**TITLE PAGE**

**Title:**

XDR-TB TRANSMISSION IN LONDON: CASE MANAGEMENT AND CONTACT TRACING INVESTIGATION ASSISTED BY EARLY WHOLE GENOME SEQUENCING

**Running Title:**

XDR-TB TRANSMISSION IN LONDON

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**MANUSCRIPT**

**Summary**

**Objectives:** We describe the first published cluster of extensively drug resistant Tuberculosis (XDR-TB) in the UK and show how early whole genome sequencing (WGS) of *Mtb* can assist in case management and contact investigations.

**Methods:** We describe the contact tracing investigation undertaken after the presentation of an adult with XDR-TB. Active cases were treated with an XDR-TB drug regimen and contacts underwent a programme of follow-up for 2 years. All isolates of *Mycobacterium tuberculosis* (*Mtb)* were assessed early using whole genome sequencing (WGS) as well as routine drug susceptibility testing (DST).

**Results:** 33 contacts were screened. In the first year one confirmed and one probable case were identified through contact tracing. A further possible case was identified through epidemiological links. Two confirmed cases were identified through WGS two years later. 25 (80%) contacts without evidence of tuberculosis were adherent to 1 year of follow-up and 14 (45%) were adherent to two years of follow-up.WGS of *Mtb* was used to guide drug choices, rapidly identify transmission events, and alter public health management.

**Conclusion:** WGS of *Mtb* enabled rapid effective individualised treatment and facilitated public health interventions by early identification of transmission events.

**Key words**

Tuberculosis

Drug resistance

Contact tracing

Disease outbreaks

Pathology, Molecular

**Highlights**

* This is the first report in the UK of a complex XDR-TB cluster.
* Methods for 2 year follow-up of contacts and active cases are presented.
* Early whole genome sequencing (WGS) enables individualised treatment of cases.
* WGS identifies transmission events and assists rapid public health interventions.

**Introduction**

Extensively drug-resistant tuberculosis (XDR-TB) is caused by *Mycobacterium tuberculosis* (*Mtb*) resistant to the first-line drugs isoniazid and rifampicin, as well as to the fluoroquinolones and the injectable antibiotics, key second-line drugs used to treat multidrug-resistant Tuberculosis (MDR-TB).([1](#_ENREF_1)) XDR-TB accounts for 9% of MDR-TB cases worldwide,([2](#_ENREF_2)) and since 2005 there have been 20 cases reported to Public Health England.([3](#_ENREF_3)) Although the numbers are small and no onward spread of XDR-TB had been reported in the UK,([4](#_ENREF_4)) worse treatment outcomes have been reported for XDR-TB compared to MDR-TB and fully-sensitive tuberculosis,([4](#_ENREF_4), [5](#_ENREF_5)) making early effective treatment and prevention of onward transmission a priority.

Currently, the evidence base for the management of MDR-TB and XDR-TB contacts is poor and prophylaxis or a period of follow-up are both treatment options.([6-8](#_ENREF_6)) The World Health Organisation (WHO) suggests 2 years of follow-up for contacts but does not define the frequency of review of contacts or type of follow-up.([9](#_ENREF_9))

A contact with active tuberculosis is often treated with the same regimen as the source based on the epidemiological link while culture confirmation and phenotypic drug susceptibility testing (DST) results are awaited.([8](#_ENREF_8)) However, in populations with a high background risk of TB starting a MDR-TB regimen in advance of confirmation of drug-resistance may expose the patient unnecessarily to drugs with high rates of toxicity.([10](#_ENREF_10)) Failure to make an epidemiological link may delay appropriate treatment and thwart outbreak prevention. Whole genome sequencing (WGS) of *Mtb* has the potential to speed the confirmation of an epidemiological link,([11-13](#_ENREF_11)) identify previously unknown links, and direct treatment choices, while DST is awaited.([14](#_ENREF_14), [15](#_ENREF_15))

This paper outlines the outcomes of the contact tracing investigation of an infectious XDR-TB case in London and describes how early WGS assisted in rapid individualised drug treatment and identification of further linked cases.

