Asia with low prevalence of HIV (Malik et al., 2021).

None of the above-mentioned regimens for preventive therapy would be theoretically effective in contacts of patients with MDR-TB. However, no current regimen exists with proven efficacy in this situation. Three ongoing randomised controlled trials currently evaluate PT in MDR-TB children and adult contacts. Two of them, the V-Quin trial in Vietnam [ANZCT Registry-Identifier, 2016] and the TB-CHAMP trial in South Africa [ISRCTN-ISRCTN92634082, 2019] evaluate levofloxacine daily for 6 months. The third, the PHOENIx trial at ACTG sites [clinicalTrials.gov Identifier, 2018] compares delamanid with isoniazid for all contacts of MDR-TB and XDR-TB. Results of these studies will inform updated recommendations, probably by the end of 2022.

Exclusion of active TB is an essential step of the prevention cascade; despite the theoretical risk that preventive therapy might foster resistance to TB medications if active TB is not effectively excluded, there is no evidence of increased drug resistance in people who received either isoniazid – relative risk 1.24, 95% CI: 0.69-2.21 (Balcells et al., 2006) or rifampicin – relative risk 1.12, 95% CI 0.41-3.08 (den Boon et al., 2016) for prevention.

TB infection and public health

The management of TB infection, e.g. its diagnosis and treatment, has been considered core intervention to pursue TB Elimination, specifically being the fourth of the 8 activities according to the WHO Framework for TB Elimination (Lönnroth et al., 2015; Matteelli et al., 2018; WHO. Global Tuberculosis Report 2021).

In a recent UNION document reporting the clinical Standards for TB infection management (Migliori et al., 2022), a specific Public Health Standard was proposed, which recommends the following: *A TB infection screening and testing registry should be kept to inform the cascade of care.*

The present article discusses the benefits of undergoing testing and preventive therapy in terms of reduced probability of developing TB when TB infection is diagnosed. In order to reach a public health goal, it is necessary that an important proportion of individuals belonging to the groups at risk to progress to disease are screened for TB infection, accept to be treated if positive, undergo and complete the prescribed regimen. This process is called 'TB infection cascade of care', a crucial path towards TB Elimination (Lönnroth et al., 2015). A registry that reports the individuals with TB infection and the variables associated with TB infection is needed to build the "cascade". These variables need to be discussed and implemented by countries, in parallel to what is presently done for TB disease. TB infection registry is nowadays considered as best-practice for patient follow-up, programmatic planning and clinical governance tool to evaluate programmatic effectiveness of the intervention (Alsdurf et al., 2016; Collin et al., 2019; WHO. Global Tuberculosis Report 2021). The registry has a clinical value, reporting the necessary information to manage the patient (e.g. follow-up visits, notification of adverse events and successful regimen completion): it is also relevant for public health issues to notify the infected individuals, to avoid duplications, to monitor how the patients are managed, and, most importantly, to trace the individuals who started the treatment and completed it. As a general principle in surveillance, the best option is to design an electronic registry based on individual data which is much more precise and flexible than the option based on designing the registry based on aggregated data. The legislation in force (with data-protection requirements) in each country or setting and the resources available will define how the registry will be designed and will operate.

The WHO, in its recent guidelines, recommends three core indicators allowing the global evaluation of TB infection management (WHO. Global Tuberculosis Report 2021):

1 Contact investigation coverage: percentage of contacts of bacteriologically-confirmed TB patients who were evaluated for TB disease and TB infection out of those eligible;
2 TB preventive therapy coverage: percentage of individuals that initiated on TPT out of those eligible;
3 TB preventive therapy coverage completion: percentage of individuals completing TPT out of those initiating treatment.

Important to underline that whenever an individual notified in the TB infection registry progress to TB disease, this event needs to be notified to the TB Registry.

Conclusions

We need better tools to identify those that progress from infection to TB disease. Shorter preventive TB therapy regimens are needed. The scientific, clinical and public health community are working to improve the current strategies in order to reach a better control of TB worldwide.

Transparency declaration

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Declaration of Competing Interest

Delia Goletti has done lectures for Amgen, Biogen, Biomerieux, Cellgene, Diasorin, Janssen; she has been a consultant for Eli Lilly, PDB Biotec, Qiagen, Quidel. The other authors do not have any conflict of interest.

