

A Neighbor-Based Approach to Identify Tuberculosis Exposure, the Kopanyo Study

Patrick K. Moonan, Nicola M. Zetola, James L. Tobias, Joyce Basotli, Rosanna Boyd, Eleanor S. Click, Mbatshi Dima, Othusitse Fane, Alyssa M. Finlay, Matsiri Ogopotse, Xiao J. Wen, Chawangwa Modongo, John E. Oeltmann

Contact investigation is one public health measure used to prevent tuberculosis by identifying and treating persons exposed to *Mycobacterium tuberculosis*. Contact investigations are a major tenet of global tuberculosis elimination efforts, but for many reasons remain ineffective. We describe a novel neighbor-based approach to reframe contact investigations.

Tuberculosis (TB) is a global health emergency (1). The World Health Organization (WHO) End TB Strategy proposes a 90% reduction in TB incidence and 95% reduction in TB deaths by 2035 compared with 2015 (2). To reach this target, effective interventions are needed to interrupt transmission of *Mycobacterium tuberculosis*. Contact investigations help prevent *M. tuberculosis* transmission by identifying and treating persons in close contact with persons with TB disease (3). WHO recommends tuberculosis preventive treatment (TPT) for household members of bacteriologically confirmed pulmonary TB patients to prevent progression to active TB disease (4).

Contact investigations are a major tenet of the End TB Strategy but remain ineffective for various reasons (2,5,6). Many TB programs in high-burden areas limit contact investigations to household members (6). Recent studies suggest that such restrictions might miss key exposures in the community (7,8). Targeted, population-based, geographic TB screening is a potential approach to augment contact investigations (9–11)

Author affiliations: Centers for Disease Control and Prevention, Atlanta, Georgia, USA (P.K. Moonan, R. Boyd, E.S. Click, A.M. Finlay, X.J. Wen, J.E. Oeltmann); Botswana-UPenn Partnership, Gaborone, Botswana (N.M. Zetola, M. Dima, O. Fane, M. Ogopotse, C. Modongo); Northrop Grumman, Atlanta (J.L. Tobias); National Tuberculosis Program, Botswana Ministry of Health, Gaborone (J. Basotli)

DOI: <https://doi.org/10.3201/eid2605.191568>

but is resource and time intensive and rarely includes TPT (11,12). We used population-based, molecular epidemiologic data from Botswana to investigate potential use of a neighbor-based approach for contact investigations.

The Study

During August 2012–April 2016, we enrolled participants treated for TB disease at 30 healthcare facilities in Botswana for a prospective molecular epidemiologic study, Kopanyo. In brief, Kopanyo was designed to explore potential clinical, demographic, geographic, social relationships, and *M. tuberculosis* genotypic characteristics among persons with TB (13,14). We interviewed enrolled patients by using a standardized questionnaire and abstracted clinical data from medical records (13). We collected and processed sputum samples for culture and genotyped isolates with 24-locus mycobacterial interspersed repetitive units-variable-number tandem-repeats by using standard methods (15). We geocoded and validated the primary residence of each enrolled patient (Appendix, <https://wwwnc.cdc.gov/EID/article/26/5/19-1568-App1.pdf>). We excluded patients without a validated primary residential geocode and those who resided in locations outside of the study area. The study area included all 11 neighborhoods in Gaborone and 3 villages in the Ghanzi District: Ghanzi, D'Kar, and Kuke.

We defined index patients as the first culture-positive pulmonary TB patient identified and started on treatment in a household. We used residence plots to identify nearest neighbors, which we defined as those who lived immediately next door, and next-nearest neighbors, which we defined as those who lived 2 doors away (Figure). We enumerated all subsequent TB cases identified by bacteriologic confirmation and clinical diagnosis within the index home, nearest-neighbor homes, and next-nearest neighbor homes. We defined

