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Exposed! Management of MDR-TB household contacts in an evidence light era☆

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ABSTRACT

Until the three ongoing randomised controlled trials of preventive therapy are completed, there remains a large knowledge gap about how individuals known to have been exposed to multidrug-resistant TB (MDR-TB) should be managed. The evolving paradigms and improving outcomes from treatment of active MDR-TB disease play in to discussions about the relative merits and importance of intensive surveillance and/or preventive therapy for MDR-TB contacts.

The scale of the problem

In 2017 there were 558,000 estimated cases of multidrug-resistant (MDR) or rifampicin resistant (RR) TB worldwide (WHO, 2018). Mathematical modelling suggests that 1.7 billion, or a quarter of the global population, have latent tuberculosis infection (LTBI) (Houben and Dodd, 2016). This large reservoir of potential future TB transmission must be tackled if the global TB epidemic is to be controlled. The risk of progression from exposure to infection to active disease is poorly explored in MDR-TB. 90% of active disease in MDR-TB contacts occurs within the first two years and nearly all within three years (Shah et al., 2014). Improved strategies are required to advance detection and management of this ongoing reservoir of infection (Lonnroth et al., 2013).

The individual

We begin with Juan, a 16-year-old boy on treatment for laboratory confirmed MDR-TB at an urban health centre in Peru. He tells a tearful story of his cousin Ernesto, also an adolescent male, who died a year earlier from an unknown progressive illness. At post mortem, this illness was identified as MDR-TB. The two cousins, he explains, shared a poorly ventilated bedroom in a suburb of Lima. Not long after his cousin's death, Juan developed fever, cough and weight loss and was eventually diagnosed with MDR-TB on MODS testing. Today his mother also attends the clinic. She reports feeling unwell for several months and has recently developed haemoptysis. She's had a chest X-ray and is waiting for her results. She knows what is coming.

This desperate scenario highlights important questions about the management of individuals who have been exposed to infectious MDR-TB within the household. As he embarks upon a prolonged course of toxic MDR-TB treatment, with historically poor outcomes, we are obliged to ask "Could Juan's disease have been prevented?". "How likely is it that Juan acquired his infection from Ernesto?" and would this be useful to know? "Would active surveillance of Juan's mother have facilitated earlier diagnosis?" "And would this improve the likelihood of a successful treatment outcome?"

The programme

How should the National TB Control Programme approach this problem? MDR-TB treatment places a large and disproportionate burden on programmes so any case that can be averted is a helpful win. In the absence of an effective post-exposure vaccine, the only tool available to stop infection progressing to disease is preventive therapy (PT). The alternative is close observation of contacts to detect and effectively treat breakthrough disease at an early stage. There are benefits and drawbacks to both approaches (PT and close surveillance), and the relative importance that one attaches to the key knowledge gaps plays in to which strategy might be favoured.

☆ The names used in the real-life case studies have been changed.

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International guidance and recommendations

What do international agencies recommend that programmes should do? In updated 2018 guidance the World Health Organisation (WHO) (World Health Organization, 2018) indicated that "*strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment*" whilst also stating that "*in selected high-risk household contacts* [young children, the immunosuppressed] *of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification*". This conditional recommendation is acknowledged as being based upon very low-quality evidence (GRADE (World Health Organization, 2018) profile tables indicate data comparing a total of 144 PT recipients with 191 non-recipients for prevention of MDR-TB) and requires a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA), already acknowledged as a significant bottleneck for programmes trying to implement isoniazid PT for people living with HIV. The heterogeneity of the observational data brings additional uncertainty about the regimen contents and duration. The recommendations for PT in children are currently based on virtually absent data.

The European Centre for Disease Control (ECDC) 2012 guidance is supportive of careful clinical follow up [6], and in selected circumstances after thorough risk assessment, PT, whilst commenting that "*the current evidence base does neither reject nor support provision of preventive therapy*". There is a telling absence of specific comment on MDR-TB in the 2018 ECDC Scientific Advice on LTBI (ECDC, 2012).

A 2015 policy brief, summarising the consensus view of a meeting of experts convened to review existing evidence at Harvard Medical School Centre for Global Health Delivery-Dubai, comes down more clearly on the side of treating latent MDR-TB infection with PT, though stops short of defining precise regimen composition or duration (Seddon et al., 2015).