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Ethical Approval statement

No need of an ethical approval.

REFERENCES

Abubakar I, Drobniewski F, Southern J, Sitch AJ, Jackson C, Lipman M, et al. Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. Lancet Infect Dis 2018;18:1077–87. doi:10.1016/S1473-3099(18)30355-4.

Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:1269–78. doi:10.1016/S1473-3099(16)30216-X.

Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculosis. Lancet 2000;356:1099–104. doi:10.1016/s0140-6736(00)02742-2.

Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis 2006;12:744–51. doi:10.3201/eid1205.050681.

Barcellini L, Borroni E, Brown J, Brunetti E, Campisi D, Castellotti PF, et al. First evaluation of QuantiFERON-TB Gold Plus performance in contact screening. Eur Respir J 2016;48:1411–19. doi:10.1183/13993003.00510-2016.

Basu Roy R, Thee S, Blázquez-Gamero D, Falcón-Neyra L, Neth O, Noguera-Julian A, et al. Performance of immune-based and microbiological tests in children with tuberculosis meningitis in Europe: a multicentre Paediatric Tuberculosis Network European Trials Group (ptbnet) study. Eur Respir J 2020;2:1–11. doi:10.1183/13993003.02004-2019.

Belay M, Tulu B, Younis S, Jolliffe DA, Tayachew D, Manwandu H, et al. Detection of Mycobacterium tuberculosis complex DNA in CD34-positive peripheral blood mononuclear cells of asymptomatic tuberculosis contacts: an observational study. Lancet Microbe 2021;2:e267–75. doi:10.1016/S2666-5247(21)00043-4.

Belknap R, Holland D, Feng P-J, Millet J-P, Caylà JA, Martinson NA, et al. Self-administered Versus Directly Observed Once-Weekly Isoniazid and Rifapentine Treatment of Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med 2017;167:689–97. doi:10.7326/M17-1150.

den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. Int J Tuberc Lung Dis 2016;20:1065–71. doi:10.5588/ijtld.15.0908.

Cadena AM, Fortune SM, Flynn JL. Heterogeneity in tuberculosis. Nat Rev Immunol 2017;17:691–702. doi:10.1038/nri.2017.69.

Carvalho I, Goletti D, Manga S, Silva DR, Manissero D, Migliori G. Managing latent tuberculosis infection and tuberculosis in children. Pulmonology 2018;24:106–14. doi:10.1016/j.rppnen.2017.10.007.

Chiacchio T, Delogu G, Vanini V, Cuzzi G, De Maio F, Pinnetti C, et al. Immune characterization of the HBHA-specific response in Mycobacterium tuberculosis-infected patients with or without HIV infection. PLoS One 2017;2. doi:10.1371/journal.pone.0183846.

Collin SM, Wurie F, Muzyamba MC, de Vries G, Lönnroth K, Migliori GB, et al. Effectiveness of interventions for reducing TB incidence in countries with low TB incidence: a systematic review of reviews. Eur Respir Rev 2019;28. doi:10.1183/16000617.0107-2018.

Delogu G, Goletti D. The spectrum of tuberculosis infection: new perspectives in the era of biologics. J Rheumatol Suppl 2014;91:11–16. doi:10.3899/jrheum.140097.

Delogu G, Chiacchio T, Vanini V, Butera O, Cuzzi G, Bua A, et al. Methylated HBHA produced in M. smegmatis discriminates between active and non- active tuberculosis disease among RD1-responders. PLoS One 2011;29:e18315. doi:10.1371/journal.pone.0018315.

Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, et al. Incipient and Subclinical Tuberculosis: a Clinical Review of Early Stages and Progression of Infection. Clin Microbiol Rev 2018;31:e00021 -18. doi:10.1128/CMR.00021-18.

Esmail H, Cobelens F, Goletti D. Transcriptional biomarkers for predicting development of tuberculosis: progress and clinical considerations. Eur Respir J 2020;55. doi:10.1183/13993003.01957-2019.

Esmail H, Lai RP, Lesosky M, Wilkinson KA, Graham CM, Coussens AK, et al. Characterization of progressive HIV-associated tuberculosis using 2-deoxy-2-[18F]fluoro-D-glucose positron emission and computed tomography. Nat Med 2016;22:1090–3. doi:10.1038/nm.4161.

