Molecular, Spatial, and Field Epidemiology Suggesting TB Transmission in Community, Not Hospital, Gaborone, Botswana

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During 2012–2015, 10 of 24 patients infected with matching genotypes of Mycobacterium tuberculosis received care at the same hospital in Gaborone, Botswana. Nosocomial transmission was initially suspected, but we discovered plausible sites of community transmission for 20 (95%) of 21 interviewed patients. Active case-finding at these sites could halt ongoing transmission.

Tuberculosis (TB) results from rapid progression of a recently acquired Mycobacterium tuberculosis infection or from reactivation of a remote infection (1). It is critical that recent M. tuberculosis infections be identified because TB is more likely to develop in persons with recent infections (2). Furthermore, the finding of recently infected persons suggests ongoing transmission of TB, which can be interrupted by prompt identification and treatment of undiagnosed cases (3). However, finding undiagnosed cases remains a challenge (4). Name-based contact investigations have traditionally been used for this purpose, but such investigations are resource-intensive (3), making them less practical in countries to which TB is endemic. Genotyping of M. tuberculosis has emerged as a complementary method to detect ongoing transmission because persons who have the same TB genotype may be involved in the same chain of transmission (6). Although this assumption is relatively reliable in low-incidence countries, it is yet to be determined whether genotyping in TB-endemic settings can similarly detect ongoing transmission.

We investigated a TB cluster of 24 patients with matching M. tuberculosis genotypes in Gaborone, Botswana, a city with a high number of TB cases (7). Because almost half of these patients received care at the same hospital, nosocomial transmission was suspected. We conducted an investigation to determine if TB transmission occurred among these patients within the hospital and to identify possible alternate sites of ongoing transmission of this TB strain.

The Study

During August 2012–January 2015, all consenting persons with TB at 26 facilities in Gaborone provided sputum samples for culture as part of the Kopanyo study (8). M. tuberculosis isolates were genotyped by 24-locus mycobacterial interspersed repetitive units–variable number tandem repeats (9).

We assessed nosocomial transmission by reviewing dates of hospital visits for overlap among the 24 TB cluster-associated patients. The hospital’s electronic billing system was used to obtain all previous dates of admission, discharge, and visits to the accidents and emergency department that had occurred for these patients since 2004.

We interviewed each patient, using an investigation form (online Technical Appendix, https://wwwnc.cdc.gov/EID/article/23/3/16-1183-Techapp1.pdf), to learn their primary residence; contacts; places of work and worship; and other frequented locations, including bars and combi (minibus) routes used in the 6 months before diagnosis. Primary residences of patients were mapped by using global positioning system coordinates (8). Ethical approval was obtained from the University of Pennsylvania, US Centers for Disease Control and Prevention, Botswana Ministry of Health, and University of Botswana.

We looked for epidemiologic links that might suggest ongoing transmission. An epidemiologic link was defined for patients having at least 1 of the following associations: overlapping visits at the hospital, living within 1 km of another cluster-associated patient (spatial link), frequenting the same locations as another cluster-associated patient, and naming another cluster-associated patient as a contact.

During the study, ≈60% of M. tuberculosis isolates from reported TB patients in Gaborone were genotyped. The cluster discussed in this report includes 24 (2.3%) of 1,033 total genotyped cases from Gaborone.

All patients had pulmonary disease involvement (Table 1). Ten (42%) had received care at the hospital since 2004;

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most visits occurred after October 2013 (Figure 1). Except for visits by 2 patients, no patients’ visits overlapped at the hospital. Patients V and X overlapped in the hospital for 3 days, albeit in separate buildings. Patient V was admitted to the hospital with a known diagnosis of TB and had started TB therapy the day before admission. Patient X was in the hospital for a week but did not start TB therapy until 3 days, albeit in separate buildings. The patients were hospitalized in separate buildings and the time from TB exposure and treatment initiation (13 days) is an extremely short time for disease to develop (10). Instead, the combination of links among patients suggests ongoing community transmission. Plausible sites of transmission included specific neighborhoods, bars, combi routes, and churches, transmission locations consistent with reports from other TB-endemic settings (11,12). These findings demonstrate the critical role that nonhousehold-based TB transmission plays in sub-Saharan Africa and highlight the need for identifying community-based TB transmission. A multidisciplinary approach (i.e., use of genotyping, spatial analyses, and interviews) provided us with locations where additional persons may be at risk for TB.

Our study has limitations. First, because samples from every TB case in Gaborone were not genotyped and interviews were not conducted with all persons in this cluster, key linkages between patients may have been missed.
Second, underreporting of locations might have occurred due to patients’ inability to remember all locations visited; thus, some less frequented places where transmission might have occurred may have been missed. Third, we could not prove that patients who attended the same location interacted with each other at that location while infectious. Fourth, if a cluster-associated patient went to the hospital as a visitor, not a patient, their overlap with another cluster-associated patient could have been missed. Fifth, the extent to which the hospital infection-control program influenced our findings is unknown. Sixth, because 24-locus mycobacterial interspersed repetitive units–variable number tandem repeats characterizes only a portion of the M. tuberculosis genome, it is possible for 2 different strains to appear similar. Whole-genome sequencing could help confirm (or refute) the findings in this investigation.

