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LETTER TO THE EDITOR

Three common misinterpretations of the COLEP trial

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Sir,
The COLEP trial was a very large Randomized Controlled Trial (RCT) demonstrating the effect of Single Dose Rifampicin (SDR) as post-exposure prophylaxis for contacts of leprosy patients. The RCT demonstrated a clear and sustained benefit of reduced incidence of leprosy in contacts.[1] However there are 3 common misinterpretations of the results of the trial: the duration of effect; the effect on contacts of MB leprosy; and protection against MB leprosy. These misinterpretations are addressed below.

Misinterpretation 1: SDR only protects for 2 years and thus does not protect household contacts for a reasonable period of time.
Figure 1 shows the result of the COLEP study after 2, 4 and 6 years follow-up.[1,2] The outcome is expressed in incidence rate of leprosy among contacts in the SDR treatment arm and placebo (non-treatment) arm of the trial. The horizontal dashed line represents the background incidence rate of leprosy in the general population of the study area.[3] The effect of the intervention was reached at 2 years, with a more than 50% reduction in new cases among contacts compared to the placebo arm. At 4 and 6 years there are no differences any more between treatment and placebo arms. In both arms the incidence rate of leprosy has reached the background level of the general population. Apart from the provision of SDR, all contacts in both arms of the trial were examined at 0, 2, 4 and 6 years for signs of leprosy and treated with MDT when necessary. This in itself is also an important intervention to prevent leprosy in contacts of leprosy patients and explains the reduction of new cases in the placebo arm as well as in the SDR arm, although at a slower pace. The difference between the two arms of the trial represents the true effect of SDR in this RCT. With rifampicin being a chemical compound and not a vaccine, the effect is obviously time-limited because no immunological response is stimulated. However, there was no increased risk of leprosy in the

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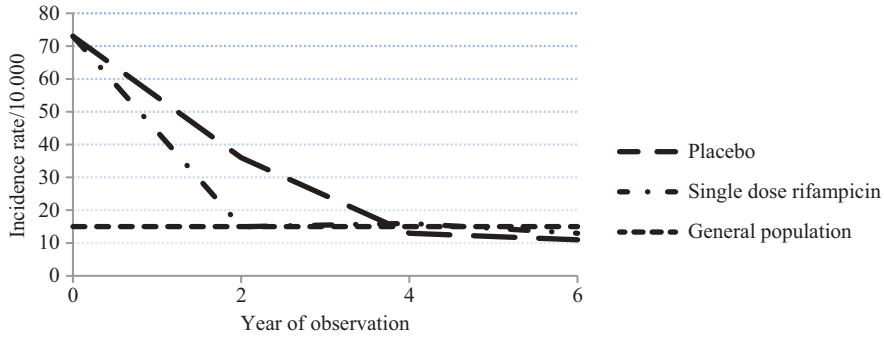

Figure 1. Results of the COLEP trial at 2, 4 and 6 years follow-up.

treatment group compared to the placebo group indicating a possible rebound effect over the 6 years that the COLEP contacts were followed. The effect of SDR is thus sustained over a long period. SDR appears to remove a number of people from the pool of those incubating leprosy. These people (about half of all those at various stages of incubating the disease) are apparently cured of the infection and do not develop leprosy in the following years.

The COLEP study is a cohort study, consisting of a fixed number of contacts, who have been followed over time. Translating the results of the trial to the situation where chemoprophylaxis is implemented in an ongoing routine control situation is not easy. The impact on the incidence rate in the whole population depends on several factors, such as the extent of the contacts surveyed (only household members, or also neighbours and other more remote contacts), household size, the age distribution in the population, the PB:MB ratio, and whether leprosy is high or low endemic in the area. Predictive calculations are traditionally performed with mathematical models, of which the SIMCOLEP is the most prominent example.[4] Figure 2 shows predictions of the relative impact (40%) of chemoprophylaxis with SDR over a 35-year period on the leprosy new case detection rate when supplied on a programmatic scale to household contacts in an endemic region (Pará State, Brazil), based on simulations with the SIMCOLEP model.[5]

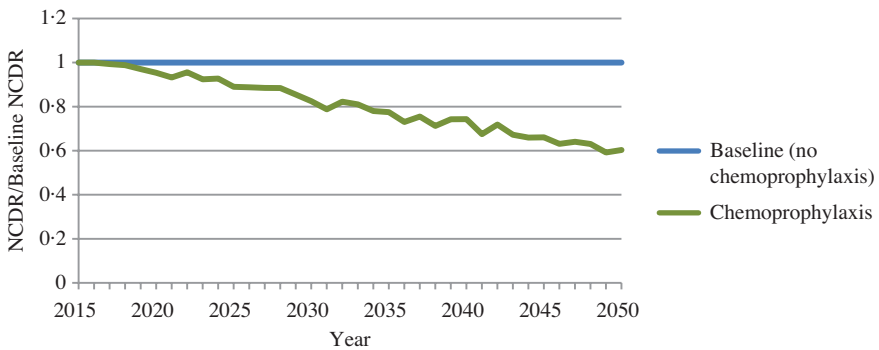

Figure 2. Predicted impact of a scenario of future leprosy control in Pará State, Brazil, with household contact tracing in combination with SDR chemoprophylaxis (dark line), set off against a baseline scenario without chemoprophylaxis (light line).

Misinterpretation 2: SDR does not protect the contacts of MB patients.
The COLEP trial was powered on the basis of establishing an effect of SDR in all contacts combined and not on sub-group analysis of specific contact groups. 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%); $P = 0{\cdot}00023$ (see also Figure 1). This is a very clear statistically significant effect. In most sub-group analyses of COLEP, including the contacts of MB patients, the odds ratio's (OR) indicate protection levels of around 50%, but due to lower numbers in these groups (smaller sample size), statistical significance at the level of $P = 0{\cdot}05$ is not always reached. For contacts of MB patients, at 2 years there were 21 new leprosy patients out of 2846 contacts in the placebo group and 10 new leprosy patients out of 2626 contacts in the SDR group.[1] This is a reduction of nearly 50%, with an OR of 0·52, a 95% Confidence Interval (CI) of 0·22–1·19, and a *P*-value of 0·1201. Technically this difference is not statistically significant, but it is not correct to conclude that therefore SDR does not protect contacts of MB patients. In fact, an OR of 0·52 is quite large and clinically important, indicating that there is very likely a protective effect of SDR in this group and that this would reach statistical significance if the power of the study (more contacts) had been higher.

Misinterpretation 3: SDR does not protect against the occurrence of MB leprosy, only of PB leprosy.
In the COLEP trial at 2 years, there were 9 new MB leprosy patients out of 10,006 contacts in the placebo group and 4 new MB leprosy patients out of 9951 contacts in the SDR group.[1] Again, we see a reduction of around 50% in the SDR group. Due to the small numbers this difference does not reach statistical significance, but also in this case it is not justified to conclude that therefore SDR does not protect against the occurrence of MB leprosy. The figures point to the contrary.

Summarizing, it can be concluded that contact survey and SDR provision as on-going activities of a routine leprosy control programme is very likely to contribute to the reduction of leprosy incidence (representing interruption of transmission of *M. leprae*) in the population, although the effect will differ according to setting. SDR is also likely to protect contacts of MB patients as well as against the occurrence of MB leprosy among the recipients of SDR, although larger sample sizes would need to demonstrate a statistically significant effect.

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