Clinics in Dermatology (2015) **33**, 19–25

ELSEVIER

Clinics in Dermatology

Protecting people against leprosy: Chemoprophylaxis and immunoprophylaxis

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Abstract Elimination of leprosy cannot be achieved by multidrug therapy alone, and new tools are needed to prevent leprosy. A randomized controlled trial with chemoprophylaxis for contacts of leprosy patients using a single dose of rifampicin (SDR) has shown an overall protective effect of approximately 60%, effective in the first 2 years after the intervention. When a contact who previously received bacillus Calmette-Guérin (BCG) vaccination also receives SDR, the protective effect is additive, approximating 80%. Vaccine trials have been conducted with BCG, often in combination with *Mycobacterium leprae* or related *Mycobacterium* vaccines as immunoprophylaxis for contacts of leprosy patients, with BCG giving the best results. Meta-analysis shows that the protective effect of BCG vaccination is larger in observational studies than in trials, 60% versus 41%, and is higher among contacts of leprosy patients than among the general population, 68% versus 53%. We believe that a future leprosy control strategy should include contact management, consisting of a contact survey, at which time preventive interventions could be added, such as chemoprophylaxis and immunoprophylaxis. Modeling studies have shown that both interventions will lower the incidence of leprosy in the population. Implementation studies of such contact-based strategy are now called for.

Introduction

The current leprosy control strategy is formulated by the World Health Organization (WHO) as the *Enhanced Global Strategy for Further Reducing the Disease Burden Due to Leprosy 2011–2015*.[1] The strategy aims to reduce the global rate of new cases with grade 2 (ie, visible) disabilities per 100,000 population by at least 35% by the end of 2015, compared with the baseline at the end of 2010. The approach underlines the importance of early detection and quality of care in an integrated service setting. WHO expects this strategy to reduce the transmission of the disease in the community and thus lower the occurrence of new cases. The basic intervention for the strategy is multidrug therapy (MDT), given to newly found leprosy cases. Preventive interventions, other than awareness raising and health education activities, are not routinely available. In 2011, a total of 219,075 new leprosy cases were registered in the world.[2] This global annual number of newly detected leprosy cases has been fairly stable over the past 6 years, indicating that transmission of *Mycobacterium leprae,* the causative agent of leprosy, is ongoing in many endemic countries. It has long been argued that elimination of leprosy cannot be achieved by a strategy based on MDT alone and that new tools and technologies are needed to attain this goal.[3]

Intensified, population-based approaches to case detection are no longer cost effective, and a new approach is now indicated that is appropriate to the current epidemiologic situation. New cases are relatively rare even in endemic countries; health care resources are scarce, with many competing health care demands; and leprosy control

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http://dx.doi.org/10.1016/j.clindermatol.2014.07.009
0738-081X/

activities are difficult to sustain within integrated programs. The main risk of exposure to leprosy occurs with close contacts of new, untreated cases, with the risk of exposure to leprosy in the general community being very low. An increasing proportion of new cases will be from household contacts.[4] In past years, progress has been made in the areas of chemoprophylaxis and immunoprophylaxis (vaccination) to prevent leprosy, and these interventions have focused primarily on contacts of leprosy patients. In this chapter, we shall summarize the current developments and knowledge regarding chemoprophylaxis and immunoprophylaxis in leprosy and discuss their potential to prevent leprosy in contacts and reduce transmission of *M leprae* in endemic communities.

Chemoprophylaxis

Dapsone and acedapsone

The idea of chemoprophylaxis in leprosy is not new. In the 1960s and 1970s, trials were carried out in Uganda employing dapsone as chemoprophylaxis among school children[5] and in India employing dapsone among whole populations of endemic villages[6] and child contacts of nonlepromatous and lepromatous leprosy patients.[6–10] Dapsone was given regularly, usually in a weekly dose, for 2 or 3 years. These studies were subsequently followed by trials with acedapsone, which was given less often and for a shorter duration (every 10 weeks for 7 months).[11,12] Meta-analysis of three eligible studies with dapsone[6,7,10] significantly favored dapsone to placebo (4337 participants, RR 0.60, 95% CI 0.48-0.76, indicating an overall reduction of leprosy among contacts of 40%), and meta-analysis of two eligible studies with acedapsone[11,12] significantly favored acedapsone to placebo (1259 participants, RR 0.49, 95% CI 0.33-0.72, indicating an overall reduction of leprosy among contacts of 51%).[13]

Rifampicin

In 1988, a chemoprophylaxis study employing a single 25 mg/kg dose of rifampicin was implemented in the southern Marquesas Islands.[14–16] This was a (noncontrolled) trial among the 2786 inhabitants of the islands, of whom 2751 (98.7%) were treated. In addition, 3144 South Marquesans living elsewhere in French Polynesia were also given the same chemoprophylaxis. During the following 10 years, five cases were detected in the treated population, a number significantly smaller than the 17 cases that were predicted based on the assumption that the case detection would have remained stable over the years without chemoprophylaxis. This suggested that the intervention was 70% effective; however, during the 10 years after implementation of the chemoprophylaxis program, the detection rate in the Polynesian population not receiving intervention declined by about 50%, suggesting an effectiveness of the chemoprophylaxis of only 35-40%.

Due to the high leprosy incidence rate in the Pacific islands, it was decided in the mid-1990s to carry out programs of chemoprophylaxis in the Federated States of Micronesia, Kiribati, and the Republic of the Marshall Islands.[17] Around 70% of the population of the countries was screened for leprosy twice with a 1-year interval and chemoprophylaxis was administered to all healthy individuals once at each round. The combination of rifampicin-ofloxacin-minocycline (ROM) was given to adults and rifampicin only to children under 15 years of age.[18] By 1999, a substantial reduction in case detection was observed, but it could not be established whether transmission of *M leprae* in the population had been interrupted by the intervention.[17] Recent prevalence and new case detection figures indicate that this has not been the case. The Federated States of Micronesia and the Marshall Islands never reached the WHO leprosy elimination target, and Kiribati even failed to maintain the elimination threshold.[19] In 1999, a workshop was convened in Pohnpei (Federated States of Micronesia) to discuss the results of the chemoprophylaxis trials in the western Pacific region and prevention of leprosy in general.[20] At this workshop, there was discussion of the needs, opportunities, and feasibility of preventive treatment of leprosy, including chemoprophylaxis and immunoprophylaxis.[21] An important conclusion of the workshop was that further evidence for the effectiveness of these preventive interventions was required.[20]

In 2000, a chemoprophylaxis intervention study with rifampicin was started on five Indonesian islands highly endemic for leprosy.[22] The intervention consisted of two doses of 600 mg of rifampicin for adults and 300 mg for children (6-14 years old) with approximately 3.5 months between doses. To form similarly sized intervention groups, three islands were combined into one intervention group. Two types of chemoprophylactic intervention strategies were compared with a control group. The blanket (complete population) group included three islands on which prophylaxis was given to all eligible persons. The contact group included an island on which prophylaxis was given to all eligible contacts of all known and newly found leprosy patients. The control group was the population of an island on which no chemoprophylaxis was given. The population was actively screened before the intervention and subsequently once a year for 3 years. The cohort consisted of 3965 people. The yearly incidence rate in the control group was 39/10,000; the cumulative incidence after 3 years was significantly lower in the blanket group. No difference was found between the contact and the control groups. This study showed that population-based prophylaxis was associated with a reduced leprosy incidence in the first 3 years after implementation. The study also showed that in this area of high endemicity rifampicin prophylaxis for spatially defined contacts only (eg, household members and neighbors) does