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Letter to the Editor

CHEMOPROPHYLAXIS: SUFFICIENT EVIDENCE FOR STARTING IMPLEMENTATION PILOTS

I have read with great interest the Editorial in Leprosy Review of Smith and Aerts regarding the role of contact tracing and preventive strategies in the interruption of leprosy transmission,[1] and the subsequent reply of Lockwood *et al.* with a call for more research on chemoprophylaxis.[2] It is very good that this scientific discourse takes place and that arguments are exchanged regarding the strengths and weaknesses of newly proposed interventions.

There are obviously many issues regarding feasibility (including cost-effectiveness), acceptability and safety of any new public health intervention, and these need to be sorted out carefully in different geographical and socio-cultural environments. This is particularly important with a disease like leprosy where stigma is still a defining factor in many countries. But key to the argument of any intervention is whether it is effective or not. What is the level of evidence of effectiveness and what measure of effectiveness can be considered sufficient for implementation?

Lockwood *et al.* in their reply to the Editorial of Smith and Aerts focus in particular on the data from the COLEP study and suggest that single dose rifampicin (SDR) given to contacts of leprosy patients is not effective protection against leprosy, based on the observation that the protective effect of SDR in certain sub-groups of contacts does not reach statistical significance. This in itself is true, but we also need to consider the larger picture of this study and its implications. The overall result of the COLEP trial is that during the first 2 years, a reduction in incidence in the SDR group was seen of 56·5% (95% confidence interval 32·9–71·9%; $P = 0{\cdot}0002$).[3] This is a very clear statistically significant effect. In addition, the effect in those who had previously received BCG vaccination as part of the childhood vaccination programme (as indicated by the presence of a BCG scar) was as high as 80% (95% confidence interval 50–92%).[4] Many people in most leprosy endemic countries receive BCG vaccination nowadays and these levels of protection compare favourably with many other public health interventions, including vaccination programmes. In most subgroup analyses of COLEP, the odds ratio's indicate protection levels of around 50%, but due to lower numbers in these groups (sample size), statistical significance at the level of $P = 0{\cdot}05$ is not always reached. There are subgroups that respond very well to SDR, such as not blood-related relatives and neighbours of neighbours and (other) social contacts, with protection levels around 70%.[3] On the other hand, there is one particular subgroup, namely blood-related relatives (i.e. parent, child and sibling) that respond poorly to SDR (24% protection).[3] This is indeed a group that needs special attention and that would benefit greatly from a diagnostic test for subclinical leprosy and an extended treatment regimen, possibly a full course of MDT.

Another point made by Lockwood *et al.*, is the duration of protection offered by SDR. This also needs to be considered in context. After two years no difference was observed any longer in the COLEP study between the treatment and placebo arms of the trial. This was caused by the fact that the risk of developing leprosy in the placebo group decreased over time to the level of that in the treatment group, and not the other way around. Obviously, with rifampicin being a chemical compound and not a vaccine, the effect is time-limited because no immunological response is stimulated. However, we could not demonstrate an increased risk of leprosy in the treatment group compared to the placebo group (rebound effect) over the six years that the COLEP contacts were followed.[5]

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The rationale of contact tracing and subsequent provision of SDR (or any other chemoprophylactic or immunoprophylactic intervention) is both early detection and prevention of leprosy. Contacts of leprosy patients are a high risk group for leprosy and contact tracing helps in finding and treating leprosy cases at an early stage. Chemoprophylaxis will prevent leprosy in individual cases, but also interrupt transmission of *M. leprae* in the household and the population at large. For the individual contact receiving SDR there is never any guarantee that he or she will never develop leprosy. I know of very little interventions that can provide 100% protection. This should be communicated carefully with contacts and advice given on what to do when signs of leprosy occur. This is part of professional leprosy control.

From a public health perspective, it is necessary to establish which level of effect of SDR is sufficient to reduce or even interrupt transmission of *M. leprae* in a population. It is usually not necessary to reach very high levels. It is very difficult to establish effective protective levels of a population-based intervention, and often mathematical models are used to estimate this effect. With the SIMCOLEP model we showed that a protective effect of 50% of SDR given to household contacts would contribute to reduction of transmission of *M. leprae* in the whole population.[6]

The COLEP study was a single centre, double blind, cluster randomised, placebo controlled trial, with sufficient power to establish the primary outcome; statistically significant overall reduction of 57% of leprosy among contacts receiving a single dose of rifampicin. This is in line with the results of previous studies using different treatment regimens over longer periods, and with the undocumented trials in India and Thailand mentioned by Lockwood *et al.*[2] that were massively underpowered and thus failed to reach statistical significance. Of course repetition of trials in different geographical locations and with different prophylactic regimens will add to the scientific evidence and should be done where possible. But this can take many years, if not decades to accomplish. The main question is whether we can afford to wait that long with innovation of leprosy control. I argue that the COLEP study, together with the previous studies on chemoprophylaxis, provide sufficient evidence for the time being to move ahead with implementation pilot studies in different places in the world.

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