Preventive therapy: can tuberculosis efforts learn anything from the leprosy approach?

Tuberculosis and leprosy are the two most important mycobacterial diseases affecting humans. Although there are several similarities between the diseases (eg, both have long incubation periods and require long-term therapy with similar drugs), one difference is in the approaches to prophylaxis (ie, the prevention of disease among symptomless individuals with presumed low bacillary load). WHO recommends a single dose of rifampicin for leprosy post-exposure prophylaxis (PEP) whereas the recommended duration for tuberculosis preventive therapy (TPT) with rifampicin alone is 4 months (112 doses). Even the shortest approved TPT regimens involve combination therapy and are comparatively lengthy (either 28 daily doses or 12 weekly doses of rifapentine and isoniazid). In this Comment, we discuss the reasons for the difference in approach, how leprosy and tuberculosis research could develop a synergistic relationship, and the prospect of ultrashort regimens for tuberculosis prophylaxis.

Single dose rifampicin (SDR) was originally conceived as a population-wide, mass drug administration strategy for leprosy control in 1988.[1] Among contacts of people with leprosy, the efficacy of SDR was 57% compared with placebo, but the effect waned after 2 years and did not protect close household contacts, the group most at risk. The number needed to treat to prevent a case of leprosy at 4 years was 297 patients.[2] Despite WHO's endorsement, implementation of SDR for contacts of people with leprosy by national programmes is variable.

TPT adopts a more targeted strategy. Tuberculin skin testing to detect immune sensitisation, a proxy for tuberculosis exposure, has come to be used to identify contacts at the highest risk for disease progression. Treating adult household contacts with 12 months of isoniazid had a number needed to treat of 32 patients.[3]

The different approaches show two ends of a risk–benefit spectrum. TPT remains lengthy, has associated adverse events, and is therefore targeted at individuals likely to benefit most. SDR for leprosy is short, with minimal risk of adverse events, and is recommended for implementation at scale, but has low benefit to the individual recipient. Both approaches are now being reconsidered, with each perhaps borrowing something from the other.

Current trials in leprosy PEP signify a shift in strategy as they seek to evaluate both drug combinations and longer durations. The PEP++ trial[4] plans to randomly assign 14 532 people in India, Brazil, Nepal, and Bangladesh to three doses of rifampicin and clarithromycin over 8 weeks or SDR alone, and the BE-PEOPLE trial[5] plans to assign approximately 75 000 people in the Comoros Islands to single doses of bedaquiline and rifampicin or SDR alone.

In tuberculosis, the 1-month rifapentine–isoniazid regimen trialled in people with HIV pioneered a less targeted approach, with 80% of participants having no evidence of immune sensitisation to *Mycobacterium tuberculosis*,[6] although they were nevertheless considered at risk of developing disease due to HIV infection. However, were a sufficiently effective ultrashort regimen, or indeed a long-acting injectable, to become available, community-wide administration of TPT could be contemplated. The RATIONS study,[7] which showed that tuberculosis incidence in household contacts could be reduced with nutritional support, already presents one model for a potential mass intervention and there are data that suggest the role of enhanced nutrition in leprosy might also be worth investigating.[8]

The fields of tuberculosis and leprosy offer both opportunities and lessons to each other given the co-endemicity of the diseases in many countries with high burdens of both. The necessary scale of leprosy prevention trials provides an opportunity to gain some insight into the effect of ultrashort strategies on tuberculosis incidence, and even on acquired resistance. Any additional cost to trials might be small compared with the benefits. Even if underpowered, the resulting data could help support the case for trials investigating shorter tuberculosis prophylaxis regimens. In the future, this same principle could also be applied to vaccines.

Given the scale of the tuberculosis problem, novel approaches to TPT are needed, as despite decades of clinical trial evidence, provision and uptake remains low.[9] If the tuberculosis community were to borrow from the leprosy approach, it might do well to balance

reduced efficacy from a shortened regimen against increased uptake and adherence, which might have a greater population-level effect. Developments in trial designs have allowed for better characterisation of the relationship between treatment duration and efficacy and determination of the shortest effective duration.[10] Such a radical change in approach must be taken together with national tuberculosis control programmes and affected communities to understand the acceptability of potential trade-offs between duration and effectiveness. There are lessons and caveats from the leprosy approach to prophylaxis, but an ultrashort prevention approach for tuberculosis is potentially transformative and worthy of cautious consideration.

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