Tuberculosis and COVID-19 Intersection
Clinical Lead Forum - COVID-19

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Global TB Program, Associate Director
Assistant Professor of Pediatrics
05-06-2020
Objectives

• Review Global TB/COVID-19 Epidemiology
• TB (and COVID-19?) prevention with BCG
• Areas of programming overlap
• TB (active or recovered) and COVID-19 co-morbidity
• Maintaining TB services
2019 WHO Global Tuberculosis Report

Approximately 300 Million Cases and 30 Million TB Deaths Since 2000

Global TB Incidence

Global TB Mortality

- All TB cases
- Total
- HIV-negative
- HIV-positive

2020 milestone (total)
TB: Higher mortality at a population level in much of sub-Saharan Africa than COVID-19 in Europe and the US

European CDC, Our World in Data, Accessed June 4th
TB Trivia Question 1: How long has *M. tuberculosis* been infecting human populations?

A. 300 years
Objectives

• Review Global TB/COVID-19 Epidemiology
• **TB (and COVID-19?) prevention with BCG**
• Areas of programming overlap
• TB (active or recovered) and COVID-19 co-morbidity
• Maintaining TB services
## BCG Efficacy Systematic Reviews

### Meningitis/Miliary: Case Control Studies: 73-77% ↓ Risk

Randomized Clinical Trials: 85% ↓ Risk

**Table 3: Meta-analysis of BCG efficacy against tuberculous meningitis and miliary tuberculosis from case-control studies**

<table>
<thead>
<tr>
<th>Publication date</th>
<th>Efficacy (% 95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tuberculous meningitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buenos Aires, Argentina</td>
<td>1988</td>
<td>98% (70 to 100)</td>
</tr>
<tr>
<td>Bahia, Brazil</td>
<td>1991</td>
<td>91% (78 to 97)</td>
</tr>
<tr>
<td>São Paulo, Brazil</td>
<td>1990/93</td>
<td>87% (72 to 94)</td>
</tr>
<tr>
<td>São Paulo, Brazil</td>
<td>1990/93</td>
<td>92% (65 to 98)</td>
</tr>
<tr>
<td>Belo Horizonte, Brazil</td>
<td>1988</td>
<td>81% (47 to 93)</td>
</tr>
<tr>
<td>Belo Horizonte, Brazil</td>
<td>1988</td>
<td>65% (17 to 86)</td>
</tr>
<tr>
<td>Yangon, Burma</td>
<td>1987</td>
<td>52% (13 to 73)</td>
</tr>
<tr>
<td>Nagpur, India</td>
<td>1996</td>
<td>87% (70 to 94)</td>
</tr>
<tr>
<td>Chennai, India</td>
<td>1996</td>
<td>77% (63 to 86)</td>
</tr>
<tr>
<td>Delhi, India</td>
<td>1996</td>
<td>64% (30 to 81)</td>
</tr>
<tr>
<td>Delhi, India</td>
<td>1989</td>
<td>84% (69 to 97)</td>
</tr>
<tr>
<td>Lucknow, India</td>
<td>1999</td>
<td>47% (-6 to 74)</td>
</tr>
<tr>
<td>Papua New Guinea*</td>
<td>1980</td>
<td>58% (-36 to 87)</td>
</tr>
<tr>
<td>Delhi, India</td>
<td>1993</td>
<td>56% (-49 to 87)</td>
</tr>
<tr>
<td><strong>Summary efficacy</strong></td>
<td></td>
<td><strong>73% (67 to 79)</strong></td>
</tr>
<tr>
<td><strong>Miliary tuberculosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buenos Aires, Argentina</td>
<td>1988</td>
<td>78% (28 to 93)</td>
</tr>
<tr>
<td>Yangon, Burma</td>
<td>1987</td>
<td>80% (45 to 92)</td>
</tr>
<tr>
<td>Papua New Guinea*</td>
<td>1980</td>
<td>70% (0 to 91)</td>
</tr>
<tr>
<td>Djakarta, Indonesia</td>
<td>1983</td>
<td>75% (5 to 94)</td>
</tr>
<tr>
<td><strong>Summary efficacy</strong></td>
<td></td>
<td><strong>77% (58 to 87)</strong></td>
</tr>
</tbody>
</table>

*Not designed as a case-control study.*

Trunz, Lancet, 2006

Mangatani, CID, 2014
If BCG is not available....