Understanding context, making sense of the evidence, individualising risk

It is unequivocally clear that screening household contacts of an individual recently diagnosed with infectious pulmonary TB to detect co-prevalent active TB is one of the highest yield active case finding strategies. This is equally true when the index case has MDR-TB. What happens after this is where the guidance starts to tie itself in knots.

For asymptomatic contacts of drug-susceptible TB determined to be at high risk for progression to disease (young children and the immunosuppressed) a TST or IGRA is performed, and if positive is followed by a standard PT regimen. Though the risk of progression to active disease remains greatest for the first two years after exposure, contacts of drug-susceptible TB are not followed up beyond this initial interaction; the large resource investment required for a low case yield of a readily treatable disease mandates against it.

What then drives such a divergent approach for those exposed to MDR-TB, in which regular surveillance for evidence of incident disease is recommended for two years? Treatment outcomes with standard MDR-TB therapy are historically so miserable that early detection and treatment of MDR-TB should mitigate transmission risk (surely true) and improve treatment outcomes (not proven) (Harris et al., 2016). Context now becomes important, as evolving MDR-TB treatment regimens and improved outcomes start to redefine some of the earlier premises. Indeed, avoidance of highly toxic MDR-TB treatment with poor efficacy has until recently been a potent argument in favour of PT over surveillance — prevention being so much better than cure.

However, after a year in which MDR-TB treatment paradigms have been radically revised (WHO, 2019a), does the prospect of shorter regimens for active disease, with much improved tolerability and efficacy, significantly shift the balance towards more conservative approaches to the MDR-exposed, such as close observation with early intervention?

Preventive therapy

Let us consider what PT might look like

There are three ongoing randomised controlled trials (RCTs) currently evaluating PT, which should start reporting around 2022. All three are using a six-month regimen and following-up for incident TB disease for 18–30 months. In Vietnam the *V-QUIN* trial is comparing levofloxacin with placebo amongst all MDR-TB contacts (ANZCT Registry-Identifier, 2016). The *TB CHAMP* trial in South Africa compares the same two arms but only amongst children under 5 years (ISRCTN-ISRCTN92634082, 2019). The *PHOENIx* trial (at ACTG sites) is comparing delaminid with isoniazid for all contacts of MDR-TB (ClinicalTrials.gov Identifier, 2018).

Whilst the evidence from these RCTs is awaited the existing evidence-base to guide PT is entirely observational. There are no agents that have yet been proven to sterilize latent MDR-TB infection and thus prevent future disease, in sharp contrast to drug-susceptible TB. Fluoroquinolone therapy, often in combination, has been used most frequently.

Two systematic reviews of observational studies of MDR-TB contacts with latent infection who received PT, found a non-significant reduction in progression to TB disease (van der Werf et al., 2012). In an outbreak of MDR-TB in French Polynesia, widely cited as strong observational evidence of PT effectiveness, none of the 104 contacts identified who received PT developed disease. Three of 15 contacts who refused PT and 15 other community members who had not been previously identified as contacts and had not received PT subsequently developed MDR-TB (Bamrah et al., 2014). Notably the regimens used were all of 12 months duration, all included either moxifloxacin or levofloxacin and 51% received ethionamide or ethambutol in addition.

186 South African child (<5 years) contacts of MDR-TB with LTBI were given triple PT for six months with ofloxacin, ethambutol and high dose isoniazid as per local guidance and followed up for a minimum of 12 months. Six developed incident TB disease, though these six had strong risk factors including poor compliance, and six developed grade 3 adverse events (Seddon et al., 2013). Thus observational experience is largely of multidrug therapy for six to twelve months, not a million miles from evolving regimens for treatment of active MDR disease.Exciting advances in recent years include the development of short course combination PT for drug susceptible LTBI (12 weekly doses of rifapentine/isoniazid) should provide stimulus and encouragement for trialling similar strategies in MDR-TB.

