Commemorating World Tuberculosis Day 2022: recent ERJ articles of critical relevance to ending TB and saving lives

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The ERJ commemorates World TB Day 2022 by publishing relevant articles to contribute to the fight against tuberculosis https://bit.ly/3gNby7P


Introduction

Tuberculosis (TB) remains a major public health concern worldwide. In 2020, it was the 13th leading cause of death and the second leading infectious killer after coronavirus disease 2019 (COVID-19), above HIV/AIDS. In 2020 a total of 1.5 million people died from TB, while about 10 million people are estimated to have suffered from the disease: 5.6 million men, 3.3 million women and 1.1 million children [1].

Since 2020, the COVID-19 pandemic dramatically increased demands on health providers. TB services were particularly affected given that many of them were at the frontline of care for people with COVID-19 and other pulmonary or infectious diseases [1–5].

A recent multi-country study indicated that, globally, fewer cases of TB (both drug-susceptible and drug-resistant) and TB infection were notified in 2021 versus 2020, with lower access to health services for patients and increased death rates [2].

The World Health Organization (WHO) estimated an increase of about 100 000 in the global number of TB deaths occurring between 2019 and 2020: a reversal of a continued decline in global TB mortality since 2005. This was accompanied by a slowing in the annual decline in the global TB incidence rate.

A fall of 18% in global TB notifications was observed between 2019 and 2020, together with 15% decline in people enrolled on treatment for multidrug-resistant (MDR)/rifampicin-resistant TB, a downturn in the number of people initiated on TB preventive treatment (TPT) and a reduction in coverage of the bacille Calmette-Guérin (BCG) vaccine among children [1]. As the effect of COVID-19 on TB services continued in 2021 and early 2022 the United Nations high-level meeting target of treating 40 million people diagnosed with TB and providing TPT to 30 million people in the 5-year period 2018–2022 is off-track [6].

The European Respiratory Journal (ERJ) has always been in the frontline in the fight against TB. As in the past, ERJ is happy to contribute to advocacy efforts by publishing a special issue in March 2022 offering to the scientific community a selection of important articles relevant to the year’s theme for World TB Day 2022, “Invest to end TB. Save lives” [7].

This editorial, written by experts from different leading organisations active in the fight against TB, presents a selection of relevant ERJ articles on TB published in late 2021 and the first quarter of 2022 [8–17].
A brief summary of the core historical discoveries in the area of prevention, diagnosis and treatment of TB is shown in table 1 [18–21].

**TB diagnosis**

In Mozambique, SaaVEDRA et al. [8] evaluated the diagnostic accuracy of Xpert MTB/RIF (Xpert) and Xpert MTB/RIF Ultra using single respiratory specimens from symptomatic adults accessing healthcare services (passive case-finding scenario, 1419 individuals), and from household and community close contacts (active case-finding scenario, 252 individuals). In the passive case-finding scenario, Xpert Ultra showed higher sensitivity than Xpert, both overall (0.95 versus 0.88; p<0.001) and among smear-negative patients (0.84 versus 0.63; p<0.001). The specificity of Ultra was lower than that of Xpert, both overall (0.96 versus 0.98; p=0.008) and among smear-negative patients (0.96 versus 0.98; p=0.05). Sensitivity of the two tests was similar in the active case-finding scenario (0.67 for both tests), although Ultra detected a higher number of microbiologically confirmed samples than Xpert (4.7% versus 2.7%). The study demonstrates a higher sensitivity of Xpert Ultra under different case-finding scenarios in the field.

In Uganda, ORIKIRIZA et al. [9] evaluated the diagnostic accuracy of Xpert MTB/RIF from stool and urine of Alere lipoolarabinomannan (LAM) test in a prospective cohort of hospitalised children with presumptive TB and at risk of disseminated disease (being either age <2 years, HIV-positive or with severe malnutrition). Non-sputum-based diagnostic approaches are of particular interest in such patients, who cannot expectorate sputum. The sensitivity and specificity of stool Xpert MTB/RIF against the microbiological reference on respiratory samples were 50.0% and 99.1%, while those of urine Alere LAM were 50.0% and 74.6%, respectively. The authors concluded that Xpert MTB/RIF assay has excellent specificity on stool, but sensitivity is suboptimal; in contrast, urine Alere LAM test has poor sensitivity and specificity in children.