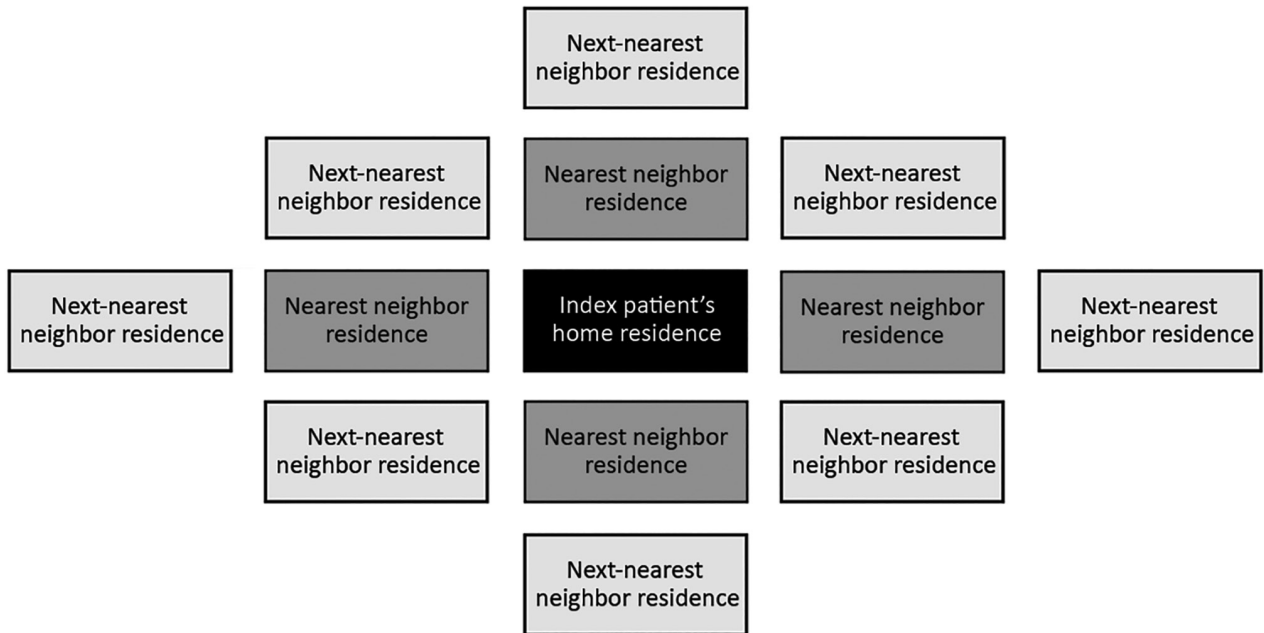


Figure. Illustration of possible nearest neighbors and next-nearest neighbors for tuberculosis (TB) screening and possible TB preventive treatment. Black box represents the home of a TB index patient; dark-gray boxes represent the nearest-neighbor homes; light-gray boxes represent the next-nearest neighbor homes. This figure does not reflect the true number of neighbor homes, and index patients might have >4 next-door neighbors, depending on the geographic orientation of residential plots.

future-related patients as culture-positive patients with matching genotypes diagnosed after exposure to an index patient. Concurrent disease was TB diagnosed in a contact within 90 days of the index patient.

We enrolled 4,331 patients but excluded 595 (14%) without a residential geocode and 547 (13%) who resided outside the study area. We analyzed data on the remaining 3,189 patients. Among 1,072 index patients, 143 (13%) had subsequent TB patients in the home ($n = 426$); 30 (7%) in-home subsequent patients had concurrent disease. Of 1,072 index patients, 73 (7%) had future-related patients ($n = 123$) in their homes; 5 (3.94%) of those had concurrent TB disease.

When we applied a neighbor-based approach, we noted that 257 (24%) index patients could have subsequent TB patients living next door ($n = 749$), 41 of which could have concurrent disease. Among next-nearest neighbors of index patients, 390 (36%) could have subsequent TB, 23 of which could have concurrent disease (Table). In addition, 29 (2.7%) index patients could have future-related patients among their nearest neighbors ($n = 42$), and 5 (0.5%) future-related patients among next-nearest neighbors ($n = 10$), 3 with concurrent TB disease (Table).

