Clinical course and outcomes of people with coronavirus disease and tuberculosis: a multicentre cohort study

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Summary

Title **Clinical course and outcomes of people with coronavirus disease and tuberculosis: a multicentre cohort study**

Background, Introduction and Rationale	Tuberculosis (TB) remains a first-class public health emergency [1]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) pandemic has attracted interest because of its global rapid spread, clinical severity, high mortality rate, and capacity to overwhelm healthcare systems [2,3]. SARS-CoV-2 transmission occurs mainly through droplets, although surface contamination contributes and debate continues on aerosol transmission [4-6]. The disease is usually characterized by initial signs and symptoms [5-10] similar to those of related viral infections (e.g., SARS, Middle East Respiratory Syndrome [MERS]) and tuberculosis (TB), although prognosis and complications sometimes differ. Experience with concomitant TB and COVID-19 is extremely limited. One case-control study of COVID-19 patients with IGRA-confirmed TB infection [11] and a single case of TB with COVID-19 were submitted but not yet published in peer-reviewed journals [12]. In a recent analysis of 1,217 consecutive respiratory specimens collected from COVID-19 patients *Mycobacterium tuberculosis* was not detected [13]. The first 2 published cohorts suggest that COVID-19 can be diagnosed before, simultaneously or after TB and can appear in patients with post-TB sequelae [14]. Furthermore, in the countries surveyed (Belgium, Brazil - Rio Grande do Sul State; France, Italy , Russia (Moscow Region), Singapore, Spain and Switzerland (Vaud Canton) mortality is limited to patients with severe morbidities and older age [15,16]. However, the numbers available (69 patients in 2 cohorts) are no sufficient to allow a comprehensive analysis of the interactions between the 2 diseases. This prospective, anonymised, non-interventional study will aim to describe the characteristics of the patients with COVID-19 and TB (including patients with post-treatment sequelae). The study will build up and use the same approach and methods of the previously published collaborative efforts of the Global Tuberculosis network (GTN); GREPI (Groupe de Recherche et d'Enseignement en Pneumo-Infectiologie), a working group from SPLF (Société de Pneumologie de Langue Française); SEPAR (Sociedad Española de Neumología and Cirugía Torácica); and Moscow Society of Phtisiology [14,15].
Aim of the study	To describe the characteristics and outcomes of COVID-19 patients with concurrent or past TB using an anonymised, prospective, non-interventional study approach.

Study design	Prospective, observational, cohort study. The study will build-up on the data collected and use the same approach and methods of the previously published collaborative studies [14,15].
Study objectives	<u>Primary objective</u> 1. Description of the characteristics of patients with COVID-19 and TB (current or past), including diagnostic testing and treatments in use. <u>Secondary objectives</u> 1. Feasibility of creating a global repository for patients with COVID-19 and TB. 2. Description of the outcomes of these patients (outcome of COVID-19, assessment of bacteriological conversion, interim and final outcomes of treatment of TB cases).
Study period	1st June 2020 onwards (after a pilot study was implemented in March 2020 in a few centres to assess the feasibility of the project, resulting in findings that were recently published [13-15].
Study sites	All clinical centres, organizations and/or national programmes willing and able to participate in this project, by agreeing to collect basic demographic, epidemiological, microbiological, and clinical information (including outcomes) on TB and COVID-19 patients during the study period.
Study population (eligibility)	Consecutively diagnosed and registered TB patients with COVID-19 (concomitant and non), including paediatric cases, treated in the participating centres, with no exclusion criteria.

Ethical issues	The coordinating centre has the Ethic Committee approval to conduct anonymized, non-interventional, multi-centre studies on TB and COVID-19. Each participating centre will seek ethical approval according to national/local regulations on personal data protection, considering the observational nature of the study.
Data collection	Anonymized data will be exported in a common electronic format from local databases, into a central excel database managed by the coordinating centre (WHO Collaborating Centre in Tradate), which will be created in collaboration with WHO. Anonymized individualized data to be collected for each patient include the following variables: 1. Patient characteristics: Patient ID, demographic information, and risk factors. The original data collection form of previous collaborative studies has been simplified and adapted to facilitate data collection and analysis. 2. Clinical data: clinical features, diagnosis and treatment details, bacteriological conversion information, adverse events, and treatment outcomes. The sharing of data by contributors will be covered by an agreement that will specify the purposes of the exercise and the rights of all parties involved in the collaborative work.
Target Population	People co-infected with both COVID-19 and TB (or post-treatment TB sequelae) consecutively diagnosed, registered and managed by the participating centres.
Data analysis plan/statistical support	Statistical analysis will be performed by the coordinating centre in collaboration with WHO and a team of international experts.
Budget	Cost for data collection and management at the individual centre level will be covered by the individual participating centres. Services related to the maintaining of the central database, data quality control, communication, project management, analysis and publication will be offered by the coordinating centre in collaboration with WHO.

Coordinating Committee

The WHO Collaborating Centre for TB and lung diseases will coordinate the study in collaboration with all study contributors.

Scientific Secretariat: Rosella Centis and Lia D'Ambrosio (Italy)
Methodology support: Giovanni Sotgiu (Italy)

List of Abbreviations and Definitions

BCG- Bacillus Calmette-Guérin

BMI – Body Mass Index

COPD- Chronic Obstructive Pulmonary Disease

COVID-19- Coronavirus Disease 19

CT - Computed Tomography

DST – Drug Susceptibility Test

FEV1- Forced Expiratory Volume in the 1st second

FiO2- Fractional Inspired Oxygen

FVC- Forced Vital Capacity

HAIs – Hospital acquired infections

ICU – Intensive Care Unit

IVDU – Intravenous Drug User

LPA- Line Probe assay

MWT- Minutes Walking Test

PaO2- Partial Pressure of Arterial Oxygen

TB – Tuberculosis

TST- Tuberculin Skin Test

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