In a systematic review and meta-analysis by VELEN et al. [10], the effectiveness of contact investigation among contacts of TB patients was evaluated in comparison to passive case-detection alone. Data were extracted from 244 studies (187 studies assessed TB disease in contacts and 135 studies measured prevalence of TB infection). The authors evaluated the effectiveness of contact investigation in randomised trials in which contact investigation was compared to standard “passive” approaches to case detection. They further evaluated the yield of contact investigation (co-prevalent and incident TB and TB infection) in non-randomised studies. The three available randomised trials demonstrated that contact investigation: 1) increased TB case notification in Vietnam (relative risk 2.5) and TB case detection in Uganda (odds ratio 1.34), the definitions being different in the two studies; 2) decreased mortality (relative risk 0.6) in Vietnam and population TB prevalence (risk ratio 0.82) in South Africa and Zambia. In non-randomised studies the overall pooled prevalence of TB was 3.6% and the pooled prevalence of microbiologically confirmed TB was 3.2%. The pooled incidence of TB was highest in the first year after exposure to index patients (2.0%) and then lower 5 years after exposure to the index patient (0.5%). The pooled prevalence of TB infection among contacts was 42.4%. The authors concluded that contact investigation was effective in high-burden settings. The higher pooled prevalence estimates of microbiologically confirmed TB compared to previous reviews suggest that newer rapid molecular diagnostics contribute to an increased case detection.

**TABLE 1**

<table>
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<th>Year</th>
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<tr>
<td>1859</td>
<td>The first sanatorium was opened in Germany in 1859 by Hermann Brehmer, with the goal of isolating patients and offering them rest, quality food and physiotherapy.</td>
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<td>1882 (24th March)</td>
<td>Robert Koch presented in Berlin his findings on the aetiological agent of the disease, <em>Mycobacterium tuberculosis</em> [18–20]. Each year the TB community commemorates this date as World TB Day. Starting from the ancestral culture developed by Koch, this date represents also the beginning towards the discovery of new diagnostics, from culture and drug-susceptibility testing to the new rapid molecular diagnostics [19–21].</td>
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<td>1882</td>
<td>Pneumothorax was introduced by Carlo Forlanini [19–21].</td>
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<td>1895</td>
<td>Wilhelm Conrad Röntgen discovered X-rays, opening the way to the discovery of new imaging tools [19, 20].</td>
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<td>1921</td>
<td>BCG vaccination with the attenuated <em>Mycobacterium bovis</em> strain invented by Albert Calmette and Camille Guérin was introduced in clinical practice [19, 20].</td>
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<td>1944</td>
<td>William H. Feldman and Horton Corwin Hinshaw from the Mayo Clinic treated a young lady with TB using extracts from <em>Streptomyces griseus</em> (called streptomycin), with good results [19, 20]. This discovery followed the observations by Selman A. Waksman in 1914 that secretions of <em>Streptomyces griseus</em> inhibit bacterial growth, and a first publication in 1943 showing this was true also for <em>M. tuberculosis</em>.</td>
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Treatment of TB and management of TB infection

Cheson et al. [11] analysed pre-existing and emerging bedaquiline resistance in bedaquiline-containing MDR-TB regimens and the risk factors associated with treatment failure and death. At baseline, all isolates were susceptible to bedaquiline. Among the 26 patients with available baseline and follow-up isolates, four (15.3%) harboured strains with bedaquiline resistance acquired during treatment. A single patient (3.8%) was reinfected with a different bedaquiline-resistant strain. The authors concluded that bedaquiline resistance emerged among >15% of the strains from MDR-TB patients with available bacterial isolates prior and during bedaquiline therapy. MDR-TB regimens with an insufficient number of active drugs and cavitory disease were considered risk factors for treatment failure and death in this cohort. Although the sample size of patients with complete information is modest, the results are important and of general interest.

Ghodousi et al. [12] discussed the microevolution of a pre-XDR (MDR-TB with additional resistance to fluoroquinolones) Mycobacterium tuberculosis strain isolated from a pulmonary TB patient at different time points over 18 months during treatment with a regimen containing bedaquiline (with moxifloxacin, linezolid, cycloserine, ethionamide and pyrazinamide). The authors reported the acquisition of high-level resistance to bedaquiline and the subsequent development of XDR-TB (defined as MDR-TB resistant to a fluoroquinolone and to either bedaquiline or linezolid or both) due to emergence of an Ala63Pro mutation in atpE gene encoding the bedaquiline target ATP synthase. The authors also discussed the gradual disappearance of Ala63Pro mutation following by the emergence and fixation of a premature stop codon mutation in Rv0678 during this period. The authors concluded that bedaquiline-containing regimens for MDR-TB require effective companion drugs to prevent emergence of additional resistance and achieve high cure rates, and that mutations affecting bedaquiline resistance behave differently due to their fitness cost. The emergence of target-based resistance within 3 months of bedaquiline treatment also shows the risk of resistance amplification in a relatively short time. The authors conclude that countries with a high burden of MDR-TB need to develop capacity not only for phenotypic drug-susceptibility testing but also for minimal inhibitory concentration testing and whole genome sequencing.