We found that a neighbor-based approach could identify 1,565 additional subsequent TB patients, including 175 future-related patients, and 102 patients with concurrent TB disease. The number of persons

living with a bacteriologically positive patient varied by geography; however, $\approx 23,630$ contacts potentially could benefit from TPT. Of note, 9% (97/1,072) of index patients interviewed stated they lived alone, but 91 (94%) had subsequent patients identified in the home, and 84 (87%) had subsequent future-related patients living in the home.

Conclusions

We explored the use of a nearest-neighbor approach to expand TB contact investigations. This approach does not rely on name-based contact identification, which has been shown to be ineffective (6,16–18). In addition, the neighbor-based approach would not require mobile screening units or mass screening campaigns in the community. By simply expanding the number of homes visited to nearest and next-nearest neighbors, the Botswana National TB Program could increase the number of TB case diagnoses by 146% and potentially interrupt 175 secondary patient transmission events.

Preventing future TB disease through TPT could also hasten TB elimination in at-risk neighborhoods and reduce deaths in the community (11,12). Cegielski et al. effectively used TPT to eliminate TB from 2 at-risk neighborhoods in Texas, USA (11). The focus on nearest and next-nearest neighbors gives programs a tangible and practical approach to locating persons at risk for TB exposure and progression to TB disease.

The neighbor-based approach differs from a neighborhood screening, which places an additional burden on TB programs by unnecessarily screening many persons at lower risk. For example, 59,100 persons reside in neighborhood C in Gaborone (data not shown). Under the neighbor-based approach, only 5,470 (9%) persons, including in-home and nearest neighbor residents, would be targeted for testing.

Previous reports suggest that contact investigations fail to identify key relationships, even within households (16,17). Potential stigma and lack of trust in government officials also play a role in contact investigations (16–18). In our cohort, many (n = 97) index patients said they lived alone, but 94% of them had subsequent cases identified in the home. In addition, 48% of future-related patients were linked to index patients who claimed no household contacts during name-based contact solicitation interviews conducted at the enrollment clinic. Household membership composition could have changed over time, and some connections might not have existed at the time of the interview. However, our study reinforces the necessity of home visits at times convenient to the index patient and when most household members are in the home, which might warrant home visits outside of business hours and flexibility in staff workplans.

Our analysis emphasizes the opportunity to prevent future TB patients and future-related TB patients by providing TPT. Household contacts, especially young children and persons living with HIV, are eligible for TPT by national policy, but TPT has not been

practiced routinely in Botswana. As the Botswana Ministry of Health scales up access to TPT throughout the country, the neighbor-based approach could improve identification of most likely contacts and help target interventions where they are most needed.

Our study has limitations. Living in proximity to an index patient is not the only opportunity for transmission and might not always translate into time spent together. In addition, our analysis of future-related patients included only patients with culture-positive disease and genotyping results; excluding them did not affect the main analysis enumerating subsequent patients but might have underestimated the number of future-related patients. Also, our estimates for TPT represent the maximum number of persons who could benefit because we used the average number of persons per household and assumed all household members would be eligible for TPT without a reliable and available test for infection.

A neighbor-based approach should not supplant household investigations, and community-based interventions should not divert essential resources from those already devoted to finding and treating TB patients. Wide-scale implementation of this approach would require adequate resources to ensure that all patients complete the full cascade of treatment. To reach the ambitious global goal of TB elimination, we need simple, easy to implement, location-based approaches. Screening index patient households and nearest neighbors could help identify additional TB patients and persons who could benefit from TPT.

