Leprosy post-exposure prophylaxis risks not adequately assessed

Author's reply

We thank Diana Lockwood and colleagues for their concerns about leprosy post-exposure chemoprophylaxis with single-dose rifampicin (SDR-PEP) for contacts of people diagnosed with leprosy.[1] Some of their concerns against SDR-PEP are based on misunderstandings of the outcome of the COLEP trial.

For clarity, antibiotic-based chemoprophylaxis provides protection by reducing the bacterial load during the incubation period, reducing the risk of progression from infection to disease. It does not induce lasting immunological protection against infection as a vaccine would. Even with vaccination, protection is usually not 100% and lifelong. In the COLEP trial, the overall protective effect of SDR-PEP of 57% was seen after 2 years with a difference of 38 patients between the placebo and the intervention group, without a catch-up effect in the intervention group afterwards. There was a true prevention of leprosy.[2] Stating that SDR-PEP only lasts for 2 years is not correct and disqualifying the intervention on grounds of being short-lived and partially effective is not appropriate.

It also cannot be concluded from the COLEP study that contacts of people with multibacillary leprosy only have 24% protection. The study was not designed to provide statistically significant results for subgroups, but to show an overall effect for all contacts together. An effect was observed in every subgroup (54% for household contacts, 76% for social contacts, 48% for multibacillary leprosy contacts, 62% for paucibacillary leprosy contacts, 58% for single-lesion leprosy contacts, and 24% for blood-related contacts), but the subgroups were small and the CIs wide. Therefore, the results are not statistically significant at the level of p=0·05.[3]

Informing participants fully on an intervention and obtaining informed consent is a fundamental ethical requirement for research involving humans as laid out in the declaration of Helsinki and Good Clinical Practice rules, and was taken very seriously in the LPEP programme. Besides the information given on potential consequences of leprosy, such as disability and stigmatisation, contacts were informed that SDR-PEP leads to a risk reduction and not absolute prevention. Potential participants were also informed about possible side-effects of SDR-PEP, and the advantages and disadvantages of study participation. Finally, they were given information on how and when they could reach the health services in case of questions or problems. Study protocols were assessed and approved by appropriate medical and ethical review boards in each participating country, including Brazil, and the quality of participant information was assessed in the frame of the frequent supervisory visits. Schoenmakers and colleagues[4] do not mention the full information provided to participants, because their point specifically refers to disclosure of the disease status of the index patient, but this does not mean additional information was not given.

The aim of the LPEP programme was to study the feasibility of implementing SDR-PEP within leprosy control programmes. A study on effectiveness would require a different study design (ie, a randomised controlled trial). We believe the results on the feasibility of the intervention to be generalisable beyond the study areas and are conscious that the effect of the intervention will vary according to epidemiological, demographic, and health system variables. This will be estimated separately in a modelling study and reported in due course.

Rifampicin resistance is a joint concern for both tuberculosis and leprosy and there is strong collaboration between leprosy and tuberculosis programmes in monitoring drug resistance. To promote resistance, there must be a large pool of bacilli and several doses of rifampicin must be given over a short time. This applies equally to *Mycobacterium tuberculosis* and *Mycobacterium leprae*. The risk of SDR-PEP causing rifampicin resistance in either infection is considered negligible.[5] The sporadic cases of rifampicin resistance in leprosy developed over decades (and did not become at all widespread), and are most likely due to tuberculosis treatment (which contains rifampicin but no other antileprosy drug) given to someone unknowingly harbouring large numbers of *M leprae*.[6] Chemoprophylaxis with 3 months of isoniazid and rifapentine is now being recommended for tuberculosis programmes worldwide.[7] Thus, regimens containing rifampicin but no other antileprosy drug are being prescribed to large numbers of people, some of whom might be infected with *M leprae*. Based on currently available evidence, the benefit of chemoprophylaxis in both tuberculosis and leprosy is considered much greater than the risk of future drug resistance.

In 2019, the Brazilian Ministry of Health agency CONITEC decided not to routinely implement SDR-PEP.[8] We emphasise that the same agency had authorised SDR-PEP to be used in the Brazilian group of the LPEP programme,[9] and understand that the abrogation in 2019 was based mainly on expert opinion, without due consideration of existing evidence in favour of the intervention.[10,11] Of note, the Ministry of Health of Brazil approved a monitoring and evaluation study focusing on the LPEP project that will be carried out starting in 2021, and aims to explore political and operational aspects that influenced the operationalisation of the intervention in Brazil. In the frame of this study, contacts who had received SDR-PEP and subsequently

developed leprosy will be identified, in addition to possible spatial changes in leprosy epidemiology in the study areas.

We declare no competing interests.

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