DOES SUBCLINICAL TB HAVE A ROLE IN TRANSMISSION?

BARUN MATHEMA, PHD
VANCOUVER, CANADA
FEBRUARY 2023

Learning objectives

1. Participants will learn about the current knowledge of subclinical TB transmission, how it clarifies and complicates our global understanding of TB transmission.
2. Participants will learn about approaches to measuring transmission potential of subclinical TB, challenges, and opportunities.

Outline

- What is subclinical TB?
- Problem statement(s)
- Minimum requirement for TB transmission
- Do individuals with subclinical TB expel organisms?
- Role of subclinical TB in ongoing transmission?
- Looking ahead

WHAT IS SUBCLINICAL TB?

Definition:

- disease due to viable *M. tuberculosis* bacteria that does not cause clinical TB-related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays (Drain et al. CMR 2018)

Practical definition:

- a disease state that is detectable by sputum culture or chest radiography but during which patients would respond "no" if asked whether they are currently experiencing any TB symptom (cough, fever, night sweats, or weight loss) (Kendall et al. AJRCCM 2021).

- **Individuals likely unaware of their TB status, unlikely to seek care, and likely missed by health care facility performing symptom-screen only.**

Restating Dr. Kendall's point: these definitions/categories are evolving

Asymptomatic transmission has precedence

- Number of examples of asymptomatic transmission of infection (viral, parasitic as well as bacterial). In fact, likely the norm rather than the exception.
- From not invasive (*e.g., MRSA carriage*) to infections causing mild symptoms and where disease is not recognized (*e.g., SARS-CoV-2*).
- Asymptomatic transmission events are often difficult to detect due to recognition and sampling.
- What is asymptomatic or subclinical can (has) been debated; blurry lines do exist. TB a commensal?

Asymptomatic sexually transmitted diseases: the case for screening

Thomas A. Farley, M.D., M.P.H.,[a,b,*] Deborah A. Cohen, M.D., M.P.H.,[c,d] and Whitney Elkins, M.P.H.[c]

[a] Louisiana Office of Public Health, New Orleans, LA 70160, USA
[b] Department of Community Health Sciences, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA 70118, USA
[c] Department of Public Health and Preventive Medicine, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA
[d] RAND Corp., Santa Monica, CA 90406, USA

Article | Open Access | Published: 19 July 2017

Asymptomatic Transmission and the Dynamics of Zika Infection

Seyed M. Moghadas, Affan Shoukat, Aquino L. Espindola, Rafael S. Pereira, Fatima Abdirizak, Marek Laskowski, Cecile Viboud & Gerardo Chowell

Scientific Reports **7**, Article number: 5829 (2017) | Cite this article

ORIGINAL INVESTIGATION

Carriage of Methicillin-Resistant *Staphylococcus aureus* in Home Care Settings

Prevalence, Duration, and Transmission to Household Members

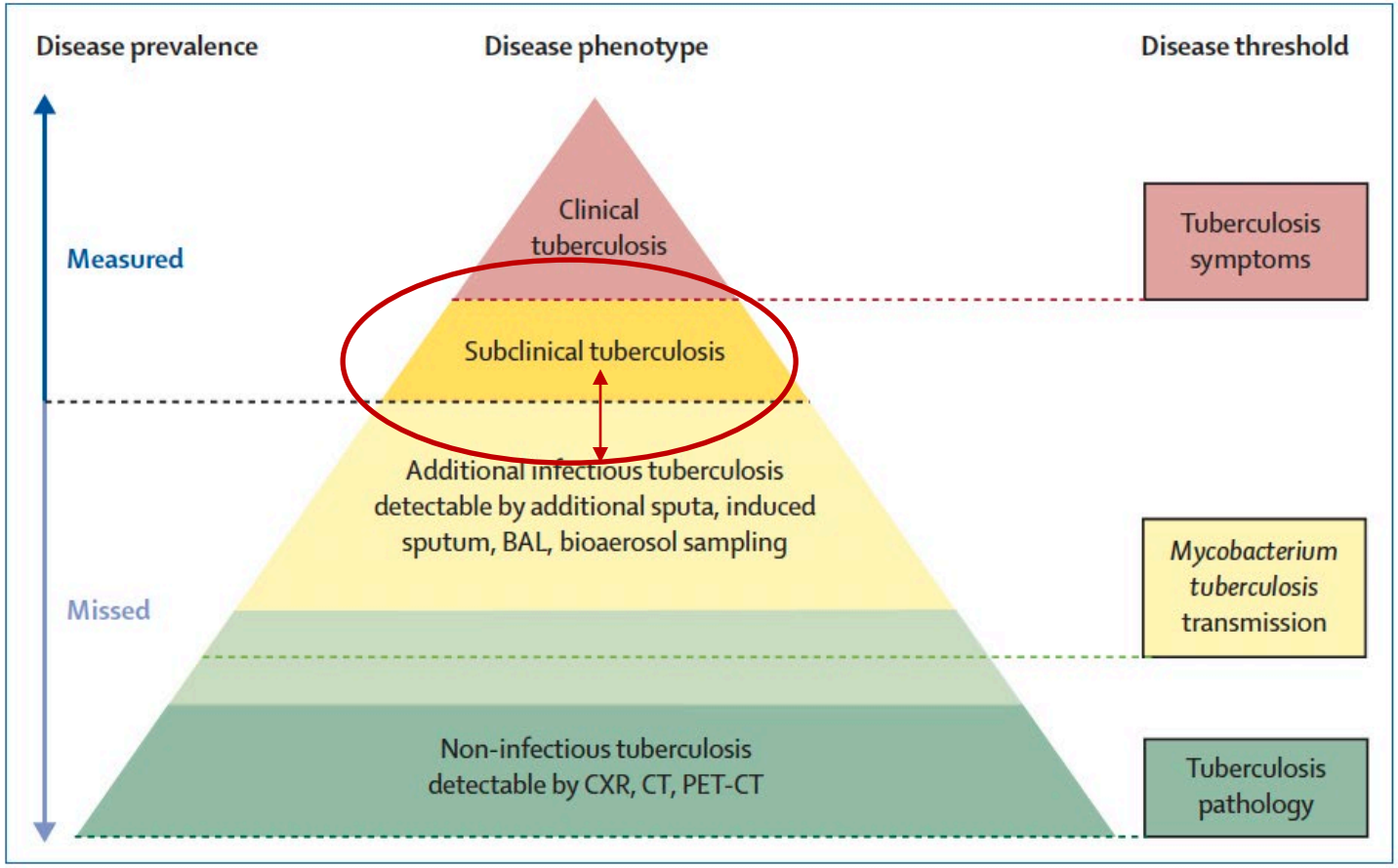
Jean-Christophe Lucet, MD, PhD; Xavier Paoletti, PhD; Christine Demontpion, RN; Marie Degrave, RN; Dominique Vanjak, MD; Corinne Vincent, MSc; Antoine Andremont, MD, PhD; Vincent Jarlier, MD, PhD; France Mentré, MD, PhD; Marie-Hélène Nicolas-Chanoine, MD, PhD; for the Staphylococcus aureus *Résistant à la Méticilline en Hospitalisation A Domicile (SARM HAD) Study Group*