Table. Number of index patients and possible additional subsequent contacts and future-related patients identified by using a nearest-neighbor approach to tuberculosis screening, Botswana*

Geographic area	No. index patients†	No. household members (FR)‡	No. nearest-neighbors (FR)‡	No. next-nearest neighbors (FR)‡	Total subsequent patients (FR)‡	No. screened to identify 1 TB patient (95% CI)§	Household contacts that could benefit from TPT¶	Neighbor contacts that could benefit from TPT¶
Gaborone								
A	123	57 (16)	93 (0)	47 (2)	197 (18)	21 (13–32)	861	3,472
B	58	19 (4)	41 (0)	21 (0)	81 (4)	18 (11–28)	307	1,230
C	210	83 (22)	146 (8)	84 (1)	313 (31)	16 (9–26)	1,092	4,368
D	195	58 (10)	110 (0)	56 (2)	224 (12)	19 (11–30)	878	3,510
E	79	28 (6)	46 (0)	30 (0)	104 (6)	11 (5–20)	253	1,011
F	129	53 (2)	84 (2)	51 (2)	188 (6)	15 (8–25)	593	2,374
G	51	14 (0)	29 (0)	18 (0)	61 (0)	9 (4–17)	128	510
H	20	5 (0)	12 (0)	6 (0)	23 (0)	7 (3–14)	38	152
I	6	2 (0)	9 (0)	4 (0)	15 (0)	2 (0–7)	10	41
J	6	2 (0)	2 (0)	1 (0)	5 (0)	22 (14–33)	23	94
K	11	6 (0)	11 (0)	6 (0)	23 (0)	7 (3–14)	35	141
Ghanzi District								
Ghanzi	141	83 (57)	143 (24)	57 (3)	283 (84)	6 (2–16)	398	1,590
D'kar	35	9 (2)	14 (8)	7 (0)	30 (10)	11 (5–20)	86	280
Kuke	8	7 (4)	9 (0)	2 (0)	18 (4)	8 (3–15)	28	128
Total	1,072	426 (123)	749 (42)	390 (10)	1,565 (175)	16 (9–26)	4,730	18,901

*FR, future related; TB, tuberculosis; TPT, tuberculosis preventive treatment.

†No. index patients is equivalent to the number of standard contact investigations.

‡Future related, i.e., all culture-positive patients with matching *M. tuberculosis* genotype as an index patient.

§Limits of 95% CI assume a Poisson distribution.

¶Number exposed to bacteriologically confirmed pulmonary TB who do not have TB disease.

Members of the Kopanyo Study Group: Joyce Basotli, Ebi Bile, Cynthia Caiphus, Eleanor Click, Rosanna Boyd, Mbatshi Dima, Othusitse Fane, Alyssa Finlay, Sambayawo Gwebe-Nyirenda, Thandi Katlholo, Pilara Khumongwana, Chawangwa Modongo, Patrick Moonan, John Oeltmann, Matsiri Ogopotse, Kitso Ramogale, Christopher Serumola, James Shepherd, Tsaone Tamuhla, James Tobias, Goitseone Thamae, Onani Zimba, and Nicola Zetola.

Acknowledgments

We thank the tuberculosis patients and their families for participating in this study. We thank the district health team and recruitment and retention officers who helped us contact patients and coordinate clinic visits. We are indebted to the Botswana National Tuberculosis Program and Botswana Ministry of Health for their partnership in this effort, especially Botshelo Kgwaadira and Tom Lere. We also thank Tefera Agizew, Susan Cookson, Katina Pappas-DeLuca, Jonathan Smith, and Diya Surie for their thoughtful reviews and suggestions to improve our manuscript.

This work was funded by the National Institutes of Health (grant no. R01AI097045) and in part, by the US President's Emergency Plan for AIDS Relief through the US Centers for Disease Control and Prevention. National Institutes of Health did not participate in study design, data collection, or interpretation of results. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

About the Author

Dr. Moonan works in the Division of Global HIV and Tuberculosis, Center for Global Health, at the US Centers for Disease Control and Prevention. His research interests include tuberculosis transmission dynamics, drug-resistant tuberculosis, and applying locally relevant, operational research to influence program policy and improve program performance.