**Methods**

Index case:

In April 2013 the index case (case 1) presented to a district general London hospital with a 9-month history of cough. The index case was diagnosed with smear positive pulmonary XDR-TB. Treatment and isolation were initiated at a specialist infectious diseases centre and an extended contact tracing exercise was undertaken.

Contact tracing

Classical named contact-based tracing was initiated in line with National Institute for Clinical Excellence (NICE) guidance.([16](#_ENREF_16)) The index case was interviewed and a home-visit arranged. Contacts were defined as household residents if they had lived with the index case whilst infectious. The house of the index case was the hub of a complex social network, and a ‘concentric circles approach’ was used to broaden the investigation.([17](#_ENREF_17)) Persons with prolonged contact with the index case either through regular visits to the index case’s house (house social) or through work (work contacts) were also screened. When further cases were identified the process was repeated and their close contacts were screened.

Contacts were investigated with a symptom questionnaire, chest radiograph and either a Mantoux or interferon gamma release assay (IGRA) or both. If the screening occurred within 6 weeks of the contact a repeat IGRA was offered at 3 months. Sputum samples were collected for mycobacterial microscopy and culture and a physician review was initiated for all contacts who had abnormal chest radiography or suggestive symptoms. Sputum induction, bronchoscopy and computed tomography (CT) imaging were available at the physician’s discretion.

Latent Tuberculosis (LTBI) was defined in line with NICE guidance at the time as a Mantoux equal to or over 15mm diameter in the presence of a Bacille Calmette-Guerin (BCG) vaccination scar, over 5mm diameter without a BCG vaccination scar, a positive IGRA result or imaging suggestive of old tuberculosis.([16](#_ENREF_16))

Cases were classified as: Confirmed cases; defined by an *Mtb* isolate with <5 single nucleotide polymorphisms (SNPs) different from that of the index case following WGS.([11](#_ENREF_11)) Probable cases; those with a strong epidemiological link, suggestive symptoms and radiology. Possible cases; those where the epidemiological, clinical and radiological evidence were suggestive but could be explained by alternative diagnoses (eg bacterial pneumonia). Adults were defined as 16 years or over.

Microbiology

All sputum and pleural samples were analysed by fluorescent microscopy following auramine-phenol staining for acid alcohol fast bacilli (AAFB) and then cultured in an automated liquid culture media system. All sputum samples positive for AAFB by microscopy (smear positive) and those negative by microscopy (smear negative) from patients with a high risk of MDR-TB were routinely analysed using the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) ,([18](#_ENREF_18)) to detect the presence of *Mtb* and mutations in the *rpoB* gene associated with rifampicin resistance. Molecular assessment using Xpert® MTB/RIF assay or GenoType MTBDR*plus* assay(Hain Lifescience GmbH, Nehren, Germany) to identify the species of *Mtb* and look for rifampicin resistance were undertaken on all *Mtb* isolates (no reference to risk of MDR-TB) at the district general hospital (sent to National Mycobacterium Reference Laboratory (NMRL)), and the local Infectious Diseases unit. All isolates found to harbour mutations in the *rpoB* gene were sent for WGS at St George’s Institute of Infection and Immunity laboratories, University of London, performed as described by Witney et al.([14](#_ENREF_14)) All positive cultures were sent to the NMRL for first (rifampicin, isoniazid, ethambutol, pyrazinamide) and second (fluorquinolone, prothionamide, injectable agents) and third line (Para aminosalicylic acid (PAS) and linezolid) DST. The time delay between WGS result and full DST was defined as the number of days between WGS result availability and the date of arrival at the source lab of second line DST because third line are often very delayed. Minimum inhibitory concentrations of fluoroquinolones were determined for the positive culture from the index case([19](#_ENREF_19)) at St George’s Institute of Infection and Immunity laboratories, University of London.([19](#_ENREF_19))