Although genotyping is an imperfect tool for confirming transmission between patients, we know that numerous

Table 2. Epidemiologic links between patients in a tuberculosis cluster, Gaborone, Botswana, 2012–2015

| Link               | No./no. total | %  |
|--------------------|---------------|----|
| **Location**       |               |    |
| Any                | 20/21*        | 95 |
| Hospital A         | 2/24†         | 8  |
| Combi routes       | 16/21         | 76 |
| Spatial            | 13/24         | 54 |
| Bars               | 11/21         | 52 |
| Churches           | 8/21          | 38 |
| **Named contacts** |               |    |
| >2                 | 14/21         | 67 |
| ≥3                 | 11/21         | 52 |
| ≥4                 | 3/21          | 14 |

*Only 21/24 cluster-associated patients were reachable for interview regarding epidemiologic links associated with contacts, combi routes used, and places of socialization and worship.
†Hospital visits for 2 patients overlapped, but tuberculosis transmission between them probably did not occur because the patients were hospitalized in separate buildings and the time between tuberculosis exposure and treatment initiation (13 d) is an extremely short time for disease to develop.

Figure 2. Residence-associated data for patients in a tuberculosis cluster, Gaborone, Botswana, 2012–2015. A) Primary residences of 20 patients are indicated by red dots. Inset map shows location of Gaborone in Botswana. Black lines demarcate neighborhoods; gray lines demarcate property parcels; pink circles represent 0.5-km radius around a patient’s residence; and red rectangles indicate presence of 14 patients in 4 distinct neighborhoods, 13 of whom had spatial links. Four patients who are not depicted on this map lived outside of Gaborone and did not have any spatial links between them. B) Primary residences of 5 patients who lived in the same neighborhood. Parcels locations were intentionally not shown to protect individual case anonymity. Geodata were sourced from Statistics Botswana (http://www.cso.gov.bw).
patients in this cluster visited the same community locations while they were potentially infectious, which alone could justify further active case-finding at these locations. With an estimated incidence of 385 TB cases/100,000 persons in Botswana (7), such clues are needed to focus TB control efforts. Active case-finding targeted at the most frequently visited community locations could help stop ongoing transmission of this strain.

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References

1. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. Lancet. 2003;362:887–99. http://dx.doi.org/10.1016/S0140-6736(03)14333-4

2. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med. 2004;350:2060–7. http://dx.doi.org/10.1056/NEJMsa031667

3. Yuen CM, Amanullah F, Dharmadhikari A, Nardell EA, Seddon JA, Vasilyeva I, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. Lancet. 2015;386:2334–43. http://dx.doi.org/10.1016/S0140-6736(15)00322-0

4. Stop TB Partnership. The Global Plan to End TB 2016–2020 [cited 2016 Jan 20]. http://www.stoptb.org/global/plan/plan2/

5. National Tuberculosis Controllers Association; Centers for Disease Control and Prevention (CDC). Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Recomm Rep. 2005;54(No. RR-15):1–47.

6. Barnes PF, Cave MD. Molecular epidemiology of tuberculosis. N Engl J Med. 2003;349:1149–56. http://dx.doi.org/10.1056/NEJMra021964

7. World Health Organization. Global tuberculosis report 2015. Geneva: the Organization; 2015.

8. Zetola NM, Modongo C, Moonan PK, Click E, Oeltmann JE, Shepherd J, et al. Tuberculosis and multidrug-resistant tuberculosis transmission dynamics among communities with high HIV prevalence: the Botswana Kopanyo Study. BMJ Open. 2016;6:e010046. http://dx.doi.org/10.1136/bmjopen-2015-010046

9. Supply P, Allix C, Lesjean S, Cardoso-Oelemann M, Rüsch-Gerdes S, Willery E, et al. Proposal for standardization of optimized mycobacterial interspersed repetitive repetitive unit–variable-number tandem repeat typing of Mycobacterium tuberculosis. J Clin Microbiol. 2006;44:4498–510. http://dx.doi.org/10.1128/JCM.01392-06

10. Wallgren A. The time-table of tuberculosis. Tubercle. 1948;29:245–51. http://dx.doi.org/10.1016/S0041-3879(48)80033-4

11. Chamie G, Wandera B, Marquez C, Kato-Maeda M, Kamya MR, Havlir DV, et al. Identifying locations of recent TB transmission in rural Uganda: a multidisciplinary approach. Trop Med Int Health. 2015;20:537–45. http://dx.doi.org/10.1111/tmi.12459

12. Verver S, Warren RM, Munch Z, Richardson M, van der Spuy GD, Borgdorff MW, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. Lancet. 2004;363:212–4. http://dx.doi.org/10.1016/S0140-6736(03)15332-9

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Technical Appendix

Kopanyo TB Cluster Investigation Form

| Study ID:          | Interview Date: | Site ID: GA=Gaborone, GH=Ghanzi |
|--------------------|-----------------|----------------------------------|
| Interviewer’s initials: | MIRU Cluster ID: |                                  |

To be used at Cluster Investigation visit only

Instructions: Explain that you will be asking a series of questions to try to identify where we might be able to find other people who have TB. Acknowledge that the patient has already participated in an interview when he/she was first enrolled in the study. Some of the questions we are going to ask have already been answered. However, we may need to get additional details and will therefore repeat some questions. Reassure the patient that all answers will be kept confidential, and that the purpose of the interview is to learn information that can help stop the spread of TB and prevent other people from getting sick (emphasize protection of friends and family). List all responses on a separate sheet of paper. Thank the patient for his or her time and for speaking with us.

1. Name the places where the patient spent time in the six months before the diagnosis of this episode of TB

2. In the six months prior to diagnosis of this episode of TB, name the places where the patient has studied or worked
3. In the six months prior to diagnosis of this episode of TB, mention the places where the patient worships

4. In the six months prior to diagnosis of this episode of TB, mention the places where the patient goes for social activities, leisure (e.g. bars/shebeens, shopping malls, homes other than primary residence).

5. In the six months prior to diagnosis of this episode of TB, list all combi routes used by the patient

6. In the six months prior to diagnosis of this episode of TB, list the friends, family, church members, buddies with whom the patient spent significant time with

Comments

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