References

- World Health Organization. Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: The Organization; 2014.
- Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al.; for WHO's Global TB Programme. WHO's new end TB strategy. *Lancet*. 2015;385:1799-801. [https://doi.org/10.1016/S0140-6736\(15\)60570-0](https://doi.org/10.1016/S0140-6736(15)60570-0)
- World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low and middle-income countries. Geneva: The Organization; 2012.
- Weis S. Contact investigations: how do they need to be designed for the 21st century? *Am J Respir Crit Care Med*. 2002;166:1016-7. <https://doi.org/10.1164/rccm.2207007>
- Rodriguez CA, Sasse S, Yuengling KA, Azzawi S, Becerra MC, Yuen CM. A systematic review of national policies for the management of persons exposed to tuberculosis. *Int J Tuberc Lung Dis*. 2017;21:935-40. <https://doi.org/10.5588/ijtld.17.0061>
- Wang W, Mathema B, Hu Y, Zhao Q, Jiang W, Xu B. Role of casual contacts in the recent transmission of tuberculosis in settings with high disease burden. *Clin Microbiol Infect*. 2014;20:1140-5. <https://doi.org/10.1111/1469-0691.12726>
- Surie D, Fane O, Finlay A, Ogopotse M, Tobias JL, Click ES, et al.; Kopanyo Study Group. Molecular, spatial, and field epidemiology suggesting TB transmission in community, not hospital, Gaborone, Botswana. *Emerg Infect Dis*. 2017;23:487-90. <https://doi.org/10.3201/eid2303.161183>
- Moonan PK, Oppong J, Sahbazian B, Singh KP, Sandhu R, Dreyer G, et al. What is the outcome of targeted tuberculosis screening based on universal genotyping and location? *Am J Respir Crit Care Med*. 2006;174:599-604. <https://doi.org/10.1164/rccm.200512-1977OC>
- Fatima R, Qadeer E, Yaqoob A, Haq MU, Majumdar SS, Shewade HD, et al. Extending 'contact tracing' into the community within a 50-metre radius of an index tuberculosis patient using Xpert MTB/RIF in Urban, Pakistan: did it increase case detection? *PLoS One*. 2016;11:e0165813. <https://doi.org/10.1371/journal.pone.0165813>
- Cegielski JP, Griffith DE, McGaha PK, Wolfgang M, Robinson CB, Clark PA, et al. Eliminating tuberculosis one neighborhood at a time. *Am J Public Health*. 2013;103:1292-300. <https://doi.org/10.2105/AJPH.2012.300781>
- Moonan PK, Weis SE. Assessing the impact of targeted tuberculosis interventions. *Am J Respir Crit Care Med*. 2008;177:557-8. <https://doi.org/10.1164/ajrccm.177.5.557a>
- World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: The Organization; 2018.
- Zetola NM, Modongo C, Moonan PK, Click E, Oeltmann JE, Shepherd J, et al. Protocol for a population-based molecular epidemiology study of tuberculosis transmission in a high HIV-burden setting: the Botswana Kopanyo study. *BMJ Open*. 2016;6:e010046. <https://doi.org/10.1136/bmjopen-2015-010046>
- Click ES, Finlay A, Oeltmann JE, Basotli J, Modongo C, Boyd R, et al. Phylogenetic diversity of *Mycobacterium tuberculosis* in two geographically distinct locations in Botswana—the Kopanyo Study. *Infect Genet Evol*. 2020;81:104232 [Epub ahead of print]. <https://doi.org/10.1016/j.meegid.2020.104232>
- Supply P, Allix C, Lesjean S, Cardoso-Oelemann M, Rüsch-Gerdes S, Willery E, et al. Proposal for standardization of optimized mycobacterial interspersed repetitive unit-variable-number tandem repeat typing of *Mycobacterium tuberculosis*. *J Clin Microbiol*. 2006;44:4498-510. <https://doi.org/10.1128/JCM.01392-06>
- Oeltmann JE, Oren E, Haddad MB, Lake L, Harrington TA, Ijaz K, et al. Tuberculosis outbreak in marijuana users, Seattle, Washington, 2004. *Emerg Infect Dis*. 2006;12:1156-9. <https://doi.org/10.3201/eid1207.051436>
- Asghar RJ, Patlan DE, Miner MC, Rhodes HD, Solages A, Katz DJ, et al. Limited utility of name-based tuberculosis contact investigations among persons using illicit drugs: results of an outbreak investigation. *J Urban Health*. 2009;86:776-80. <https://doi.org/10.1007/s11524-009-9378-z>
- Nyenswah TG, Fallah M, Calvert GM, Duwear S, Hamilton ED, Mokashi V, et al. Cluster of Ebola virus disease, Bong and Montserrado Counties, Liberia. *Emerg Infect Dis*. 2015;21:1253-6. <https://doi.org/10.3201/eid2107.150511>

