Tuberculosis Surveillance Data Analysis Proposal (ASC1): Sociodemographic and clinical manuscript

Date(s) Submitted:	August 31, 2021
Title of Project:	TB disease and COVID-19 as comorbidities in a U.S. cross-sectional sample, 2020-2021
DTBE Dataset(s)	☒ National Tuberculosis Surveillance System ☐ National Surveillance for Severe Adverse Events in Persons Receiving Treatment for Latent Tuberculosis Infection
Years Requested:	2017-2020

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BACKGROUND

Abstract

TB and COVID-19 were leading causes of death globally in 2020. Several underlying health conditions have been shown to worsen COVID-19 disease severity and outcomes, including a number of lung diseases. A few published reports suggest that comorbid TB increases mortality associated with COVID-19 but data from low TB incidence settings is limited.

TB program project areas funded by CDC's Division of TB Elimination (DTBE) will voluntarily identify COVID-19 case report data for any person with verified comorbid TB disease and COVID-19, working with their local counterpart surveillance colleagues, systems, or operations in their local COVID-19 response team as feasible. Per guidance from DTBE, programs are requested to report comorbid COVID-19 in the "Other" free text option of the "Additional TB Risk Factors" variable on the RVCT. In addition, funded project areas will be asked to report comorbid COVID-19 and TB from a variety of methodologies, including probabilistic matches of TB and COVID-19 surveillance registries. Programs will enter select variables from the COVID-19 Case Report Form into a secure REDCap interface. These COVID-19-associated data will be merged with de-identified NTSS data using the RVCT number as the unique key. Descriptive characteristics of TB patients reported to CDC with count dates of 1/1/2020-12/31/2020 and identified as having COVID-19 through 8/31/21 (or the latest date for which data will be available) by project areas will be compared with two groups: 1) TB cases counted from 1/1/2017-12/31/2019, and 2) TB cases counted from 1/1/2020-12/31/2020 without COVID-19 reported through 10/31/2021 (or the latest date for which data will be available).

This ASC proposal aims to describe the clinical presentation, diagnosis, and clinical course of a convenience sample of patients with TB disease and COVID 19 in the United States. TB treatment outcomes will be addressed in a separate ASC proposal. In combination, the results from these ASC proposals are expected to inform public health and clinical recommendation development related to improving the diagnosis and clinical outcomes for people with comorbid COVID-19 and TB.

Literature Review

On January 30, 2020, WHO declared coronavirus disease caused by *SARS-CoV-2* (COVID-19) to be a public health emergency of international concern, and on March 11, 2020, upgraded that assessment to a global pandemic. On April 14, 2020, the first U.S. patient with both TB disease and confirmed *SARS-CoV-2* co-infection came to the attention of CDC DTBE's Field Services Branch (FSB) from New York State. Since then, over 200 additional patients have been anecdotally reported. CDC has become aware of clinician inquiries from U.S. project areas related to *M. tuberculosis* and *SARS-CoV-2* co-infection, such as inquiries into the risk of COVID-19 disease progression/poor clinical outcomes in patients with TB disease. Current CDC COVID-19 guidance identifies underlying lung disease as a risk factor for poor outcomes with *SARS-CoV-2* infection and only recently refers to TB disease specifically.

TB and COVID-19 are primarily respiratory diseases with overlapping signs and symptoms. Numerous reports of comorbid TB/COVID-19 have been published by the international scientific community, however a large number are case reports. A small number of observational cohort studies have shown an elevated risk of death in persons with comorbid TB and COVID-19 when compared with COVID-19 cases without TB.[1-3] However, other studies demonstrated no COVID-19 mortality difference for persons

with comorbid TB.[4,5] These publications used a variety of data sources and some had very few TB cases for analysis. Finally, some studies report on the frequency of death among persons with comorbid TB and COVID-19 such as that from Tadolini et. al.,[6] but this type of paper lacks a comparison group and is therefore difficult to interpret. There is a need for additional work with higher quality data sources that afford reasonable comparisons in the clinical experience of COVID-19 between people with TB and people without TB and from a variety of epidemiological settings. Reports from the U.S. and other low TB incidence countries are few. Another important gap in the literature is the assessment of outcome measures other than mortality and hospitalization (e.g. delayed *Mycobacterium tuberculosis* culture conversion). These are areas of the literature, and potentially CDC COVID-19 guidance, that our work aims to inform.