Ewer K, Deeks J, Alvarez L, Bryant G, Waller S, Andersen P, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet 2003;361:1168–73. doi:10.1016/S0140-6736(03)12950-9.

Fukushima K, Akagi K, Kondo A, Kubo T, Sakamoto N, Mukae H. First clinical evaluation of the QIAreachTM QuantiFERON-TB for tuberculosis infection and active pulmonary disease. Pulmonology 2022;28:6–12. doi:10.1016/j.pulmoe.2021.07.003.

Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J 2015;46:1563–76. doi:10.1183/13993003.01245-2015.

Global tuberculosis report 2020. n.d. https://www.who.int/publications-detail-redirect/9789240013131 (accessed February 1, 2022).

Goletti D, Raja A, Syed Ahamed Kabeer B, Rodrigues C, Sodha A, Carrara S, et al. Is IP-10 an accurate marker for detecting M. tuberculosis-specific response in HIV-infected persons? PLoS One 2010;5:e12577. doi:10.1371/journal.pone.0012577.

Goletti D, Sanduzzi A, Delogu G. Performance of the tuberculin skin test and interferon-γ release assays: an update on the accuracy, cutoff stratification, and new potential immune-based approaches. J Rheumatol Suppl 2014;91:24–31. doi:10.3899/jrheum.140099.

Hamada Y, Cirillo DM, Matteelli A, Penn-Nicholson A, Rangaka MX, Ruhwald M. Tests for tuberculosis infection: landscape analysis. Eur Respir J 2021;58. doi:10.1183/13993003.00167-2021.

Hedid C, Kokhreidze E, Tukvadze N, Banu S, Uddin MKM. Biswas S,et al. Association of baseline white blood cell counts with tuberculosis treatment outcome: a prospective multicentered cohort study. Int J Infect Diseases 2020;100:199–206. doi:10.1016/j.ijid.2020.09.017.

Horsburgh CR, Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. N Engl J Med 2011;364:1441–8. doi:10.1056/NEJMcp1005750.

van Ingen J, de Zwaan R, Dekhuijzen R, Boeree M, van Soolingen D. Region of difference 1 in nontuberculous Mycobacterium species adds a phylogenetic and taxonomical character. J Bacteriol 2009;191:5865–7. doi:10.1128/JB.00683-09.

Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis 2017;64:111–15. doi:10.1093/cid/ciw778.

Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J 2015;45:928–52. doi:10.1183/09031936.00214014.

Malik AA, Farooq S, Jaswal M, Khan H, Nasir K, Fareed U, et al. Safety and feasibility of 1 month of daily rifapentine plus isoniazid to prevent tuberculosis in children and adolescents: a prospective cohort study. Lancet Child Adolesc Health 2021;5:350–6. doi:10.1016/S2352-4642(21)00052-3.

Martinez L, Cords O, Horsburgh CR, Andrews JR. Pediatric TB Contact Studies Consortium. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. Lancet 2020;395:973–84. doi:10.1016/S0140-6736(20)30166-5.

Matteelli A, Rendon A, Tiberi S, Al-Abri S, Voniatis C, Carvalho ACC, et al. Tuberculosis elimination: where are we now? Eur Respir Rev 2018;27. doi:10.1183/16000617.0035-2018.

McElroy PD, Ijaz K, Lambert LA, Jereb JA, Iademarco MF, Castro KG, et al. National survey to measure rates of liver injury, hospitalization, and death associated with rifampin and pyrazinamide for latent tuberculosis infection. Clin Infect Dis 2005;41:1125–33. doi:10.1086/444463.

Meier NR, Volken T, Geiger M, Heininger U, Tebruegge M, Ritz N. Risk Factors for Indeterminate Interferon-Gamma Release Assay for the Diagnosis of Tuberculosis in Children-A Systematic Review and Meta-Analysis. Front Pediatr 2019;7:208. doi:10.3389/fped.2019.00208.