Table 2 Estimated additional annual admissions to the paediatric neurology ward

<table>
<thead>
<tr>
<th>Supply shortfall (%)</th>
<th>Number of additional admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3</td>
<td>16.5</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>20</td>
<td>52</td>
</tr>
<tr>
<td>27.6</td>
<td>71.8</td>
</tr>
<tr>
<td>100</td>
<td>260</td>
</tr>
</tbody>
</table>

Figure: Annual case load (top) and birth cohort analysis (bottom) of children admitted with tuberculous meningitis or tuberculomas to the paediatric neurology ward at Tygerberg Hospital, Cape Town, South Africa over a 10-year period

Marais, Lancet Global Health, 2017 and Harris, BMC Medicine, 2016
BCG vaccine may also have non-specific immunologic effects to mitigate COVID-19...
Non-specific BCG Effects: Epidemiologic Studies and Systematic Reviews

**Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review**
Julian P T Higgins,¹ Karla Soares-Weiser,² José A López-López,¹ Artemisia Kakourou,³ Katherine Chaplin,¹ Hannah Christensen,¹ Natasha K Martin,¹ 4 Jonathan A C Sterne,¹ Arthur L Reingold⁵

**BMJ, 2016:** Relative risk reduction: 0.70 (95% confidence interval 0.49 to 1.01) from five clinical trials and 0.47 (0.32 to 0.69) from nine observational studies at high risk of bias

**CID, 2016:** Children in Spain-hospitalization with respiratory infection preventive fraction (PF) of 41.4% (95% confidence interval: 40.3–42.5; P-value <.001) and sepsis PF of 52.8% (43.8–60.7; P-value <.001)

**Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis**
Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination


Reduction in Upper Respiratory Infections:

- **BCG 2.1%**
- **H4:IC31 9.4%**
- **Placebo: 7.4%**
- **P < 0.001**
Evidence specific to COVID-19?

Is BCG vaccination affecting the spread and severity of COVID-19?
# RESEARCH LETTER

## SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults

<table>
<thead>
<tr>
<th></th>
<th>Birth year</th>
<th></th>
<th></th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population</strong></td>
<td>297,340</td>
<td>301,600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immigrants in total population, No. (%)</strong></td>
<td>14,569 (4.9)</td>
<td>13,873 (4.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of tests</strong></td>
<td>3,064</td>
<td>2,869</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proportion of population tested, %</strong></td>
<td>1.02</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men tested, No. (%)</strong></td>
<td>15,09 (49.2)</td>
<td>14,58 (50.8)</td>
<td></td>
<td>.29</td>
<td></td>
</tr>
</tbody>
</table>

### Positive results

<table>
<thead>
<tr>
<th></th>
<th>Birth year</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%)</strong></td>
<td>361 (11.7)</td>
<td>299 (10.4)</td>
<td>1.3 (-0.3 to 2.9)</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td><strong>No. per 100,000 population in age group</strong></td>
<td>121</td>
<td>100</td>
<td>21 (-10 to 50)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td><strong>Men with positive result, No. (%)</strong></td>
<td>181 (50)</td>
<td>152 (51)</td>
<td></td>
<td>.87</td>
<td></td>
</tr>
<tr>
<td><strong>No. with severe disease</strong></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cell Host & Microbe

BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity
BCG Vaccine-COVID STRATEGY

BACILLUS CALMETTE-GUÉRIN VACCINATION AS DEFENSE AGAINST SARS-CoV-2 (BADAS).
A RANDOMIZED CONTROLLED TRIAL TO PROTECT HEALTH CARE WORKERS BY ENHANCED TRAINED IMMUNE RESPONSES

Baylor College of Medicine (A. DiNardo) is a study site
Bacille Calmette-Guérin (BCG) vaccine and the COVID-19 pandemic: responsible stewardship is needed

H. S. Schaaf,¹ K. du Preez,¹ M. Kruger,² R. Solomons,² J. J. Taljaard,³ H Rabie,² J. A. Seddon,¹,⁴ M. F. Cotton,² M. Tebruegge,⁵,⁶ N. Curtis,⁵ A. C. Hesseling¹

Demand for BCG Vaccine Due to Unproven Claims of its Role in Preventing COVID-19 Is Causing Shortages of Vaccines for Infants in Japan

Kuroda, Naoto MD  Author Information ☑

The Pediatric Infectious Disease Journal: May 5, 2020 - Volume Online First - Issue -
doi: 10.1097/INF.00000000000002724
Considering BCG vaccination to reduce the impact of COVID-19

Nigel Curtis, Annie Sparrow, Tedros A Ghebreyesus, Mihai G Netea

1. BCG vaccine is already in short supply, and indiscriminate use could jeopardise the supply needed to protect children against tuberculosis in high-risk areas
2. Whether BCG will be effective remains unknown: findings from the ecological studies suggesting less COVID-19 in countries with routine BCG immunisation are weak evidence. BCG administered in childhood is unlikely to impact COVID
3. BCG vaccination could engender a false sense of security
4. Careful safety monitoring in randomised trials is needed to guard against the remote possibility that up-regulation of immunity by BCG will exacerbate COVID-19 in a minority of patients with severe disease
TB Trivia 2: How many times and over how many years was the strain of *Mycobacterium bovis* sub-cultured in potato and ox bile culture media to reduce its virulence and create the BCG vaccine strain?