Treatment

Active XDR-TB cases were treated for 24 months based on the WHO guidance and phenotypic and genotypic drug sensitivity data.([20](#_ENREF_20)) The *Mtb* isolates from the confirmed cases were reported by the NMRL as susceptible only to capreomycin and linezolid. The starting regimens were once-daily capreomycin (15mg/kg), high-dose fluroquinolone (600-800mg of moxifloxicin or 1g of levofloxacin if used in combination with bedaquiline), linezolid 600mg, clofazimine 100mg, twice daily cycloserine (as per therapeutic drug monitoring (TDM)) and three times daily amoxicillin (500mg) and co-amoxiclav (625mg) plus high dose pyridoxine. Applications for the use of bedaquiline were made under the Janssen Therapeutics compassionate program for the culture-confirmed cases, and latterly from NHS England for the culture negative cases. Medications were modified in the light of side-effects, TDM ([21](#_ENREF_21)) results and availability of bedaquiline. TDM was performed for cycloserine to reduce the likelihood of neurological side effects and for the fluroquinolones to ensure high trough levels.([19](#_ENREF_19)) All patients treated with bedaquiline gave consent for its use and underwent regular electrocardiograms (ECG) as per guidance.([22-24](#_ENREF_22)) All cases were treated with daily directly observed therapy (DOT) or video observed therapy (VOT) for the entirety of treatment.

Prevention of *Mtb* Transmission

All patients admitted with suspected pulmonary disease were admitted to HEPA-filtered single patient rooms maintained at negative pressure and appropriate respiratory precautions were maintained by staff([16](#_ENREF_16)) until three sputa each taken a week apart were culture-negative at 6-weeks of incubation.

Follow-up of contacts

Contacts were enrolled on a 24 month follow-up program. All were carefully counselled and given written information regarding the risks of disease. No treatment for LTBI was given. The two year follow-up program for adults consisted of a nurse review and chest radiography at 3, 6, 9 and 21 months. Children were assessed 3-monthly by a paediatrician. All contacts were also told to self-present between reviews if symptoms occurred. After 24 months all contacts were discharged from active follow-up with a letter explaining ongoing risks except for children with LTBI who are to be assessed yearly until adulthood and one adult contact with new nodules on imaging (see below).

Patients in whom further investigations for active TB were required were assessed more frequently and seen by specialist TB respiratory or Infectious Diseases physicians. Phone call prompts and home visits were undertaken if patients did not attend (DNA) appointments. If a contact failed to attend the final outpatient appointment, or 3 further appointments arranged over the following 4 months with phone calls and home visits, the contact was recorded as not completing 2 years of follow-up.

**Results**

Named contact-based tracing outcomes

35 named contacts of the index case were identified during the contact tracing exercise (Table 1).

33 named contacts underwent an initial screen. Two of the contacts did not have a baseline screen due to leaving the country. Two cases of XDR-TB (2/33=6%) (case 2 confirmed and case 3 probable) and 12 cases of LTBI were identified (12/33=36%), all at baseline screen. No conversion to LTBI was identified. The 2 cases were treated for XDR-TB and 31 named contacts (8 were children) were entered into the two year follow-up program (Table 2).

14 (45%) contacts completed the two years of follow-up. Of the three children who did not undertake two years of follow-up, two completed 15 months of follow-up before physician decision to discharge (no evidence of latent TB and difficulties attending). The other one attended for 3 months but failed to attend afterwards and the physician made a joint decision with the family that the contact had been brief and due to the lack of evidence of latent TB, formal follow-up could be ceased. Of the 14 adults that did not complete the 2 year follow-up 7 were not contactable (phone, letter, home visit), 5 were contactable and either refused to come or expressed willing but did not attend and 2 were discharged early after discussions with physicians (limited contact, no evidence of latent TB).

Active cases

Case 1 (index case) required hospital admission for 7 months due to bilateral cavitating disease with involvement of the whole left lung, a left broncho-pleural fistula and an empyema requiring prolonged chest drainage. Cases 2 and 3 were diagnosed with active XDR-TB during the initial named contact-basedscreen and started on treatment within 3 months of the index case (Table 3).

Both were started on XDR-TB regimens based on symptoms, the epidemiological link to the patient and radiology. On day 28 of treatment, *Mtb* was isolated in sputum from case 2 which was found to be identical to that of the index case by DST and WGS (no differences in numbers of SNPs). Sputum from case 3 did not grow *Mtb.* Named contacts included those for the index case plus 4 more adult household contacts for case 3 and a child contact for case 2. All three cases required significant enhanced case management by TB services to ensure treatment completion, including regular case conferences, ensuring stable accommodation and provision of DOT and/or VOT. All three patients improved symptomatically and radiologically; the culture positive cases culture converted and did not revert. All completed 24 months of therapy, and remain well with follow-up 6-9 months after completing, at the time of writing.