Mendelsohn SC, Fiore-Gartland A, Penn-Nicholson A, Mulenga H, Mbandi SK, Borate B, et al. Validation of a host blood transcriptomic biomarker for pulmonary tuberculosis in people living with HIV: a prospective diagnostic and prognostic accuracy study. Lancet Glob Health 2021;9:e841–53. doi:10.1016/S2214-109X(21)00045-0.

Menzies D, Long R, Trajman A, Dion M-J, Yang J, Al Jahdali H, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med 2008;149:689–97. doi:10.7326/0003-4819-149-10-200811180-00003.

Migliori GB, et al. Clinical standards for the diagnosis, treatment and prevention of TB infection. Int J Tuberc Lung Dis. http://dx.doi.org/10.5588/ijtld.21.0753, in press.

Migliori GB, Ong CWM, Petrone L, D'Ambrosio L, Centis R, Goletti D. The definition of tuberculosis infection based on the spectrum of tuberculosis disease. Breathe (Sheff) 2021;17. doi:10.1183/20734735.0079-2021.

Migliori GB, Nardell E, Yedilbayev A, D'Ambrosio L, Centis R, Tadolini M, et al. Reducing tuberculosis transmission: a consensus document from the World Health Organization Regional Office for Europe. Eur Respir J 2019;53. doi:10.1183/13993003.00391-2019.

Miotto P, Goletti D, Petrone L. Making IGRA testing easier: First performance report of QIAreach QFT for tuberculosis infection diagnosis. Pulmonology 2022;28:4–5. doi:10.1016/j.pulmoe.2021.07.010.

Petruccioli E, Petrone L, Chiacchio T, Farroni C, Cuzzi G, Navarra A, et al. Mycobacterium tuberculosis Immune Response in Patients With Immune-Mediated Inflammatory Disease. Front Immunol 2021;12. doi:10.3389/fimmu.2021.716857.

Petruccioli E, Scriba TJ, Petrone L, Hatherill M, Cirillo DM, Joosten SA, et al. Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis. Eur Respir J 2016;48:1751–63. doi:10.1183/13993003.01012-2016.

Sali M, Buonsenso D, D'Alfonso P, De Maio F, Ceccarelli M, Battah B, et al. Combined use of Quantiferon and HBHA-based IGRA supports tuberculosis diagnosis and therapy management in children. J Infect 2018;77:526–33. doi:10.1016/j.jinf.2018.09.011.

Sandul AL, Nwana N, Holcombe JM, Lobato MN, Marks S, Webb R, et al. High Rate of Treatment Completion in Program Settings With 12-Dose Weekly Isoniazid and Rifapentine for Latent Mycobacterium tuberculosis Infection. Clin Infect Dis 2017;65:1085–93. doi:10.1093/cid/cix505.

Scriba TJ, Fiore-Gartland A, Penn-Nicholson A, Mulenga H, Kimbung Mbandi S, Borate B, et al. Biomarker-guided tuberculosis preventive therapy (CORTIS): a randomised controlled trial. Lancet Infect Dis 2021;21:354–65. doi:10.1016/S1473-3099(20)30914-2.

Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011;365:2155–66. doi:10.1056/NEJMoa1104875.

Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. N Engl J Med 2019;380:1001–11. doi:10.1056/NEJMoa1806808.

Tang J, Huang Y, Cai Z, Ma Y. Mycobacterial heparin-binding hemagglutinin (HBHA)-induced interferon-γ release assay (IGRA) for discrimination of latent and active tuberculosis: A systematic review and meta-analysis. PLoS One 2021;16. doi:10.1371/journal.pone.0254571.

Verma R, Swift BMC, Handley-Hartill W, Lee JK, Woltmann G, Rees CED, et al. A Novel, High-sensitivity, Bacteriophage-based Assay Identifies Low-level Mycobacterium tuberculosis Bacteremia in Immunocompetent Patients With Active and Incipient Tuberculosis. Clin Infect Dis 2020;70:933–6. doi:10.1093/cid/ciz548.

Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, 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. doi:10.1001/jamapediatrics.2014.3158.

WHO. Global Tuberculosis Report 2021: Executive Summary. Geneva, Switzerland; 2021.

WHO. Consolidated guidelines on tuberculosis: tuberculosis preventive treatment: Module 1: prevention. Geneva: World Health Organization; 2020.

Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Ann Intern Med 2017;167:248–55. doi:10.7326/M17-0609.