Decroo et al. [13] added to the body of knowledge how to manage the treatment of TB resistant to the most important first-line anti-TB drug, rifampicin, when resistance to fluoroquinolones is unknown. Given the complexity of describing details of the regimens evaluated in a short editorial, we invite the interested reader to read the manuscript. The authors concluded that in the original standardised short treatment regimen for rifampicin-resistant TB, bedaquiline proved to be an important core drug in the presence of fluoroquinolone resistance, ensuring early conversion and relapse-free cure. The use of linezolid, the other WHO group A drug, did not have the same early effect.

In China, Zheng et al. [14] investigated the association between drug exposure, susceptibility and response to MDR-TB treatment. Random forest and classification and regression tree (CART) analysis were used to identify key predictors and their clinical targets among patients on WHO-recommended regimens. Drug exposure and corresponding susceptibility were available for 197 patients with MDR-TB. The probability of target attainment was highly variable, ranging from 0% for ethambutol to 97% for linezolid, while patients with fluoroquinolones above targets had higher probability of 2-month culture conversion (56.3% versus 28.6%, adjusted OR 2.91) and favourable outcome (88.8% versus 68.8%, adjusted OR 2.89). Higher exposure values of fluoroquinolones, linezolid and pyrazinamide were associated with earlier sputum culture conversion. The authors concluded that target attainment of second-line drugs was associated with response to MDR-TB treatment. The CART-derived thresholds may serve as targets for early dose adjustment in future randomised controlled studies.

Saluzzo et al. [15] evaluated the clinical performance of a new point-of-care test to diagnose TB infection, the QIAreach QuantiFERON-TB test (QIAreach QFT, QIAGEN, Hilden, Germany). This new technology allows detection of TB infection using only a single blood collection tube (TB2), with single use cartridges (eStick) on a portable platform (eHub), capable of performing up to eight tests and providing a final qualitative result (positive or negative) within 20 min. The study was performed in 304 HIV-uninfected patients with microbiologically confirmed pulmonary TB in a low-incidence setting. In absence of a gold standard test for TB infection [22], the authors assessed QIAreach QFT test accuracy, sensitivity, and specificity against surrogate reference standards. Sensitivity was estimated in confirmed TB cases, while specificity was assessed in 174 low-risk individuals with unknown TB exposure. Sensitivity of QIAreach QFT for detection of TB infection was 93.7% and 95.1%, respectively, for the untreated and treated groups. The specificity was 97.7%. The overall percentage agreement with QuantiFERON-TB Gold Plus (QFT) Plus was 95.7% with a Cohen’s χ of 0.96. The positive percent agreement (sensitivity) versus QFT plus was 99.1% and a negative percent agreement (specificity) versus QFT Plus was 93.4%.
QIAreach QFT overall error rate was 1.3% (4/304). The authors concluded that an improved accessibility to TB infection testing may increase diagnosis and acceptability of preventive therapy. Therefore, the use of QIAreach QFT in remote settings may favour TB elimination by indirectly potentially reducing the number of patients developing active disease.

Spruijt et al. [16] analysed data from three recent Dutch TB infection screening and treatment studies among various migrant populations (566 immigrants, 718 asylum seekers, 257 settled Eritrean migrants) to assess factors facilitating TB infection uptake and completion. The study demonstrated differences in TB infection treatment uptake (range 52–97%) and completion (range 69–97%) among three different migrant groups and showed that treatment uptake and completion was lowest and most challenging among newly arriving immigrants. A verbal education session about TB, TB infection and treatment and the risk of development of TB, in combination with committed and supportive TB care staff and the use of professional interpreters, were important facilitators for treatment initiation and completion among asylum seekers and settled Eritrean refugees and should also be applied among immigrants eligible for treatment.