2 further cases of XDR-TB and one possible case were identified outside the named contact tracing exercise. Case 4 (possible case) was being investigated for an episode of fever and pneumonia associated with pleural effusion, 3 months after admission of the index case. In addition to bacterial infection, tuberculous pleurisy was considered and he reported visiting the household of the index case on a number of occasions.

Case 4 was extensively investigated with repeated pleural biopsies. One of 2 samples tested positive for rifampicin mutations on Xpert® MTB/RIF assay but *Mtb* was never grown. Histology showed only non-specific inflammation. His symptoms all resolved leaving some residual pleural thickening. After extensive discussions case 4 was advised and agreed to take treatment for possible XDR-TB in order to reduce the probability of subsequent progression. However, after 14 months, case 4 wished to stop treatment; a joint decision was made to stop early, and case 4 instead remains under long-term follow-up.

Cases 5 and 6 presented with active tuberculosis in the same month, 2 years after the index case. Case 5 presented to the local hospital with weight loss and sputum smear-negative pulmonary disease and multiple significant age-related co-morbidities such as bronchiectasis and chronic kidney disease. Case 5 was not initially thought to be at high risk of resistant TB due to lack of epidemiological links or overseas travel. *Mtb* was cultured from a bronchoscopy specimen and Xpert® MTB/RIF assay performed on the isolate to identify the mycobacterium species revealed rifampicin mutations which led to the initiation of an MDR-TB regimen. XDR-TB treatment was considered based on the close proximity of case 5’s home to the index case home (streets apart) but due to co-morbidities initiation was difficult. WGS result received 21 days before the secondline DST results revealed only one SNP difference from the index case. The WGS result led to further epidemiological investigations. Although case 1 was unknown to case 5, they lived close to each other (streets apart), and so, in addition to usual contact enquiries, a diary of daily activities was compiled to identify potential relevant congregate settings. Case 5’s routine included considerable time each week in a local amenity. Further questioning of the index case did not confirm attendance at the amenity, however third party information suggested that case 1 had spent time there whilst infectious 2 years earlier. Household contacts of case 5 were screened and entered on a 2 year follow-up program (ongoing, results not presented here). Case 5 died of TB whilst on treatment.

Case 6 self-presented to hospital with cough and fever and was found to have sputum smear and culture positive tuberculosis. Xpert® MTB/RIF assay results suggesting rifampicin-resistance lead to early WGS which showed only one SNP difference to that of the index case (different to case 5) suggesting a direct or indirect transmission event within the cluster ([11](#_ENREF_11)). The WGS result was available 50 days before the second line DST result. Case 6 was started on a tailored XDR-TB regimen, bedaquiline use was requested and further public health investigations were initiated, all based on early WGS results, before DST result availability.

Public health investigations started with extensive and repeated questioning about contacts and usual daily activities which did not reveal links to either case 1, 5, the amenity, other known cases/contacts, or congregate settings. However this case lived near to the index case (streets apart) and, based on his patterns of known behaviour, could plausibly have had contact with the index case. A multi-agency outbreak meeting was undertaken, and a risk assessment and feasibility study undertaken with reference to the local amenity. Active screening at the amenity was ruled out.

LTBI cases that required increased surveillance and management

*Adults*

One adult case with significant social contact with the index case (house social) and with LTBI at baseline screen was found at the 3 month screen to have a new 10mm opacity in the right upper zone on chest radiography and confirmatory CT scan. At 2 years he is well and there is no change to the lesion. It is planned to keep him under intermittent long-term follow-up, with instructions to present immediately if symptomatic.

*Paediatric*

A household contact of the index case diagnosed with LTBI at baseline, was reported to have a two-week history of cough and night sweats at baseline. The initial chest radiograph was normal but scanty AAFB was reported on one out of 5 sputum samples (3 on induction) which remained culture and Xpert® MTB/RIF assay negative. A chest CT scan showed 2 nodules within the right lung. His symptoms resolved rapidly without treatment. After wide discussion the consensus was to observe and only treat if he became symptomatic or his chest lesions worsened. At two years he remains well and his repeat CT has shown no progression.

