Leprosy post-exposure prophylaxis risks not adequately assessed

We thank Jan Richardus and colleagues for their feasibility study of single-dose rifampicin for contacts of individuals diagnosed with leprosy.[1] Single-dose rifampicin was incorporated into the WHO Guidelines for the Diagnosis, Treatment and Prevention of Leprosy as a conditional recommendation based on moderate evidence.[2] The roadmap for neglected tropical diseases 2021–30 targets leprosy for elimination (interruption of transmission) with single-dose rifampicin as a "core strategic intervention".[3] We have raised our concerns about single-dose rifampicin previously.[4]

Richardus and colleagues acknowledge that single-dose rifampicin's 57% protective effect only lasts for 2 years, and contacts of those with multibacillary disease only have 24% protection.[1] Individuals receiving single-dose rifampicin need to understand the temporary and limited effect against leprosy. The Article has insufficient detail to determine whether fully informed consent of the participants was obtained in all centres. Brazilians were reportedly told, "There is leprosy in your area, and that is why we offer people preventive treatment against leprosy" when being informed about the Leprosy post-exposure prophylaxis (LPEP) study, without indicating the temporary and partial effect of single-dose rifampicin.[5]

The definition of contacts in this study differed from that in the COLEP cluster randomised controlled trial in Bangladesh.[6] In Richardus and colleagues' study, contacts were given single-dose rifampicin up to 2 years after diagnosis of the index case; whereas, in the COLEP study, single-dose rifampicin was given to contacts of newly diagnosed index cases.[6] The paediatric proportion of index leprosy cases was high in India (31·3%) and Nepal (28·7%), compared with reported national rates of 6·8% and 7·6%, respectively.[7] The high proportion of cases in children resulted in a lower proportion of multibacillary cases (28·9%) in India than the national rate of 54·2%.[7] These unusual leprosy cohorts and the variation in the selection of contacts mean that the results are not generalisable. The main outcome measure was the number of single-dose rifampicin given. No evaluation of the effect of this intervention on leprosy rates is planned.

WHO advises that tuberculosis needs to be excluded in patients before administering single-dose rifampicin to reduce the risk of producing rifampicin-resistant *M tuberculosis* strains.[2] Screening individuals for tuberculosis using clinical symptoms before administering single-dose rifampicin lacks sensitivity. Only one Indian participant (of 42 333 screened) was excluded on a suspicion of tuberculosis in a state with a reported incidence rate of 194 per 100 000 in 2019.[8] This low exclusion rate suggests that some leprosy control programmes cannot effectively screen for tuberculosis. The widespread use of single-dose rifampicin might promote the development of *Mycobacterium leprae* rifampicin resistance. The risk of *M tuberculosis* developing rifampicin resistance has not been assessed rigorously, it was deemed to be negligible by an expert group convened by the Novartis foundation and the LPEP group, without a systematic review. The authors extrapolate their interpretation of the risk of *M tuberculosis* resistance data to *M leprae*, but this is not described.[9] WHO have recommended multidrug therapy for patients with leprosy since 1982, to reduce the risk of rifampicin resistance.[10] The presence of *M leprae* rifampicin resistance genes has already been detected.[11] Dispensing millions of doses of single-dose rifampicin might jeopardise the effectiveness of the key antibacterial component of leprosy multidrug therapy. This policy recommendation undermines the global strategy to combat antimicrobial resistance.

Richardus and colleagues' study shows that with active case finding, many people with leprosy are found and at rates greater than the reported national statistics.[7] The Brazilian Ministry of Health, following wide consultation, has decided not to implement single-dose rifampicin because of lack of evidence for its efficacy.[12] Brazil has the second highest case numbers globally and was an LPEP study site. the diagnosis and management of people with leprosy should be prioritised rather than the short-lived, partial efficacy of single-dose rifampicin for contacts. WHO should review their recommendation to implement this intervention and the Global Leprosy Programme and other advocates of single-dose rifampicin should ensure robust mechanisms are in place to detect adverse effects of this policy.

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1 Richardus JH, Tiwari A, Barth-Jaeggi T, et al. Leprosy post-exposure prophylaxis with single-dose rifampicin (LPEP): an international feasibility programme. *Lancet Glob Health* 2021; **9:** e81–90.

2 WHO. Guidelines for the diagnosis, treatment and prevention of Leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia, 2018.

3 WHO. Ending the neglected to attain the sustainable development goals: a roadmap for neglected tropical diseases 2021–2030. Geneva, Switzerland: World Health Organization, 2020.

4 Lockwood DNJ, Krishnamurthy P, Kumar B, Penna G. Single-dose rifampicin chemoprophylaxis protects those who need it least and is not a cost-effective intervention. *PLoS Negl Trop Dis* 2018; **12:** e0006403

5 Schoenmakers A, Mieras L, Budiawan T, van Brakel WH. the state of affairs in post-exposure leprosy prevention: a descriptive meta-analysis on immuno- and chemo-prophylaxis. *Res Rep Trop Med* 2020; **11:** 97–117.

6 Moet FJ, Pahan D, Oskam L, Richardus JH. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ* 2008; **336:** 761–64.

7 WHO. Global leprosy (Hansen disease) update, 2019: time to step-up prevention initiatives. *Wkly Epidemiol Rec* 2020; **95:** 417–40.

8 TBFacts. TB statistics India. https://tbfacts.org/tb-statistics-india/ (accessed Nov 24, 2020).

9 Mieras L, Anthony R, van Brakel W, et al. Negligible risk of inducing resistance in Mycobacterium tuberculosis with single-dose rifampicin as post-exposure prophylaxis for leprosy. *Infect Dis Poverty* 2016; **5:** 46.

10 WHO. Chemotherapy of leprosy for control programmes. Tech Rep Ser 675. Geneva: World Health Organisation, 1982.

11 Cambau E, Saunderson P, Matsuoka M, et al. Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009–15. *Clin Microbiol Infect* 2018; **24:** 1305–10.

12 Exclusão da rifampicina para quimioprofilaxia de contatos de pacientes com hanseníase. Brasilia: Ministério da Saúde, 2020. http://conitec.gov.br/images/Relatorios/2020/Relatorio_Rifampicina_Quimioprofilaxia_Hansenase_525_2020_FINAL.pdf (accessed Nov 24, 2020).