Response to 'Elimination of leprosy in India: An analysis'

Sir,

I read an interesting review article by U Sengupta on elimination of leprosy in India.[1] Of all the issues discussed by the author, the one supporting and even recommending single-dose rifampicin for prevention and controlling leprosy is not supported by scientific facts available currently.

Single-dose rifampicin treatment is being offered to household contacts of new leprosy patients by the National Leprosy Eradication Program of India in most endemic districts of the country from November 2017. It is a matter of concern because this is not an effective method for preventing multibacillary leprosy and does not protect immediate household contacts for a reasonable period of time. There are serious ethical problems about identifying contacts of patients with leprosy. It is not cost-effective for household contacts, and the possibility with the widespread use of single-dose rifampicin promoting the development of rifampicin resistance genes in *M. leprae* is real. The author himself has commented on this real possibility.

Taking note of the implementation of single-dose rifampicin by the National Leprosy Control Program of India – me and other colleagues submitted our views in the form of a letter which has been accepted in the *PLoS Neglected Tropical Diseases* and will be published soon.[2] Given below is the summary of the letter.

The basis of recommendation of single-dose rifampicin is the COLEP trial from Bangladesh.[3] In this study, 21,711 contacts of newly diagnosed leprosy patients were randomized to receive single-dose rifampicin or placebo. In the second follow-up after 3 and 4 years, it was found that the household contacts who took single-dose rifampicin did not have significant protection against developing leprosy [odds ratio 0.46 (0.15–1.38); $P = 0.1652$]. It only protected neighbors of neighbors odds ratio 0.24 (0.11–0.52) against the development of leprosy. Single-dose rifampicin did not protect against the development of multibacillary leprosy [0.52 (0.22–1/19); $P = 0.1201$]; however, it did protect against the development of paucibacillary leprosy [0.38 (0.16–0.87) $P = 0.0218$] and single lesion leprosy [0.42 (0.20–0.89)].[4] Significant protection of 56% only lasted 2 years. These findings suggest that single-dose rifampicin treatment is only effective when patients have a low mycobacterial load, hence, the protection is only against the development of paucibacillary leprosy. Because single-dose rifampicin does not significantly reduce the number of patients with multibacillary leprosy, it is unlikely to have an effect on the transmission because these are the patients that need to be diagnosed and treated at the earliest. Moreover, one cannot assume that the index case is the only source of infection to contacts in high endemic settings when there is a possibility of exposure to *M. leprae* from multiple sources outside the home. We know that a history of contact in the family is present in only one-third of the leprosy patients.

Single-dose rifampicin is being promoted because it is an easier intervention and any intervention that requires more than one dose of the drug/vaccine would be very challenging to administer. More importantly, previous studies on leprosy chemotherapy have found that killing

M. leprae often requires multiple doses of an active agent over several months. In the nude mouse model, up to 20 doses of rifampicin 10 mg/kg were required to significantly decrease levels of *M. leprae* mRNA in experimental leprosy, which again suggests that multiple doses of rifampicin will be needed if this intervention is to be effective.[5]

The important major benefit of giving single-dose rifampicin is that household contacts of leprosy patients will be examined. We know that these people are at the highest risk of developing leprosy, making this is a good public health intervention. However, the ethical problems of identifying and examining all household contacts requiring consent of the leprosy patient need to be explored carefully. There is a risk that hasty implementation of this intervention could increase stigmatization by identifying patients with leprosy. There are also ethical problems in telling people that they will be protected against the development of leprosy, but in reality, it would protect them only from some types of leprosy and that too only for 2 years.

The intervention is least cost-effective for household contacts. The Bangladesh study (from 2002 to 2007) found that the cost of prevention of one case of leprosy was US$ 158 and the preventive therapy was most effective in neighbors of neighbors, social contacts and household contacts in that order.[6] A multicentric, double-blind, randomized and placebo controlled study in over 7500 household contacts in India reported that to prevent occurrence of one case of leprosy, 1556 persons need to be treated.[7] This number would rise further as the prevalence of leprosy goes down.

A recently published study from India found a delay in disease detection and institution of treatment long enough for children with leprosy to develop grade-2 deformity in significant numbers.[8] So, it would be better to invest economically and effortwise in improving early case detection and institution of treatment.

Another aspect that has not been satisfactorily addressed is the practical implications of giving single-dose rifampicin to people who also have concurrent infections, which may be either latent or fully manifest. This aspect has been discussed by an expert panel but there was no data support in the report.[9] The report did not make any clear recommendations as to how concurrent tuberculosis infections should be managed. Effectively screening large number of patients for tuberculosis infection is challenging in every setting.

Development of rifampicin drug resistance in *M. leprae* may be a consequence of giving single-dose rifampicin to thousands of persons. In 1982, World Health Organization recommended multidrug therapy to prevent the emergence of rifampicin resistance. The almost absence of rifampicin resistance in *M. leprae* is something that the leprosy world is very fortunate with. This might be threatened by the widespread use of single-dose rifampicin as chemoprophylaxis. Unfortunately, this fear has come true. Recently, the genes coding for rifampicin resistance in *M. leprae* DNA have been isolated from biopsies taken from leprosy patients – both new and relapsed, from several countries including India and Brazil, the two countries with maximum number of leprosy cases in the world.[10] If this occurs on a wider scale, the global leprosy program will be severely jeopardized.

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Conflicts of interest
There are no conflicts of interest.

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