CORONAVIRUS

Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2)

Ruiyun Li[1]*, Sen Pei[2]*†, Bin Chen[3]*, Yimeng Song[4], Tao Zhang[5], Wan Yang[6], Jeffrey Shaman[2]†

Problem statement(s)

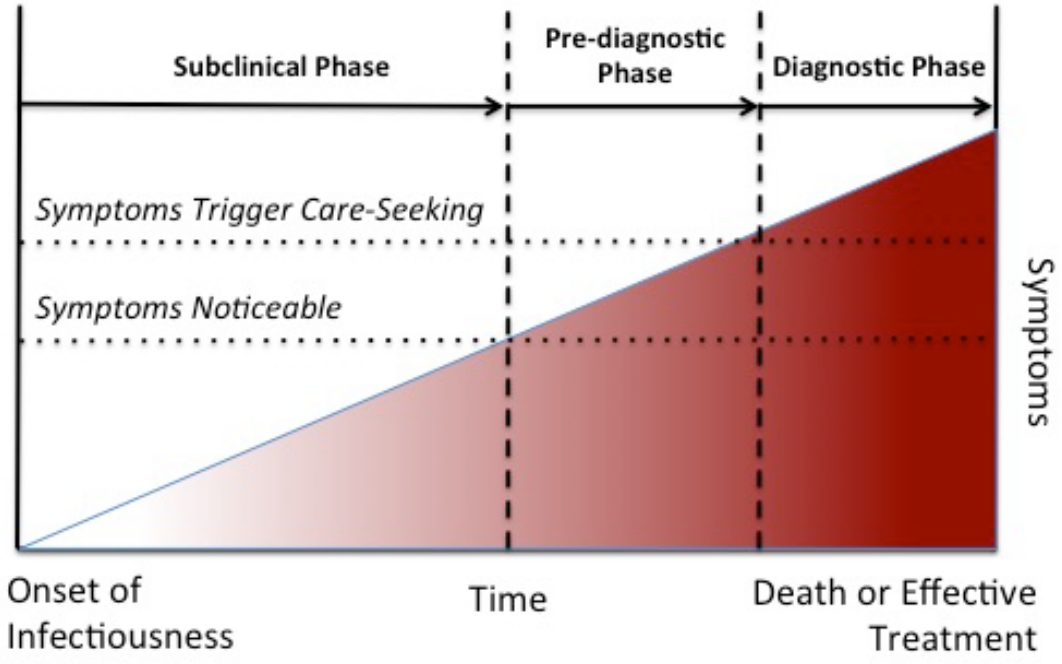


Houben *et al.* Lancet. 2022

Is Passive Diagnosis Enough?