A. 16 times over 1 year  
B. 42 times over 6 years  
C. 230 times over 11 years  
D. 1100 times over 25 years
Objectives

• Review Global TB/COVID-19 Epidemiology
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Intensified Case Finding

- TB Symptom Screening
- >100,000 screenings at BIPAI Clinics Annually
- Identify patients with possible TB
- Offer early diagnostics and treatment
- Protect vulnerable patients without symptoms
- All apply to SARS-COV-2 with important caveats
Focusing Existing TB Infection Prevention and Control Measures in a High TB/HIV Burden Setting to Mitigate COVID-19

(G. Mtetwa abstract submission to Union)

- February 1\textsuperscript{st} to May 5\textsuperscript{th} 2020
- 3240/3596 patients screened (90%)
- 110 (3%) with TB or COVID-19 symptoms
- 3 met the case definition COVID-19 testing (0/3 positive for COVID-19)
- 4/110 were diagnosed with TB Disease

- We can still find people with TB!
Testing Platform Overlap for TB and COVID

Cons
- High Cost ~ USD 20
- Low throughput

Pros
- Widely available and possibly (?) lower infection control risk
- TAT ~ 30-45 minutes
- Highly accurate/self contained
- Low skill requirement

Treatment Action Group Statement on the High Price of Cepheid’s Xpert Test for COVID-19

Cepheid is profiteering during a pandemic, with dangerous consequences for countries with vulnerable populations and health systems.
Contact Tracing TB-COVID-19

- Identify high risk index cases-exposure environments-contacts
- Adapt to the stage of transmission
- Ensure community engagement
Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset

Hao-Yuan Cheng, MD, MSc; Shu-Wan Jian, DVM, MPH; Ding-Ping Liu, PhD; Ta-Chou Ng, BSc; Wan-Ting Huang, MD; Hsien-Ho Lin, MD, ScD; for the Taiwan COVID-19 Outbreak Investigation Team
Contact Tracing TB-COVID-19: High and Low Tech

**Covid-19: The US state copying a global health template for contact tracing success**

Contact tracing is widely considered to be key to ending the pandemic. Tinker Ready visits the pioneering Massachusetts effort taking a leaf out of west Africa’s book.

**Apple and Google partner on COVID-19 contact tracing technology**

[Link to Hopkins COVID-19 Contact Tracing Course]
Learn from TB and HIV: Avoid Stigma
Social Stigma associated with COVID-19

- Words matter: People who may have COVID-19 not COVID suspects
- Spread facts and support No-stigma journalism, social media, and government policies

FULL STORY

RFM NURSE COULD BE CHARGED WITH MURDER
TB Trivia 3: How do lions most often get infected with a *Mycobacterium tuberculosis* complex species in Kruger Park?

A. From eating cows?
B. From others lions coughing?
C. From tourists?
D. Eating cape buffalo?
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## COVID-19 and TB Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Azithromycin</th>
<th>Chloroquine</th>
<th>Hydroxychloroquine</th>
<th>Lopinavir/ritonavir</th>
<th>Remdesivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
<td>✧</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>🔴</td>
<td>🔴</td>
<td>🔴</td>
<td>🔴</td>
<td>🔴</td>
</tr>
</tbody>
</table>

**University of Liverpool COVID-19 Dosing and Drug Interaction Guide**

- **Consider drug interactions in any patient on rifampicin**
TB Disease Progression Risk Factors

- Transplant
- Renal Disease
- Age
- Malignancy
- Low BMI
- Male Gender
- Advanced HIV
- Smoking
- Uncontrolled DM

Risk Factors for COVID Mortality/Severe Disease
Outcomes TB and COVID-19

- One study, 69 patients
- Global Tuberculosis Network: European Countries, Brazil, Russia, Singapore
- 8 of 69 patients died (11.6%)
- Death was more likely in older patients with co-morbidities and seemed less associated with TB disease status
- Many unanswered questions!