References:

1. Jassat W, Cohen C, Tempia S, et al. Risk factors for COVID-19-related in-hospital mortality in a high HIV and tuberculosis prevalence setting in South Africa: a cohort study. *Lancet HIV.* 2021.
2. Boulle A, Heekes A, Tiffin N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *Int J Popul Data Sci.* 2019;4(2):1143.
3. Sy KTL, Haw NJL, Uy J. Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19. *Infect Dis (Lond).* 2020;52(12):902-907.
4. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol.* 2020;146(1):110-118.
5. Fisman DN, Greer AL, Hillmer M, Tuite R. Derivation and Validation of Clinical Prediction Rules for COVID-19 Mortality in Ontario, Canada. *Open Forum Infect Dis.* 2020;7(11):ofaa463.
6. Tadolini M, Codecasa LR, Garcia-Garcia JM, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J.* 2020;56(1).

Analytic Questions

The aim of this ASC proposal is to characterize the epidemiologic, diagnostic and clinical features, and for a cross-section of TB patients reported with COVID-19 in comparison to TB patients without COVID-19. TB treatment outcomes will be addressed in a separate ASC proposal.

Hypotheses: TB patients reported to CDC with COVID-19 and having a TB count date between 1/1/2020 and 12/31/2020 will have different demographic characteristics and present with more advanced disease (e.g., smear positive, cavitary, TB diagnosis at death) than TB patients without COVID-19.

Public Health Benefit

The goal of this project is to provide insight into the TB and COVID-19 as comorbidities in U.S. settings, as well as lay foundation for future studies. Active communication with TB programs about concurrent COVID-19 diagnoses when appropriate could facilitate more collaborative collection of information about co-infected patients and allow for early recognition of atypical presentations and shared risk factors. These data may further help to inform future best practices related to TB-COVID coinfected patients and potentially inform CDC COVID-19 guidance.

METHODOLOGY

***Study population**:*

TB cases reported to CDC from U.S. states, District of Columbia, territories, and affiliated Pacific Islands with TB count dates during 1/1/2020-12/31/2020, regardless of TB treatment status, are the primary descriptive analysis population. Descriptive characteristics of TB patients reported to CDC with count dates of 1/1/2020-12/31/2020 and identified as having COVID-19 through 8/31/21 (or the latest date for which data will be available) by state health departments will be compared with two groups: 1) TB cases counted from 1/1/2017-12/31/2019, and 2) TB cases counted from 1/1/2020-12/31/2020 without COVID-19 reported through 8/31/2021 (or the latest date for which data will be available). Two comparison populations are preferred because we cannot be certain that TB patients counted within the COVID-19 pandemic period without COVID-19 identified by the local/state health department did not have COVID-19. TB patients counted in 2020 may also be fundamentally different from "typical" TB patients counted in the U.S. due to the pandemic's impact on TB diagnosis and reporting.

A confirmed case of TB must meet the CDC DTBE case definition. A probable or confirmed case of TB with COVID-19 must also meet the CDC case definition for COVID-19 (Coronavirus Disease 2019 (COVID-19) | 2020 Interim Case Definition, Approved April 5, 2020 (cdc.gov)). The process for identifying comorbid COVID-19 and TB will vary by local and state jurisdictions, which have employed different methods to date. Those methods include probabilistic name-based registry matching, TB program chart abstraction, and communicable disease database reviews. In addition, some states elected to report cases to CDC using the Other Risk Factor variable on the RVCT. This project will invite jurisdictions who reported in that way to include these already identified cases.

Inclusion Criteria: Any case of TB counted from 1/1/2017-12/31/2020 and reported to CDC from local/state/territorial jurisdictions agreeing to participate in this voluntary project.