The Impact of Subclinical Disease on Diagnostic Strategies for Tuberculosis

David W. Dowdy[1,2], Sanjay Basu[3,4], and Jason R. Andrews[5]



13.5 months infectiousness prior to seeking care

Dowdy et al AJRCCM 2013

Community prevalence surveys to determine undiagnosed TB

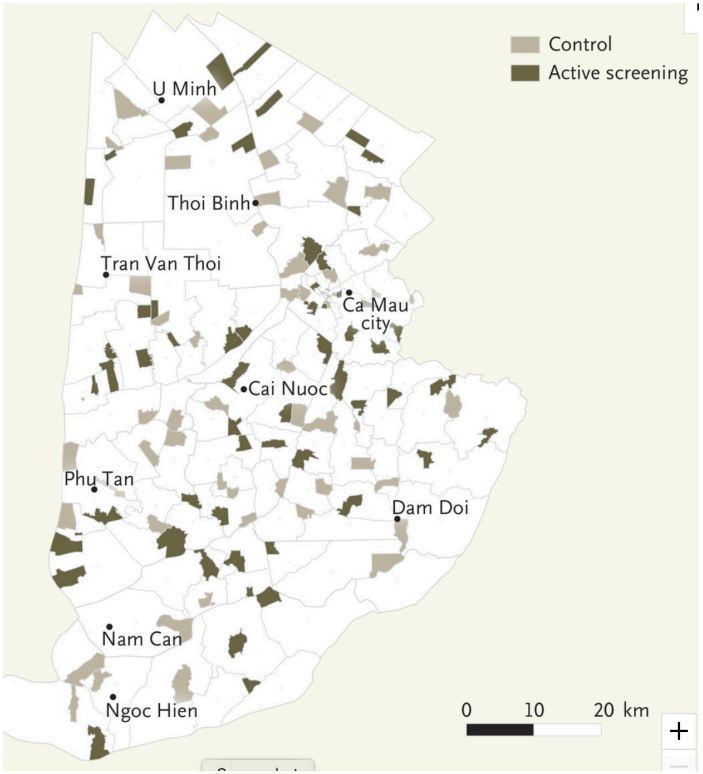
Author	Country	Number screened	% with sputum	%HIV	Number Culture +ve	**Prev. undiag TB**	**Smear+**	**Asympt**	CXR - Norm
den Boon et al	S.Africa - 2002	2,608	45 %	NK	27	**1.0%**	**63%**	**33%**	4%
Wood et al	S.Africa - 2005	762	100 %	23 %	12	**1.6%**	**50%**	**67%**	ND
Corbett et al	Zimbabwe - 2006	12,426	81 %	21 %	66	**0.7%**	**61%**	**NK**	ND
Ayles et al	Zambia - 2005	8,325	91 %	29 %	79	**1.0%**	**28%**	**10%**	ND
van't Hoog et al	Kenya - 2006	20,566	99 %	17 %	119	**0.6%**	**39%**	**40%**	6%
Shapiro et al	S.Africa - 2009	983	80 %	14 %	4	**0.4%**	**NK**	**NK**	ND

Adapted from Corbett and MacPherson IJTLD 2013

ORIGINAL ARTICLE

Community-wide Screening for Tuberculosis in a High-Prevalence Setting

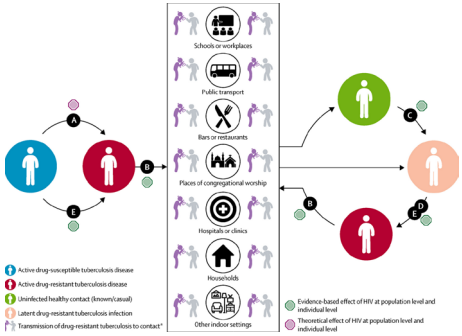
Guy B. Marks, M.B., B.S., Ph.D., Nhung V. Nguyen, M.D., Ph.D., Phuong T.B. Nguyen, Ph.D., Thu-Anh Nguyen, M.D., Ph.D., Hoa B. Nguyen, M.D., Ph.D., Khoa H. Tran, M.D., Son V. Nguyen, M.D., Khanh B. Luu, B.P.H., Duc T.T. Tran, M.P.H., Qui T.N. Vo, B.A., Oanh T.T. Le, B.P.H., Yen H. Nguyen, B.P.H., Vu Q. Do, Ph.D., Paul H. Mason, Ph.D., Van-Anh T. Nguyen, Ph.D., Jennifer Ho, M.B., B.S., Ph.D., Vitali Sintchenko, M.D., Ph.D., Linh N. Nguyen, M.D., Ph.D., Warwick J. Britton, M.B., B.S., Ph.D., and Greg J. Fox, M.B., B.S., Ph.D.



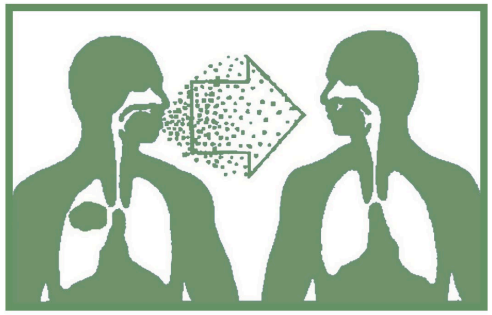
- Annual house-to-house, community-wide screening (regardless of symptoms) was associated with a 44% lower prevalence of tuberculosis than routine passive case finding after 3 years.

- This result provides important proof-of-principle that community-based active case finding in conjunction with improved diagnostic tools (e.g., the Xpert MTB/RIF assay) can help achieve the case reduction targets set forth in the END TB Strategy by the WHO.