Motta, Pulmonology, May 2020
Current TB, TB Sequelae and COVID-19

Current TB

TB Sequelae

Chin, IJTLG, 2019
<table>
<thead>
<tr>
<th>Symptom</th>
<th>COVID-19</th>
<th>TB in PLHIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Progression</td>
<td>Fast</td>
<td>Slow Variable</td>
</tr>
<tr>
<td>Cough Type</td>
<td>Dry</td>
<td>Productive</td>
</tr>
<tr>
<td>Fever</td>
<td>High</td>
<td>Low/Persistent</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Respiratory Distress/Hypoxia</td>
<td>Severe/Rapid</td>
<td>Rare/End Stage</td>
</tr>
<tr>
<td>CXR Findings</td>
<td>Multifocal</td>
<td>Multifocal</td>
</tr>
<tr>
<td></td>
<td>Opacities and</td>
<td>Disease</td>
</tr>
<tr>
<td></td>
<td>Nodules</td>
<td>Opacities and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nodules</td>
</tr>
<tr>
<td>Incubation Period</td>
<td>1-14 days</td>
<td>Weeks to Months</td>
</tr>
</tbody>
</table>
Testing for TB vs. COVID-19

World Health Organization: Simultaneous testing?

☑ Clinical features that are common to both diseases
☑ Simultaneous exposure to both diseases
☑ Presence of a risk factor for poor outcomes to either disease
Approach to Specimen Collection and Diagnosis

• Continue Expectorated Sputum Collection

• We have held aerosol generating TB diagnostic procedures (sputum induction and gastric aspiration)

• Maintain the same high suspicion for TB in our settings where it is still a more common illness
TB Trivia 4: How does one test an elephant for *Mycobacterium tuberculosis* disease?

A. Trunk washings?

B. Gastric Aspiration?

C. Induced Sputum?

D. Checking TSTs in their zoo keepers?
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COVID-19 and TB Intersection

1. Reduced access to diagnostic, treatment and prevention services
2. Increased TB transmission due to delays in diagnosis
3. Supply chain interruptions for diagnostics and medications

2020-2025 6.3 Million Excess Cases (↑ 10.7%) and 1.4 Million Excess Deaths (↑ 16%)

Stop TB Partnership, Imperial College, Johns Hopkins
World Health Organization (WHO) Information Note

Tuberculosis and COVID-19

Date: 12 May 2020

COVID-19: Considerations for tuberculosis (TB) care

As the world comes together to tackle the COVID-19 pandemic, it is important to ensure that essential services and operations for dealing with long-standing health problems continue to protect the lives of people with TB and other diseases or health conditions. Health services, including national programmes to combat TB, need to be actively engaged in ensuring an effective and rapid response to COVID-19 while ensuring that TB services are maintained.

Modelling work suggests that if the COVID-19 pandemic led to a global reduction of 25% in expected TB detection for 3 months – a realistic possibility given the levels of disruption in TB services being observed in multiple countries – then we could expect a 13% increase in TB deaths, bringing us back to the levels of TB mortality that we had 5 years ago. This may even be a conservative estimate as it does not factor in other

WHO: Maintaining TB Services

Frequently Asked Questions: COVID-19 and Tuberculosis
Version 1, 25 March 2020. This version supersedes previous versions

The novel coronavirus-19 (nCoV-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus that was only recently discovered in 2019. The virus causes coronavirus disease 2019 (COVID-19).

Tuberculosis (TB) is caused by Mycobacterium tuberculosis, a bacterium known since 1882 when it was discovered by Dr Robert Koch, but there is historical evidence of TB in humans for thousands of years.

The following questions are answered in this document:

1. What are the similarities between COVID-19 and TB?
   a. Comparison of TB and COVID-19
2. How deadly is COVID-19 compared to TB?
3. I am taking TB treatment, is there any guidance or recommendations for what a person on TB treatment should do if they get infected with COVID-19?
4. What symptoms should I look for to know if I have either TB or COVID-19, given that some of the symptoms are the same?
5. I have recovered from TB, am I at greater risk of getting infected with COVID-19?
6. Do I need to wear a face mask?
7. How will the TB response be affected?
8. Do I need to stockpile my TB medicines?
9. What alternatives are available to ensure people in treatment for TB can continue to be given the proper support and supervision if directly observed therapy (DOT) is restricted due to social distancing and national quarantine measures?
10. I keep reading about new treatments and novel ways to protect yourself from COVID-19, how do I know if they are true?
11. What can I do to reduce stigma related to COVID-19 and other communicable diseases?

Union: FAQ COVID/TB
Maintaining TB Services

1. Transport Limitations
2. Risk of nosocomial infections in a vulnerable population
3. Ensure PPE is preserved for MDR TB providers
4. Work to maintain medication and diagnostic supplies
1. Community Based Care  
   *(H. Gama abstract submission to the Union)*

2. Visit spacing

3. VOT or telephone support *(MSF)*
How will COVID-19 Strain the TB-HIV Response? How can TB/HIV gains improve the COVID response?

What does the COVID-19 pandemic mean for HIV, tuberculosis, and malaria control?

New diseases and old threats: lessons from tuberculosis for the COVID-19 response

How can we use the COVID-19 Response to further improve HIV and TB Programming??
Thank you to the whole Global TB and Baylor-Eswatini Team

Questions?