**Discussion**

We describe the first recognized transmission cluster of XDR-TB cases in the UK and present a large named contact-based tracing exercise. Importantly, we show the crucial role of early WGS to inform drug treatment decisions, confirm epidemiological links and enable public health interventions before DST is available.

Contact tracing exercise

Our named contact-based tracing exercise identified and screened a large number of contacts (n=33) of which 6% (2/33) were diagnosed with active disease. The number screened per index case is well above the average of 5.1 (95% CI 3.1-10.4) contacts screened per index case for high-income countries described in a meta-analysis.([25](#_ENREF_25)) Notwithstanding the large numbers screened, the proportion with active disease among household contacts at 9% (household and house social) is similar to that described in a meta-analysis by Shah, Yuen et al. ([26](#_ENREF_26)), who found an average rate of TB in household contacts of drug-resistant cases of 7.8% (95% CI, 5.6%–10.0%).

Despite effectively identifying contacts, the contact-tracing exercise, even when undertaken as an iterative process, did not identify three of the five cases described, one of whom died. Our experience is not unique and contact-tracing exercises have long been known to be interventions of potential high impact but with severe limitations,([17](#_ENREF_17)) increasingly brought to light by retrospective molecular typing investigations.([11](#_ENREF_11), [27](#_ENREF_27), [28](#_ENREF_28)) As well as the standard contact tracing methods, extended public health questionnaires were undertaken for each active case which focus on daily routines, locations and shared space. However, these questionnaires are still dependent on information given by the index case and we were not able to identify disease earlier in cases 5 and 6.

In terms of contact management, randomised controlled trial evidence assessing prophylaxis versus a period of follow-up for MDR-TB is currently lacking.([7](#_ENREF_7)) For XDR-TB there is even less evidence as fluoroquinolones, the corner stone of MDR-TB treatment, may not be effective in XDR-TB cases.([7](#_ENREF_7), [8](#_ENREF_8), [29](#_ENREF_29), [30](#_ENREF_30)) Many guidelines therefore suggest a period of follow-up rather than prophylaxis. However, how to undertake this follow-up, who to include, and how long to continue follow-up remain unclear.([31](#_ENREF_31)) We followed guidance suggesting a two-year follow-up period ([9](#_ENREF_9), [17](#_ENREF_17), [20](#_ENREF_20)) based on evidence that progression to active infection is greatest after exposure and then follows an exponential decline over the first 7 years.([17](#_ENREF_17), [32](#_ENREF_32)) Other guidance is less specific about the duration of follow-up with older UK guidance([16](#_ENREF_16)) suggesting ‘long term’ and newer not commenting (42); European guidance does not specify a duration.([7](#_ENREF_7), [8](#_ENREF_8)) We front-loaded our follow-up appointments for adults based on evidence from the pre-prophylaxis era in the UK and later MDR-TB studies that have indicated over 80-90% of patients with active disease are identified in the first year of follow-up ([33-36](#_ENREF_33)) and we provided more frequent follow-up for children due to higher risk of progression.([37](#_ENREF_37))

We followed up all contacts without regard to the LTBI status due to the degree of resistance and poor prognosis in XDR-TB treatment. We were cautious because early on in the contact investigation transmission events were identified. We acknowledge that the work-load could have been reduced if only those with LTBI had been followed, but at the time the NICE 2011([16](#_ENREF_16)) guidance had a relatively high threshold for a positive Mantoux([17](#_ENREF_17)) for those with BCG exposure (15mm or more for those with a previous BCG). We have shown that follow-up in the UK for two years with hospital reviews and chest radiography is possible but that fall out from review is common at 2 years despite home visits and phone call reminders. The numbers who completed 2 year follow-up are similar to UK studies from the pre-routine prophylaxis era for fully sensitive TB where between 35 and 50% of contacts are reported to attend follow-up for two years despite phone and household visits.([36](#_ENREF_36)),([33](#_ENREF_33)) With these results we are considering following up future contacts without LTBI for 1 year at hospital and then giving an open letter of invitation to both the patient and GP if symptoms occur.