MINIMUM REQUIREMENT FOR TB TRANSMISSION



Khan *et al.* Lancet Infect Dis. 2019

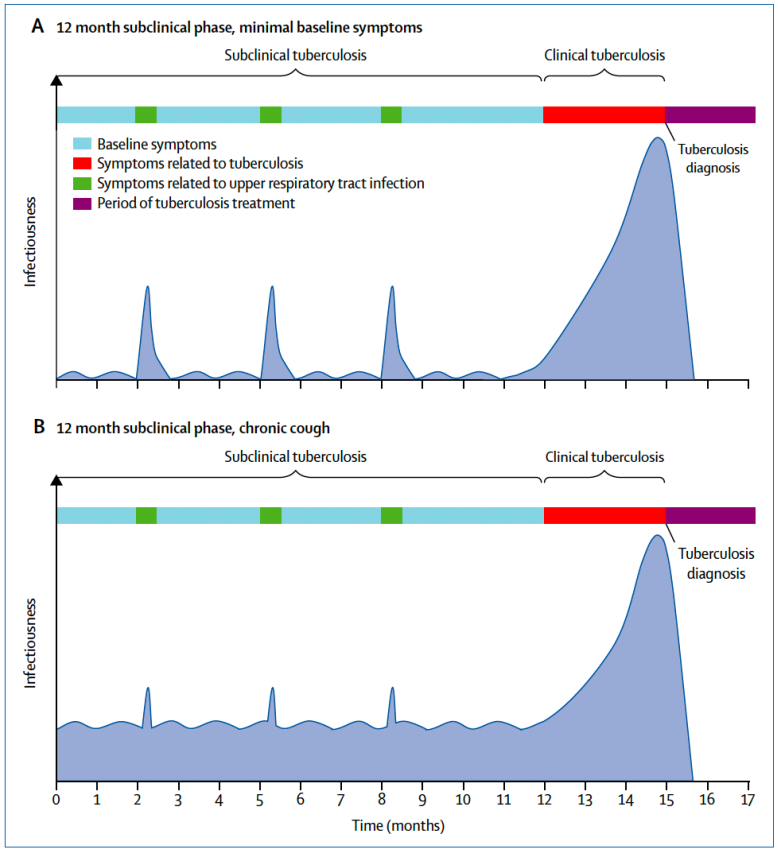


www.cdc.gov

Wood et al. PLoS One 2016

- Persons need to share airspace (for what duration?)
- Index needs to generate bioaerosols that harbor live/viable *Mtb* and inhaled by contact.
- Productive flight of bioaerosol, highly dependent on host and environment

- Bacillary burden generally impacts relative infectiousness (sputum-positive, Xpert-positive, symptomatic, cavitary disease)
- Cough frequency, talking, singing and more recently tidal breathing



- Transmission potential in subclinical and clinical tuberculosis. Could unrelated cough play a part? (*Esmail et al. Lancet. 2018)*

Aerosolization of *Mycobacterium tuberculosis* by Tidal Breathing

Ryan Dinkele[1,2], Sophia Gessner[1,2], Andrea McKerry[3], Bryan Leonard[3], Juane Leukes[3], Ronnett Seldon[3], Digby F. Warner[1,2,4], and Robin Wood[2,3]

[1]South African Medical Research Council/National Health Laboratory Services/University of Cape Town Molecular Mycobacteriology Research Unit & Department of Science and Innovation, National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research, Department of Pathology, [2]Institute of Infectious Diseases and Molecular Medicine, [4]Wellcome Centre for Infectious Diseases Research in Africa, Faculty of Health Sciences, and [3]Desmond Tutu Health Foundation, University of Cape Town, Cape Town, South Africa

ORCID IDs: 0000-0001-6456-7530 (R.D.); 0000-0002-4146-0930 (D.F.W.).

- TiBr is likely to contribute more than 90% of the daily aerosolized Mtb from symptomatic Tb patients irrespective of cough frequency.

Exhaled *Mycobacterium tuberculosis* output and detection of subclinical disease by face-mask sampling: prospective observational studies

Caroline M Williams, Mohamad Abdulwhhab, Surinder S Birring, Elsabe De Kock, Natalie J Garton, Eleanor Townsend, Manish Pareek, Alaa Al-Taie, Jingzhe Pan, Rakesh Ganatra, Anton C Stoltz, Pranabashis Haldar, Michael R Barer

- No association seen between the quantity of exhaled *Mtb* and cough frequency, sputum grade, or severity of X-ray.

Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli

Dr MA Behr, MD • SA Warren, BSc • H Salamon, PhD • PC Hopewell, MD • A Ponce de Leon, MD • CL Daley, MD • PM Small, MD • Show less

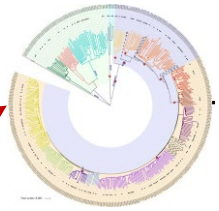
Published: February 06, 1999 • DOI: https://doi.org/10.1016/S0140-6736(98)03406-0

- Smear-negative culture-positive tuberculosis appear responsible for about 17% of tuberculosis transmission

DO INDIVIDUALS WITH SUBCLINICAL TB EXPEL ORGANISMS?