Data Sources:

1) National Tuberculosis Surveillance System (NTSS) 2017-2020
2) COVID-19 Case Report Form 2020-2021 (by local and state health department staff via a REDCap database developed expressly for this purpose)
3) CDC COVID-19 Historical Case Counts
4) CDC Social Vulnerability Index

Sociodemographics and TB risk characteristics will be obtained from NTSS while symptoms, clinical severity, and outcomes at the time of COVID-19 diagnosis will be obtained from COVID-19 surveillance (COVID-19 CRF). Local and state TB programs will work with their communicable disease colleagues to access their COVID-19 surveillance records. They will be responsible for entering selected data elements from the COVID-19 CRF into the project's REDCap database (or directly submitting electronic files containing these data by CDC ShareFile) developed expressly for this purpose. The project will not access or utilize case-level data elements received from state and local health departments by CDC.

Data Elements for Analysis

Category (Source)	Variables
Demographic and TB Risk Factor Variables (RVCT):	Age, Sex, Race, Ethnicity, Origin of Birth, Years in the U.S. (for non-U.S.-born), Count Date, Report Date, State Case Number, City/County Case Number, State Code, County code, Primary Reason Evaluated for TB, Homeless within Past Year, Resident of Correctional Facility at Time of Diagnosis, Resident of Long-term Care Facility at Time of Diagnosis, Injecting Drug Use within Past Year, Non Injecting Drug Use within Past Year, Excess Alcohol within Past Year, Primary occupation, Other Risk Factor (and COVID-19 specification) Because age is one of the strongest predictors of poor outcome/death based on prior reports, we would like to have the flexibility to analyze it as a continuous variable. Doing so would also allow for more direct comparison of age distributions available from other sources, including those that don't necessarily use the same age brackets as DTBE.
Clinical Variables (RVCT):	HIV Status at Diagnosis, Diabetes Mellitus, ESRD, Other immunosuppression (include other immunosuppression, TNF-alpha inhibitor use, post organ transplant), Previous TB, TST result, IGRA result, Primary Reason Evaluated for TB Disease, Collection Dates of Sputum Smear, of Sputum Culture, of Tissue Smear, of Tissue Culture, of NAAT; Dates of Sputum Culture Reported, of Tissue Culture reported, of NAAT reported; Results of Sputum Smear, of Sputum Culture, of Tissue Smear, of Tissue Culture, of NAAT; Date of initial DST specimen collection; Initial Chest Radiograph Results and Evidence of cavitary lesion; Initial CT Results and Evidence of cavitary lesion; Initial Drug Susceptibility Results; Initial Drug Regimen; Site of TB; Type of outpatient care provider
Outcome Variables (RVCT):	Status (alive, dead) at Diagnosis, Date of death (if dead at TB diagnosis), Date TB therapy started
COVID-specific Variables (COVID CRF):	COVID case number, Reporting Jurisdiction, Case classification, Process Case Identified, Report Date, Date of First Positive Specimen, Was Patient Hospitalized, Admission Date, Discharge Date, Was Patient Admitted to ICU, Death Attributed to COVID, Death Date, Location at Illness Onset, Symptomatic vs. asymptomatic at COVID-19 diagnosis, Symptom profile, Pregnancy status (female), Underlying medical conditions, Pneumonia, ARDS, Abnormal CXR, Alternate Diagnosis, Intubation, ECMO

Statistical analysis

We will classify stages of the COVID-19 pandemic using the daily rate of new COVID-19 infections in the United States and its territories. We will also calculate the number of days between TB and COVID-19 diagnosis dates for stratification. We will define the TB diagnosis date as the first date out of the following: smear or tissue collection, NAAT result, treatment start, first specimen collected for DST. We will define the COVID-19 diagnosis date as the earliest collection date for a PCR- or antigen-positive test for SARS-CoV-2. We consider disseminated TB to have occurred in those having meningeal, miliary, or both pulmonary & extrapulmonary TB disease, or having a positive acid-fast bacilli blood culture or NAAT. We may also use the CDC Social Vulnerability Index (SVI) to assign the scores for TB patients based on county of residence at TB diagnosis (census tracts not yet available).