The first challenge to PT implementation is the requirement to undergo LTBI testing. Global availability of TST is low and IGRA even lower. The second challenge is presumptive attribution of TST/IGRA reactivity to the MDR-TB index case exposure, particularly in high TB burden settings where the discordance of index-contact strains may be highly variable (WHO, 2019b) – tailoring PT for the contact to the supposed MDR-TB index case strain susceptibility may result in dismissal of well-tolerated agents with proven efficacy, if the source was a separate drug-susceptible strain. Conversely, if delamanid or levofloxacin prove to be effective and well-tolerated in RCTs, then this effectiveness would extend to drug-susceptible organisms. The third challenge is maintaining asymptomatic healthy contacts on drug therapy,

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particularly when there is uncertainty about the cumulative dose required for effectiveness.

Given that 90% of exposed contacts with demonstrated immunological sensitivity (either by TST or IGRA) will never progress to active disease, and thus have nothing to gain from PT, administration to all close contacts exposes the majority to unnecessary risks. The current paucity of evidence on how to target PT is a barrier to individualised risk assessment and should be the focus of any future work. The development of electronic surveillance systems for MDR-TB exposed contacts is now recommended by WHO (WHO, 2019b). An internationally agreed minimal dataset for such systems would allow for identification of risk factors for developing active disease. For example, if 90% of contacts with secondary disease reported having previously shared a bedroom with the index case, PT could be limited to this narrower group with close monitoring of other household contacts.

A meta-analysis reported LTBI in around half of MDR-TB exposed household contacts, varying widely by age group and location (Shah et al., 2014). A systematic review described TB disease prevalence in household contacts of MDR-TB at 3.1% (Fox et al., 2013), however in high prevalence settings this rises to 8.7% (Shah et al., 2014). If PT is found to be effective, there will be clear benefits in high prevalence areas.

Current WHO guidelines recommend that PT be considered in selected high-risk contacts of patients with MDR-TB, based on "individualised risk" and "sound clinical justification" (WHO, 2019b). By their own admission this is based on very low quality evidence, with minimal data to guide such individualised risk assessment. Prospective epidemiological studies, which identify specific characteristics of contacts at increased risk of secondary disease, are sorely lacking. Likely beneficiaries include children under 5 years and those infected with HIV (Padmapriyadarsini et al., 2018).

What then are the benefits and pitfalls of active surveillance of contacts alone, the main alternative to PT? Clearly reduced exposure to potentially toxic therapy is desirable, particularly since only a small minority stand to get any benefit (Langendam et al., 2013). There is some evidence for low rates of incident disease in contacts (Fox et al., 2013), in that the numbers needed to treat to prevent one case of active TB are high, though recent analyses seem to lay to rest the concept that any fitness cost exerted upon *M. tuberculosis* strains with resistance-conferring mutations translates into a meaningful reduction in transmissibility or ability to cause disease (Becerra et al., 2018), when compared to drug-susceptible strains. An important argument against the "watch and wait" approach is the speed at which severe forms of paediatric disease progress, running the risk of development of life-threatening incident disease in the period between surveillance visits. Indeed, the nature of surveillance remains poorly defined, both in terms of optimal frequency of contact and what that contact should entail. In addition to the between-visit risk period, the resource implications of quarterly or biannual face-to-face assessments and the challenge of maintaining high rates of follow-up with otherwise healthy individuals suggest that alternative approaches, with a smaller-footprint but higher frequency such as telephone call consultations, may warrant consideration.

Final thoughts

Whilst the evidence remains inadequate and insufficient to exclusively support either management approach, new cases of MDR-TB still need to be identified and treated, with important attention to infection control to minimise onward transmission. The WHO advise that 'systematic recording and reporting' systems should be developed to aid management of LTBI (WHO, 2019b). There is much to learn and we should be gleaning new knowledge from every single identified MDR-TB contact; whether they have active, latent or no TB infection present or if they are recipients of PT or not. Countries are implementing a myriad of different electronic systems to enhance TB reporting and control activities, however we propose that a harmonised minimum dataset, which could be incorporated into MDR-TB contact screening, should be defined. This would simultaneously facilitate collation of a large observational cohort to address questions about the optimum surveillance approach (identifying the best combination and frequency of screening of symptoms, radiology and microbiology) and enable countries to monitor and evaluate their own contact surveillance activity performance at the touch of a button. Such in-country registries would also provide programmes with a ready-to-go list of individuals eligible for PT if current RCTs identify a suitable, effective regimen.

Disclosure

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Ethical approval

No ethical approval has been sought for this article.

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