TB services

XDR cases (and their contacts) require enhanced case management from the TB services. The factors that put people at risk of acquiring drug resistant TB often mean that they require intensive support to navigate their way through up to two years of treatment or follow-up. This paper does not capture all the phone calls, home visits, and ad hoc reviews provided by teams, nor does it attempt to quantify the number of multidisciplinary meetings, incident meetings and help provided by others, such as “*Find-and-Treat*” to ensure follow-up was achieved. The input required is at least an order of magnitude greater than that required for a fully-sensitive case. The TB workforce needs to be adequately staffed to develop the kind of rapport that facilitates disclosure of details of contacts and activities that are key to establishing epidemiological links, and to provide the level of support even a small number of medically and socially complex patients require, to ensure that treatment completion (or follow-up) is achieved. Current staffing recommendations based on fully-sensitive cases may not be adequate if a number of XDR-cases are included in the case mix.([38](#_ENREF_38), [39](#_ENREF_39))

WGS

WGS has superior discriminating power than other commonly used typing methods (variable number tandem repeats, spoligotyping and restriction fragment length polymorphism) leading to its unique ability to be used for both epidemiological and drug susceptibility purposes.(41) We have shown previously how WGS can be used to guide early patient treatment.([14](#_ENREF_14)) WGS has also been used retrospectively to confirm epidemiological links.([11](#_ENREF_11), [12](#_ENREF_12), [14](#_ENREF_14)) However, here WGS was used in real-time to both inform treatment, and confirm epidemiological links and prompt further public health investigations. Cases 5 and 6 presented two years after the initial case; the epidemiological link to the index case was very weak (proximity of address), and would not have justified an XDR-TB drug regimen with all its morbidities.([10](#_ENREF_10)) In these cases, early WGS results justified a specific XDR-TB regimen, the application for bedaquiline funding to NHS England, and further public health interventions including further interviews and the initiation of further incident meetings and planning.

Currently, guidance in the UK or Europe does not advocate the routine use of early WGS for rifampicin-resistant isolates detected by either phenotypic tests or by rapid molecular tests as we currently undertake and advocate.(8, 42) However, recent studies show that WGS for all isolates (no requirement for rifampicin resistance detection initially) is quicker, cheaper and could replace traditional DST and is low cost compared to the full package of care for XDR-TB.([40](#_ENREF_40)) Our experience reinforces the known inherent shortcomings of named contact-based tracing, and demonstrates the added value of routine early WGS in highly drug-resistant cases both to aid treatment decisions and the prevention of onward transmission.

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**Declaration of competing interests statement**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: AA has received a research studentship funding from The Jefferiss Charitable Trust, PB is funded by INNOVATE UK (UK Government Agency) in collaboration with QuantuMDx Ltd , UK, outside the submitted work, Dr. Hinds reports grants from GSK Biologicals, grants from Pfizer, grants from Sanofi Pasteur, outside the submitted work ; no other relationships or activities that could appear to have influenced the submitted work."

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**Ethics**

This work was undertaken as part of routine clinical practice and so no ethical approval was required. Data sharing with public health was according to Caldicott principles.

**Contributorship statement**

Contributors were as follows:

|  |  |
| --- | --- |
| The conception and design of the work | Amber Arnold, Tom Harrison, Anita Roche, Catherine Cosgrove, Philip Butcher |
| The acquisition of data | All AuthorsAcknowledged persons: Maria Mercer, Vera Pavlova, Katherine Bintley, Paula Ellis, Beth Villanueva |
| Analysis and interpretation of data. | All Authors |
| Drafting the work or revising it critically for important intellectual content | All Authors |
| Final approval of the version published | All Authors |
| Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. | All Authors |