Impact of COVID-19 on TB services

The TB/COVID-19 Global Study Group and the Global Tuberculosis Network (GTN) described a global cohort of TB/COVID-19 patients from 172 centres in 34 countries [17]. Individual data were pooled and analysed for 767 COVID-19 patients of all ages with either current or previous TB disease (>50% with population-based data). Among them 74.0% had TB diagnosed before COVID-19 (including 234 individuals with previous disease and TB sequelae), 9.5% had COVID-19 first and 16.5% had both

### TABLE 2 World Tuberculosis Day initiatives of leading organisations

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<th>Organisation</th>
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<td>World Health Organization (WHO)</td>
<td>WHO’s Global Tuberculosis Programme works towards the goal of a world free of TB, with zero deaths, disease and suffering due to the disease. The team’s mission is to lead and guide the global effort to end the TB epidemic through universal access to people-centred prevention and care, multisectoral action and innovation. To contribute to achieving the targets of the Sustainable Development Goal 3, the End TB Strategy and WHO’s Strategic Priorities, the team focuses on five core functions: 1) provide global leadership to end TB through strategy development, political and multisectoral engagement, strengthening review and accountability, advocacy, and partnerships, including with civil society; 2) shape the TB research and innovation agenda and stimulate the generation, translation and dissemination of knowledge; 3) develop policy options, norms and standards for TB prevention and care and facilitate their implementation; 4) provide specialised technical support, for Member States and partners, working with WHO regional and country offices to catalyse change and build sustainable capacity; and 5) monitor, evaluate and report on the status of the TB epidemic and progress in financing and implementation of the End TB Strategy at global, regional and country levels. Several initiatives will be coordinated by WHO around the world focused on the 2022 topic (“Invest to end TB. Save lives”).</td>
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<td>The UNION</td>
<td>The UNION is coordinating initiatives for the World TB Day 2022 in several countries globally, with a campaign on its website and with the launch of the second document of the Clinical Standards series, specifically on TB Infection, in the <em>International Journal of Tuberculosis and Lung Disease (IJTLD)</em> [23].</td>
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<td>The European Society of clinical microbiologists and infectious diseases specialists (ESCMID)</td>
<td>ESCMID and, within this organisation, the ESGMYC group (the ESCMID Study Group for Mycobacterial Infections) supports a course on “Diagnosis and treatment of mycobacterial infections” that will be held in concomitance of the TB day on 24–25 March 2022, in Nijmegen, the Netherlands. The aim of the event is to increase insight and practical knowledge in the clinical and diagnostic aspects of tuberculosis and non-tuberculous mycobacteria.</td>
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<td>World Association for Infectious Diseases and Immunological Disorders (WAidid)</td>
<td>WAidid and the Global Tuberculosis Network (GTN) contribute to World TB Day 2022 with collaborative research initiative on TB and COVID-19 and special content on its website.</td>
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<tr>
<td>European Respiratory Society (ERS)</td>
<td>The ERS and the <em>ERJ</em> commemorate the World TB Day 2022 with the publication of this special issue of the journal focused on TB and through other initiatives hosted on the ERS website and in the ERS Newsletter.</td>
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The outcomes of COVID-19 are carefully described: 11.1% of the patients died (14.2% in Europe and 9.2% outside Europe; p=0.03). Among those who died, the cause of death was COVID-19 in 49.4%, COVID-19 and TB in 36.5%, TB in 1.2%, while 12.9% patients died from other causes. In the univariate analysis on mortality each of the following variables reached statistical significance: age, being male, having more than one comorbidity, diabetes mellitus, cardiovascular disease, chronic respiratory disease, chronic renal disease, presence of key symptoms, invasive ventilation and hospitalisation due to COVID-19. Multivariable logistic regression showed increasing age, male sex, and invasive ventilation as independent contributors to mortality. These findings complemented those of WHO surveillance that showed a profound impact of the pandemic on global TB mortality as well as TB notification, BCG vaccination and other programmatic activities [1]. The authors concluded that TB and COVID-19 are a “cursed duet” needing immediate attention. As COVID-19 can worsen the outcome of TB patients, patients with TB should be prioritised for COVID-19 preventive efforts, including vaccination.

Conclusions
The theme for World TB Day 2022, “Invest to end TB. Save lives” [7], highlights the importance for an adequate allocation of funding and other resources to put global TB prevention and care back on track to achieve the targets that have been set by Member States and other partners forming the global TB community (table 2). Progress towards the 2018 UN High Level Meeting on TB will be comprehensively reviewed in 2023. We hope this ERJ initiative, together with that of other journals, will contribute towards ending TB and consign this proverbial scourge of humankind to history.

Conflict of interest: D. Goletti reports grants from Biomerieux and Quidel; consulting fees from Biomerieux, Quidel, Qiagen and PDB Biotec; lecture honoraria from Biomerieux, Quidel, Amgen, Biogen, Celgene, Janssen and Diasorin; and participation on advisory boards for Biomerieux, PDB Biotec and Lilly; outside the submitted work. All other authors have nothing to disclose.

References