YES and often! A few examples

- CORTIS: Large biomarker-guided TB preventative therapy RCT study found more than 1% of HIV-uninfected community volunteers had previously undiagnosed, microbiologically confirmed tuberculosis at screening, more than 80% of which was asymptomatic.



Biomarker-guided tuberculosis preventive therapy (CORTIS): a randomised controlled trial

Thomas J Scriba, Andrew Fiore-Gartland*, Adam Penn-Nicholson, Humphrey Mulenga, Stanley Kimbung Mbandi, Bhavesh Borate, Simon C Mendelsohn, Katie Hadley, Chris Hikuam, Masooda Kaskar, Munyaradzi Musvosvi, Nicole Bilek, Steven Self, Tom Sumner, Richard G White, Mzwandile Erasmus, Lungisa Jaxa, Rodney Raphela, Craig Innes, William Brumskine, Andriëtte Hiemstra, Stephanus T Malherbe, Razia Hassan-Moosa, Michèle Tameris, Gerhard Walzl, Kogieleum Naidoo, Gavin Churchyard, Mark Hatherill, and the CORTIS-01 Study Team*

- Large simultaneous clinic and community survey based on culture only and culture and Xray (Community): Most participants with Mtb culture-positive sputum were asymptomatic.

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Prevalence of *Mycobacterium tuberculosis* in Sputum and Reported Symptoms Among Clinic Attendees Compared With a Community Survey in Rural South Africa

Indira Govender,[1,2,©] Aaron S. Karat,[1] Stephen Olivier,[2] Kathy Baisley,[3,©] Peter Beckwith,[1,4] Njabulo Dayi,[2] Jaco Dreyer,[2] Dickman Gareta,[2] Resign Gunda,[2,5] Karina Kielmann,[6] Olivier Koole,[1,2,©] Ngcebo Mhlongo,[2] Tshwaraganang Modise,[2] Sashen Moodley,[2] Xolile Mpofana,[2] Thumbi Ndung'u,[2,7] Deenan Pillay,[2,8] Mark J. Siedner,[2,9,©] Theresa Smit,[2] Ashmika Surujdeen,[2] Emily B. Wong,[2,8,9,10] and Alison D. Grant,[1,2,11,12,©]; for the Umoya Omuhle Teams and Vukuzazi Study Teams

- Recurrent subclinical TB among HIV: Follow up identified recurrent TB; 35.4% of these were subclinical, 82.4% were culture positive; 35% resolved TB spontaneously.

Clinical Infectious Diseases

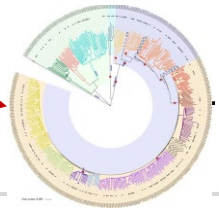
MAJOR ARTICLE

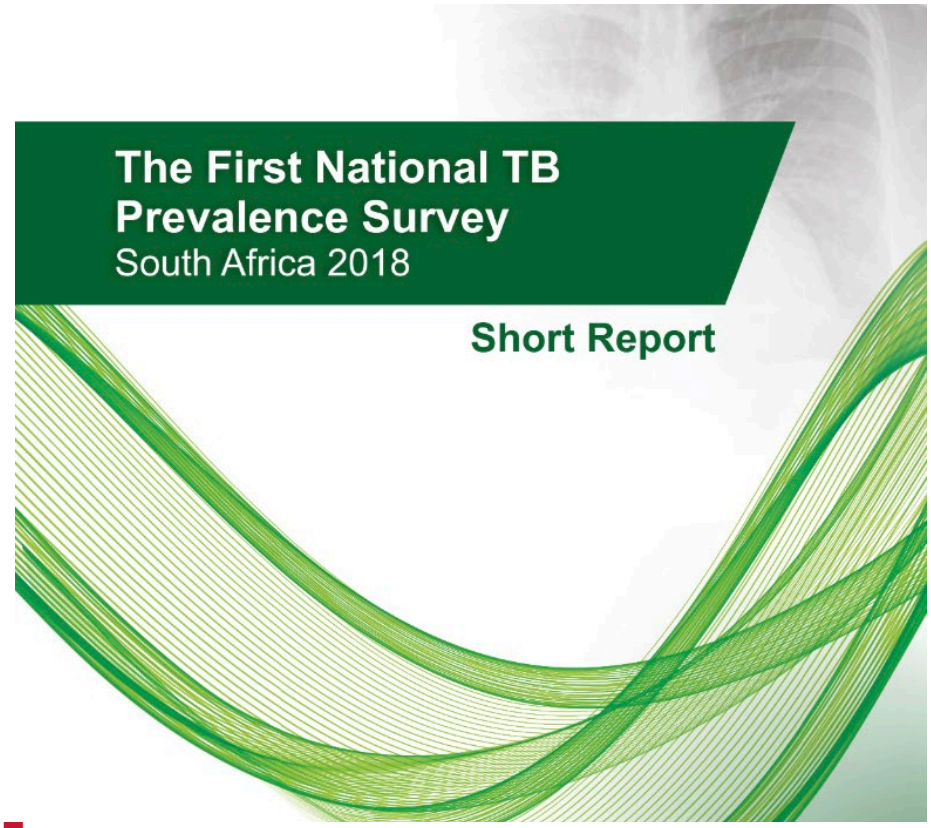
IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Recurrent Subclinical Tuberculosis Among Antiretroviral Therapy–Accessing Participants: Incidence, Clinical Course, and Outcomes