Descriptive statistics will be used to characterize epidemiologic and diagnostic features (potentially stratified by clinical vs. culture-confirmed TB, birth origin, site of TB disease, phase of COVID-19 pandemic in which TB was diagnosed, days between TB and COVID-19 diagnoses, which disease was diagnosed first, and by U.S. Census regions and divisions), as well as use of TB diagnostics (NAAT, CXR/CT, sputum smear/culture, tissue smear/culture). These features will be compared with TB patients not having COVID-19 in 2020 and will be compared separately with TB patients counted from 2017-2019. If no comorbid TB and COVID-19 cases are available from a state or county, the data for that state or county will be excluded from the comparison groups (i.e. TB patients not having COVID-19 in 2020 and compared separately with TB patients counted from 2017-2019). We will verify the homogeneity of annual TB surveillance records from 2017-2019 according to incidence, age, sex, and race-ethnicity distribution. If there is recognized heterogeneity across the years, the analysis team may need to adjust the period of comparison (e.g. 2018-2019 only). Primary outcomes include death at TB diagnosis and COVID-19-associated hospital, development of pneumonia, acute respiratory distress syndrome, intensive care admission, intubation, or use of ECMO during the COVID-19 illness.

If sample size allows, we will report characteristics in this cross-section stratified by diagnoses of the two diseases within 30, 90, and 120 days of each other. Qualitative and categorical variables will be summarized by frequencies. Quantitative variables will be summarized by mean and standard deviation for variables with normal distributions, and by median and interquartile range for variables with non-normal distributions. Results by geographic region will be reviewed alongside the phase of the COVID-19 pandemic. We will begin with univariate statistical comparisons between TB/COVID-19 and the TB only groups, if feasible and depending on sample size. These comparisons will be made using chi-square for frequencies, t-test for parametric continuous variables, and Wilcoxon rank test for non-parametric continuous variables (alpha=0.05). We will consider using a Bonferroni correction for multiple comparisons, depending on whether sample size permits multiple statistical comparisons. Finally, we will aim to characterize the magnitude of difference for the sociodemographic and clinical characteristics in Tables 1-3 between the analytic and comparison groups using prevalence ratios calculated from log-binomial equations. In order to account for confounding and produce least biased estimates of association, we will construct a multivariable log-binomial regression model. The starting model will include the variables that were statistically significant in univariate analysis (and sociodemographics regardless of significance, including age, race-ethnicity, sex, birth origin, and geographic region). We will fit a parsimonious final model by removing variables that do not retain statistical significance (alpha=0.05) in reverse stepwise fashion.

Limitations

The major limitation of this study will likely be under-ascertainment bias. Participation will be voluntary and jurisdictions are not being provided with additional funds to participate. Among participating jurisdictions, there is still likely to be under-detection of comorbid TB and COVID-19 for several reasons including underdiagnosis. Also, we anticipate selection bias due to varying methodologies for identifying people with TB and COVID-19 across sites. For these reasons, this project will not attempt to make inferences into the frequency or rate of comorbid TB and COVID-19. Additionally, as data collection will be limited to surveillance data instruments, this project will not be able to identify clinical nuances of the patient's treatment and course, such as evaluating drug-drug interactions. Attributing clinical

characteristics and outcomes to TB and/or COVID-19 will be difficult, especially when the diseases are diagnosed close together in time. Statistical comparisons are likely to be limited by small table cell sizes.

TABLE SHELLS

Table 1: Sociodemographic Characteristics of Persons with Reported Tuberculosis (TB) and Reported COVID-19 Compared with TB Patients without Reported COVID-19, United States, 2017-2020

	n (%) or median (IQR) TB/COVID-19	n (%) or median (IQR) TB without COVID-19 2020	n (%) or median (IQR) TB without COVID-19 2017-2019
Age group at TB diagnosis			
0-14 years			
15-24 years			
25-44 years			
45-64 years			
≥ 65 years			
Sex			
Male			
Female			
Pregnant (female)		NA	NA
Race/Ethnicity			
Hispanic			
Non-Hispanic American Indian or Alaska Native			
Non-Hispanic Asian/PI			
Non-Hispanic Black			
Non-Hispanic White			
Origin of Birth			
Non-US-born			
US-born			
Correctional facility resident at time of TB diagnosis			
Yes			