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**TABLES**

Table 1: Outcomes of the initial screen for tuberculosis in contacts

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Contact type** | **Number**  | **% Male** | **Number with baseline screen** | **Active cases identified** | **Cases with Latent TB (LTBI)** |
|  |  |
| Household resident | Adult 5 | 40 | 5 | 1  | 2 |
| Child 2  | 100 | 2 | 0  | 2 |
|  |  |
| House social | Adult 11 | 73 | 11 | 1 | 5 |
| Child 4 | 50 | 4 | 0 | 1 |
|  |  |
| Work contact of index case | Adult 9 | 100 | 8 | 0 | 2 |
| Child 0 | 0 | 0 | 0 | 0 |
|  |  |
| Household contacts of only cases 2 or 3 (no contact with index case) | Adult 2 | 50 | 1 | 0 | 0 |
| Child 2 | 50 | 2 | 0 | 0 |
|  | **TOTAL** |
| All named contacts | 35 | 71 | 33 | 2 | 12 |

Household residents: persons living with the index case whilst infectious

House Social: Persons with prolonged contact with the index case through regular prolonged visits to the index case’s house (house social)

Work contact: Persons with prolonged contact with the index case through work

Table 2: Follow-up for 31 contacts entered in the 24 month follow-up program

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Contacts** | **Age** | **Number (%)** | **2 or more reviews (%)** | **Follow-up to 1 year (%)** | **Follow-up to 2 years (%)** |
| Contacts with LTBI\*n=12 | Adult  | 9 (39) | 9 (100) | 8 (89) | 5 (56) |
| Child  | 3 (38) | 3 (100) | 3 (100) | 3 (100) |
| Contacts with No evidence of TB exposuren=19 | Adult | 14 (61) | 12 (86) | 10 (71) | 4 (29) |
| Child | 5 (63) | 5 (100) | 4 (80) | 2 (40) |
| Total  | All | 31 (100) | 29 (94) | 25 (80) | 14 (45) |

\*LTBI=Latent TB infection

Table 3- Description of active cases with XDR-TB

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case no.** **sex** | **Type of case** | **Identification of contact** | **Type of contact with index case** | **symptoms** | **microbiology** | **radiography** | **Reason for starting XDR-TB regimen** | **bedaquiline use** | **outcome** |
| 1 | confirmed | Index case | Index case | Cough 9 months, fever, sweats | S M+ C+S GX+ | CXR and CT cavities and empyema | DST | yes | 2 years treatmentcompleted |
| 2 | confirmed | Named contact-based tracing | Household | Initially none, then fever | S M- C- B M- C+B GX-B GX+ | CXR + CT nodules both apices | Epidemiological link  | yes | 2 years treatmentcompleted |
| 3 | probable | Named contact-based tracing | House social | 3 weeks cough lethargy and weight loss | S M- C- B M- C-S GX-B GX- | CXR + CT cavity  | Epidemiological link | yes | 2 years treatmentcompleted |
| 4 | possible | Self presentation (knew case 1) | Work contact | Fevers, cough weight loss in acute illness lasting 6 weeks. =pleural TB suspected | S M- C- Pleural biopsy positive on GX + | CXR and CT pleural thickening | Epidemiological link and Xpert® MTB/RIF assay result | no | 14 months treatment  |
| 5 | confirmed | WGS | Unknown (but proximity of Index Case's address) | Weight loss for 3 months | InitiallyS M- C- B M- C+Later after admissionS M+ C+S GX+ | CXR and CT cavities | WGS prior to DST | no | Died of TB |
| 6 | confirmed | WGS | Unknown(but proximity of Index Case's address) | Cough and fevers | S M+ C+S GX+ | CXR and CT cavities | WGS prior to DST | yes | On treatment |

House= shared house lived in by index case, M=direct smear result on specimen, C=culture , +=positive, -=negative, S= sputum, B=bronchoscopy washings, CXR=chest radiography, CT = computed tomography of chest, R=right, WGS= whole genome sequencing result on cultured *Mtb* isolate, GX+= Xpert® MTB/RIF assay positive for TB and rifampicin mutations, WGS=whole genome sequencing. DST=Drug susceptibility testing. Confirmed cases; defined by an *Mtb* isolate with <5 single nucleotide polymorphisms (SNPs) different from that of the index case following WGS.([11](#_ENREF_11)) Probable cases; those with a strong epidemiological link, suggestive symptoms and radiology. Possible cases; those where the epidemiological, clinical and radiological evidence were suggestive but could be explained by alternative diagnoses (eg lung disease caused by agents other than *Mtb*).