Kogieleum Naidoo,[1,2,©] Mikaila C. Moodley,[1] Razia Hassan-Moosa,[1,2] Navisha Dookie,[1,2] Nonhlanhla Yende-Zuma,[1,2] Rubeshan Perumal,[1,2,3] Halima Dawood,[1,4] Nomonde R. Mvelase,[5,6] Barun Mathema,[7] and Salim Abdool Karim[1,2,7]

- Numerous prevalence surveys…





Articles

Prevalence of bacteriologically confirmed pulmonary tuberculosis in South Africa, 2017–19: a multistage, cluster-based, cross-sectional survey

Sizulu Moyo*, Farzana Ismail*, Martie Van der Walt*, Nazir Ismail, Nkateko Mkhondo, Sicelo Dlamini, Thuli Mthiyane, Jeremiah Chikovore, Olanrewaju Oladimeji, David Mametja, Phaleng Maribe, Ishen Seocharan, Phumlani Ximiya, Irwin Law, Marina Tadolini, Khangelani Zuma, Samuel Manda, Charalambos Sismanidis, Yogan Pillay, Lindiwe Mvusi

Recent experience from South Africa

- Subclinical TB is underestimated as a contribution to the TB burden.
- 57.8% of TB cases did not report any TB symptoms at the time of survey, yet bacteriologically positive for TB (falls within the range of survey in Asia 40-79%).
- More common among HIV-negative individuals.

Clinical Infectious Diseases

REVIEW ARTICLE

- Owing to the robust reporting and surveillance systems, low incidence setting do not conduct population-level prevalence surveys.

- Estimates of subclinical TB among bacteriologically confirmed cases in low incidence settings? Probably data from higher risk groups.

ROLE OF SUBCLINICAL TB IN ONGOING TRANSMISSION? EXAMPLES?

(spoiler alert: not many)

Clinical Infectious Diseases

MAJOR ARTICLE

Disease Transmissior Tuberculosis

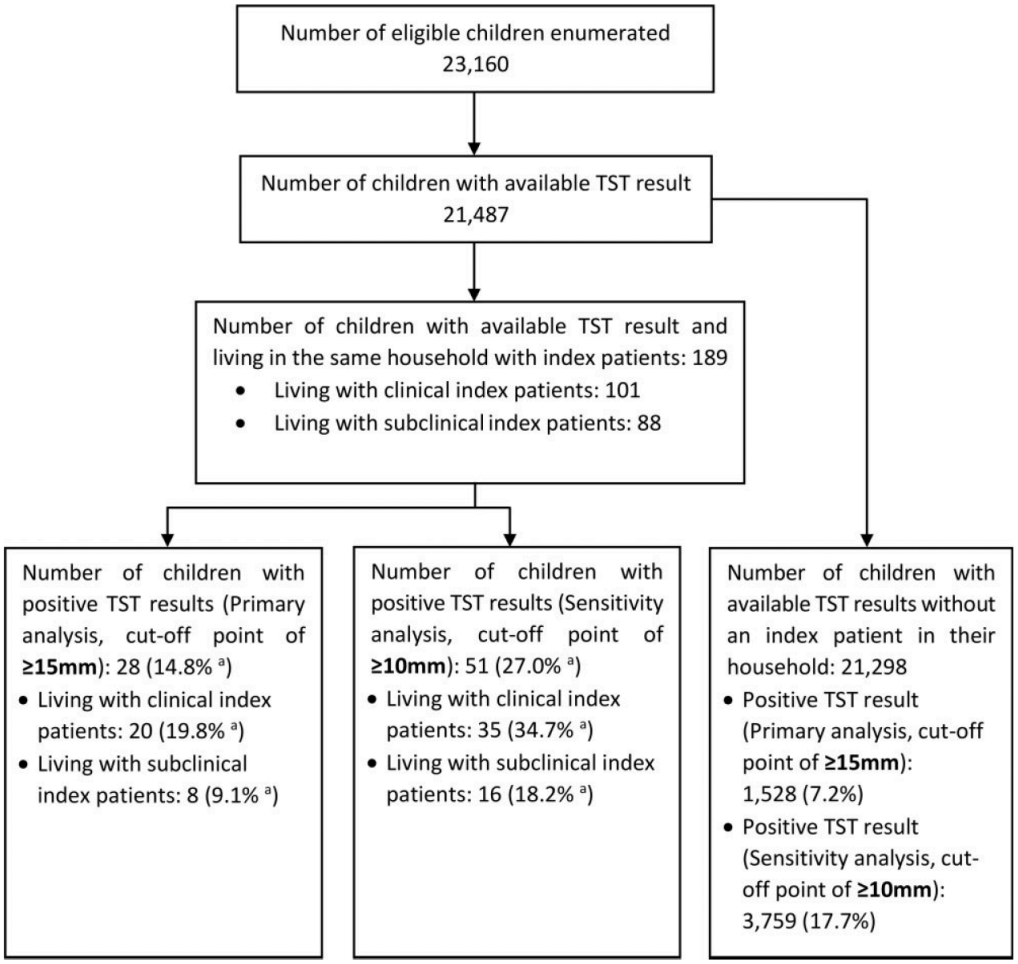
Hai Viet Nguyen,[1,2] Edine Tiemersma,[3] Nhung Viet Ng