Address for correspondence: Patrick K. Moonan, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop US1-1, Atlanta, GA 30329-4027, USA; email: pmoonan@cdc.gov

A Neighbor-Based Approach to Identify Tuberculosis Exposure, the Kopanyo Study

Appendix

Additional Methods

We obtained valid 24-locus mycobacterial interspersed repetitive units–variable-number tandem-repeats genotyping results from 2,012 patient isolates. Patient primary residential address was obtained during face-to-face interview. All addresses were verified by site visit geotagging, or through a reference layer created by manually relocating addresses in satellite imagery (*I*) by using OpenStreetMap (<http://www.openstreetmap.org>), Google Maps (<https://maps.google.com>), and ArcGIS 10.0 (Environmental System Research Institute [ESRI], <https://www.esri.com>) online geocoding services. We exported World Geodetic System 84 (WGS 84; <https://gisgeography.com>) projection system latitude and longitude coordinates with 1.1-meter precision for each address.

We obtained records on residential parcels from the Botswana Survey and Lands Department for the cities of Gaborone and Ghanzi. Botswana Land Survey Act required that each parcel of land for cadastral surveys in both urban and rural areas were complete and tied to a common spatial reference. The parcels were delineated by traditional ground-based survey methods but also aligned orthographic photos from overhead flights and imagery data (2). An integrated Geographic Information System (GIS) project brought all cadastral, geodetic, and topographic databases together into a single Geodatabase (Oracle with ArcSDE). Shapefiles of the parcels were provided to study staff via formal government request. For the rural villages of D’Kar and Kuke, building footprints were digitized by manually relocating addresses in satellite imagery using OpenStreetMap. These footprints were used as a proxy for the official government parcels to approximate homesteads.

We defined neighborhood boundaries to enumerate localized populations necessary for TB incidence rates, and to enumerate the number of homes (parcels), and number of contacts per

house based on neighborhood-level population estimates (3). An average number of household members was calculated for each geographic location based on the number of households and population estimate of each area. According to international guidelines, all household members, regardless of age, exposed to bacteriologically confirmed pulmonary TB, who are not TB-positive are eligible for tuberculosis preventive treatment (TPT), regardless of availability of testing for latent infection (4).

Ethics Approval

This study was approved by the US Centers for Disease Control and Prevention Institutional Review Board (IRB no. 6291); Health Research and Development Committee, Ministry of Health and Wellness, Botswana (reference no. 13/18/1/891); and the University of Pennsylvania IRBs (protocol no. 815718). All enrolled participants provided written informed consent.

References

1. Faure E, Danjou AM, Clavel-Chapelon F, Boutron-Ruault MC, Dossus L, Fervers B. Accuracy of two geocoding methods for geographic information system-based exposure assessment in epidemiological studies. *Environ Health*. 2017;16:15. [PubMed https://doi.org/10.1186/s12940-017-0217-5](https://doi.org/10.1186/s12940-017-0217-5)
2. Morebodi BBH. Botswana–Department of Surveys and Mapping (DSM) Cadastral Information System. 2006 Mar 13 [cited 2020 Mar 22]. https://www.fig.net/resources/proceedings/fig_proceedings/accra/papers/ts14/ts14_05_morebodi.pdf
3. Statistics Botswana. Population and housing census 2011: analytical report. Gaborone (Botswana); Statistics Botswana: 2014. [cited 2020 Mar 22] <http://www.statsbots.org.bw/sites/default/files/publications/Population%20%26%20Housing%20Census%20Dissemination%20analytical%20report%20.pdf>
4. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: The Organization; 2018.