No or Unknown			
Long-term care facility resident at time of TB diagnosis			
Yes			
No or Unknown			
Homeless within year prior to TB diagnosis			
Yes			
No or Unknown			
Excessive alcohol use within year prior to TB diagnosis			
Yes			
No or Unknown			
Injection or non-injection drug use within year prior to TB diagnosis			
Yes			
No or Unknown			
Primary Occupation			
Health care workers			
Correctional facility			
Seasonal/migrant worker			
Not employed			
Retired			
Other or unknown			

NA = pregnancy status not known from NTSS data

Table 2. Clinical Characteristics of Persons with Reported Tuberculosis (TB) with Reported with COVID-19 Compared with TB Patients without COVID-19, United States, 2017-2020

	n (%) or median (IQR) TB/COVID-19	n (%) or median (IQR) TB without COVID-19 2020	n (%) or median (IQR) TB without COVID-19 2017-2019
Site of TB disease			
Pulmonary only			
Both pulmonary & extrapulmonary			
Extrapulmonary only			
Previous episode of TB			
Yes			
No or Unknown			
HIV status at time of TB diagnosis			
Positive			
Negative			
Testing not offered			
Other or Unknown			
Additional TB Risk Factors			
Diabetes mellitus			
End-stage renal disease			
Immunosuppression (Not HIV/AIDS)			
TST Result			
Positive			
Negative			
Not done or Unknown			
IGRA Result			
Positive			
Negative			
Not done or Unknown			

Initial Chest Imaging (CXR/CT)			
Normal			
Abnormal			
N/A (if non-pulmonary)			
Evidence of Cavitary Lesion			

Table 3. Clinical Severity of U.S. Tuberculosis (TB) Patients Diagnosed with COVID-19 Compared with TB Patients without COVID-19, 2017-2020

Treatment Outcomes	n (%) or median (IQR) TB/COVID	n (%) or median (IQR) TB alone 2020	n (%) or median (IQR) TB alone 2017-2019
Disseminated TB disease			
Yes			
No			
Hospitalized for COVID			
Intensive care unit admission for COVID			
Death at TB diagnosis			
COVID-19 Diagnosis associated with Pneumonia			
Acute respiratory distress syndrome with COVID			
Intubated with COVID			
Use of ECMO for COVID			

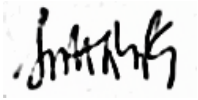
AGREEMENT TO ASC PROJECT REQUIREMENTS

The following requirements apply to all approved ASC projects:

1. All individuals with access to the restricted dataset will complete Assurance of Confidentiality training and sign a nondisclosure agreement/confidentiality pledge every 12 months while access to restricted data is still needed.
2. No individuals with access to the restricted dataset will use the dataset for any analyses not outlined in this approved proposal without first obtaining permission from the Surveillance Team Lead.

3. The PI (or a substitute acceptable to DTBE) must present preliminary results of the analytic project in a suitable forum open to DTBE staff no later than 1 year after the proposal received final approval, as indicated below.
4. The PI (or a substitute acceptable to DTBE) must submit a manuscript describing the results of this analytic project no later than 2 years after the proposal received final approval.
5. The PI (or a substitute acceptable to DTBE) must submit all information products (e.g., abstracts, presentations, manuscripts) derived from this analytic project to CDC clearance before submission to any conference, journal, or other venue according to DTBE clearance policy in effect at the time that the information product is submitted for presentation or publication.
6. All information products derived from this analytic project must comply with the DTBE data re-release policy that is in effect at the time that the information product is submitted for presentation or publication.

As the principal investigator (PI) for this proposed analytic project, I acknowledge the above requirements and agree to comply and require that all members of the project team comply.

Signature: 

(DTBE) Policy on Access to Tuberculosis Surveillance Data for Analysis