[1]Vietnam National Tuberculosis Program, Ha Noi, Vietnam; [2]Departme Amsterdam, The Netherlands; and [3]KNCV Tuberculosis Foundation, Th

RESEARCH ARTICLE

High-resolution ma transmission: Who phylogenetic mode Valencia Region, Sp

Yuanwei Xu[1], Irving Cancino-Muf Rafael Borrás[4], María Borrás-Máñe Ester Colomer-Roig[3,7], Javier Colom Rodríguez[9], Ana Gil-Brusola[10], C Bárbara Gomila-Sard[13], Damiana C Remedio Guna-Serrano[11], José Luis Rosario Moreno-Muñoz[13], David Nav Elvira Pérez[19], Josep Prat[20], Juan Ca Herme Vanaclocha[19], Caroline Colijr



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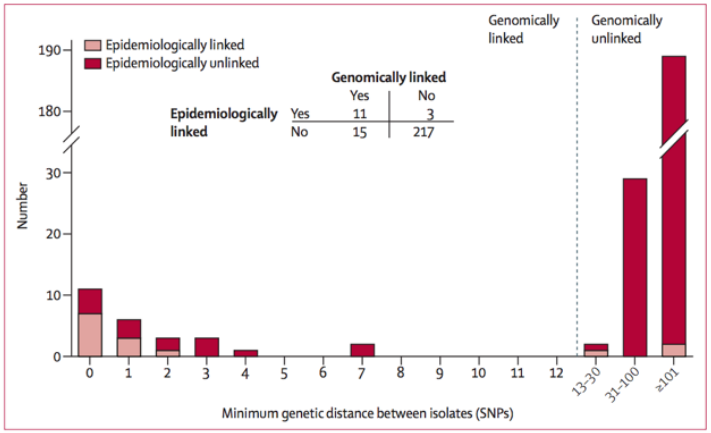
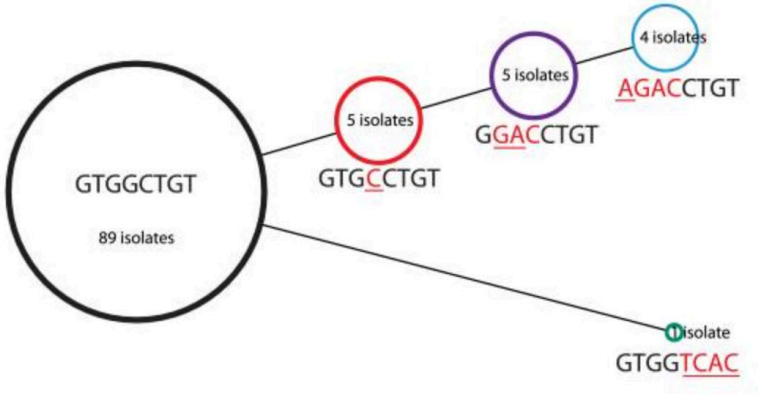
Clustering & transmission inference

SNP-difference based thresholds



Walker et al (2014)



Schürch et al (2010)

✓straightforward interpretation
✓ low-transmission settings with robust case-finding
x threshold depends on transmission, sampling, mutation rate

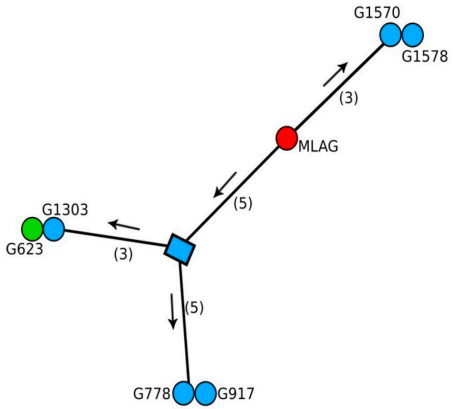
Transmission directionality inferred via **SNP accumulation**

Bayesian inference & transmission trees

$$\mathbf{P}(\theta, N_e g, \mathcal{T}|\mathcal{P}) \propto \mathbf{P}(\mathcal{P}|N_e g, \mathcal{T})\mathbf{P}(\mathcal{T}|\theta)\mathbf{P}(\theta)\mathbf{P}(N_e g)$$

Posterior **Likelihood** **Prior**

✓multiple data sources for inference: genomic and case timing
✓ incorporates missingness



Xu et al (2019)

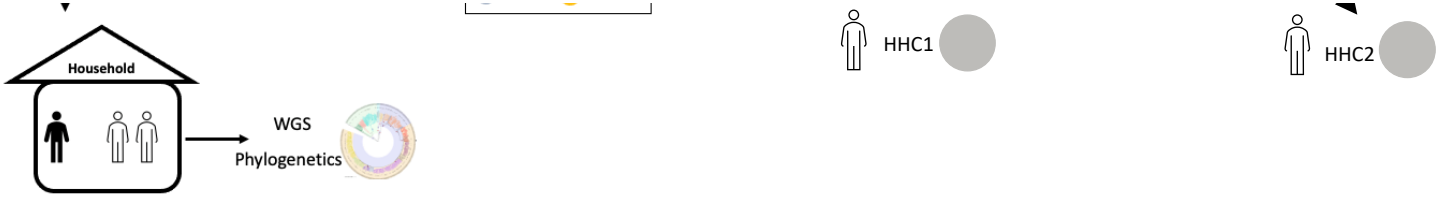
ORIGINAL ARTICLE

Detection and Quantification of Differentially Culturable Tubercle Bacteria in Sputum from Patients with Tuberculosis

