From: Leprosy Mailing List
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Subject: (LML) MALTALEP trial - discussion
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Leprosy Mailing List – October 25, 2019

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From: Diana NJ Lockwood, Barbara de Barros and Stephen L. Walker, London, UK

Dear Pieter,

We would like to contribute to the important discussion of the recently published MALTALEP trial(1). The MALTALEP trial compared the efficacy of bacillus Calmette–Guérin (BCG) vaccination followed by single dose rifampicin (SDR) with BCG vaccination alone in preventing leprosy in household contacts and next-door neighbours of newly diagnosed leprosy patients in Bangladesh(1). It was a large, well designed cluster randomised controlled trial (RCT) and 14988 contacts of 1552 new leprosy patients were randomised to receive either BCG alone (7,378) or BCG followed by SDR (7609) 8-12 weeks later. Participants were followed up for 2 years.

The primary outcome of the RCT recorded in the Netherlands Trial Register (NTR3087) and reported in the trial protocol peer-reviewed publication was "New cases of leprosy among the contacts of index cases" and "…the number of new leprosy patients emerging from the contact groups" respectively(2, 3). There were no significant differences in the proportion of contacts who developed leprosy following BCG and SDR or BCG alone at one or two years. This is an important negative finding and is in keeping with the findings of the cluster randomised, double-blind, placebo-controlled COLEP trial of SDR in household and next-door neighbour contacts(4). The COLEP trial identified that the short-term benefits of SDR were only significant in more distant contacts of index cases.

The administration of SDR to contacts (adults and children over two years old) of individuals newly diagnosed with leprosy is recommended by WHO but the guidelines do not provide criteria to determine who is a contact(5). In two of the eight countries of the Leprosy Post-Exposure Prophylaxis (LPEP) programme contacts were restricted to the household and in only two countries were social contacts included(6). Limiting SDR to close contacts is not supported by the evidence of these two large prophylaxis RCTs.

A secondary data analysis was planned to "define special groups at risk for developing leprosy" and "No significant differences of interest were found."(3) The authors also discuss the non-significant 42% reduction in the number of new cases of paucibacillary leprosy in the group which received SDR after one year. We were surprised that the significant number of individuals who developed multibacillary (MB) leprosy in the SDR group by 2 years was not similarly discussed. The odds of having developed MB leprosy at the two year follow up point were 3.68 (95% CI: 1.03-13.21) in the group randomised to receive BCG and SDR compared to BCG alone. Table 6 states that only one of the 11 new cases of MB leprosy diagnosed after completion of the intervention was slit-skin smear positive. The clinical relevance of the increased numbers of MB patients should be discussed including information about nerve function impairment. The COLEP trial did not show any significant difference in the amount of MB disease between the SDR and placebo groups during two or four years of follow up(4).

The MALTALEP study has important negative findings. It shows that SDR after BCG does not have a significant protective effect against leprosy in household and next-door neighbour contacts compared to BCG alone. This replicates the finding from the larger COLEP trial. The authors also compare data from the placebo arm of the COLEP trial with the BCG arm of the current study to infer that the protective effect of BCG is doubtful in Bangladesh.

SDR prophylaxis is widely promoted as an important tool in the prevention of leprosy and for interrupting transmission of *M. leprae*(7). Our incomplete understanding of the transmission of *M. leprae* and the factors influencing the development of disease hamper the discovery of an effective strategy for prevention.

We have concerns that the lack of clarity from WHO about the definition of contacts, the variable adherence of implementation studies to a broad definition of contacts and some contacts not being examined by trained staff may undermine any short-term benefits of SDR(6). The reinvigoration of contact examination has been a positive outcome of chemoprophylaxis strategies and alternatives to contact examination by trained staff must be rigorously studied.

Implementation studies examining feasibility and acceptability of delivery of an intervention are important but are not designed to robustly measure the effect of an intervention. We agree with Richardus and colleagues that the current evidence does not support the use of BCG followed by SDR for the contacts of leprosy patients(1) and with WHO's position that the evidence for BCG alone is conflicting with no evidence of benefit(8). We disagree with some members of our community about the utility of SDR as a strategy to prevent leprosy or achieve the target of zero transmission of *M. leprae*.

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