Melissa D. Chengalroyen[1], Germar M. Beukes[1], Bhavna G. Gordhan[1], Elizabeth M. Streicher[2], Gavin Churchyard[3], Richard Hafner[4], Robin Warren[2], Kennedy Otwombe[5], Neil Martinson[1,5,6], and Bavesh D. Kana[1]

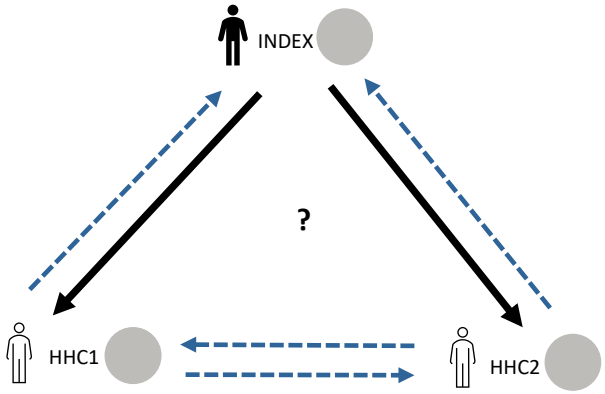
[1]Department of Science and Technology/National Research Foundation Centre of Excellence for Biomedical TB Research, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand and the National Health Laboratory Service, Johannesburg, South Africa; [2]Medical Research Council Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa; [3]The Aurum Institute, Johannesburg, South Africa; [4]Tuberculosis Clinical Research Team, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; [5]Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; and [6]Center for Tuberculosis Research, Johns Hopkins University, Baltimore, Maryland

Designed a study inform how culture methods affect the ability to study transmission within the household, with important broader implications for studying TB transmission in community settings.



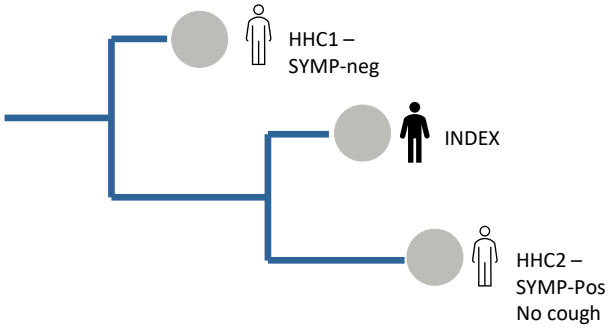
HoTT-DCTB funded NIAID/NIH (R01AI147349)
MPIs: Drs Bavesh Kana and Neil Martinson

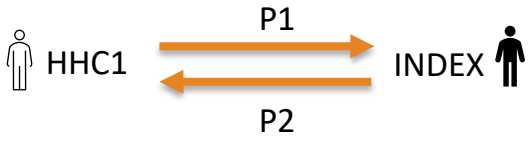
Phylogenomic analysis with epidemiologic data can help infer who infected whom.



- Phylogenetic analysis suggest HHC1 likely infected index and secondary household member.
- Index enrolled 5 days prior to household screening.
- Health seeking behavior highly subject to host characteristics (in this example all participants were HIV-uninfected).

Phylogenetic tree





P1 > P2

- **Phylodynamic analysis can help resolve order and directionality**

Looking ahead

- More empirical studies are needed to show and quantify the contribution of the subclinical period to tuberculosis transmission (individuals and population level). Many studies are underway so sta[illegible]
- Ca[illegible] inf[illegible]
- Co[illegible] dat[illegible] TB[illegible] ion [illegible]nical
- Ho[illegible] diagnostics?)? Targeted case-finding?
- Once you find them what should you do? How to treat?
- Implications for low incidence settings….is the effort “worth” it?

Antigen-Specific T-Cell Activation Distinguishes between Recent and Remote Tuberculosis Infection

Cheleka A. M. Mpande[1], Munyaradzi Musvosvi[1], Virginie Rozot[1], Boitumelo Mosito[1], Timothy D. Reid[1], Constance Schreuder[1], Tessa Lloyd[1], Nicole Bilek[1], Huang Huang[2], Gerlinde Obermoser[2], Mark M. Davis[2], Morten Ruhwald[3,4], Mark Hatherill[1], Thomas J. Scriba[1]*, Elisa Nemes[1]*, and the ACS Study Team

[1]South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine, Division of Immunology, Department of Pathology, University of Cape Town, Cape Town, South Africa; [2]Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, California; [3]Statens Serum Institute, Copenhagen, Denmark; and [4]Foundation of Innovative New Diagnostics, Geneva, Switzerland

ORCID IDs: 0000-0003-3438-2214 (C.A.M.M.); 0000-0003-1662-4961 (E.N.); 0000-0002-0641-1359 (T.J.S.)

Thank you

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