

WORKSHOP REPORT

Report of the workshop on the use of chemoprophylaxis in the control of leprosy held in Amsterdam, the Netherlands on 14 December 2006

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Summary In recent years a number of field trials have been carried out to assess the efficacy of rifampicin chemoprophylaxis for the prevention of leprosy in contacts of leprosy patients. Results from these trials are now being analysed and published. The aim of this one-day workshop was to review current evidence and discuss potential future courses of action with regard to the use of chemoprophylaxis to prevent leprosy.

During the morning session the current evidence for the contribution that chemoprophylaxis may make to leprosy prevention was presented, both the results from trials (abstracts in section 1) and the outcome of modelling (abstract in section 2); in addition presentations were given on different aspects of the use of antibiotics for chemoprophylaxis (abstracts in section 3).

The afternoon was devoted to discussions, a summary of which is presented in section 4 of this report. The conclusions and recommendations are given in section 5.

1. Results of chemoprophylactic trials so far

Close contacts of leprosy patients are at an increased risk of developing clinical leprosy. A meta analysis showed that chemoprophylaxis with oral dapsone or intramuscular acedapsone gave around 60% protection against leprosy. This protective effect of chemoprophylaxis on the incidence of leprosy gradually waned off after the end of the chemoprophylactic regimen. The Number Needed to Treat was low in trials of household contacts. Results of non-randomized trials were very similar to those of randomized controlled trials.¹ The main disadvantage of (ace)dapsone is that it had to be administered over a long period of time.

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MIRJAM BAKKER - RESULTS OF THE CHEMOPROPHYLACTIC STUDY PERFORMED ON 5 ISLANDS IN INDONESIA AFTER 69 MONTHS OF FOLLOW-UP

In 2000 a controlled chemoprophylactic intervention study started on five Indonesian islands highly endemic for leprosy. The population (4739) was actively screened for leprosy before the intervention (87% of population examined, 85 new leprosy patients detected) and subsequently once yearly for 6 years. All patients were treated with standard MDT directly after diagnosis. No chemoprophylaxis was given on one island (control group). Chemoprophylaxis was given only to household and neighbour contacts of leprosy patients on one other island ('contact' group) and to all eligible persons on three smaller islands ('blanket' group). The prophylactic regimen consisted of two doses of 600 mg rifampicin for adults and 300 mg for children (5–14 years) with 3 months between doses (90% of those eligible for chemoprophylaxis took at least one dose under supervision of the research team). The study was not randomised, not placebo-controlled and not blinded. The total cohort consisted of 3,963 persons (1251 in control, 1632 in contact and 1080 in blanket group), initially free of leprosy.

After 3 years follow-up the cumulative leprosy incidence was significantly lower in the blanket group compared with the control group ($P = 0.031$). No difference was found between the contact and the control groups. Blanket treatment was 75% effective and the number needed to treat (NNT) to prevent a single case of leprosy was 127.

After 6 years follow-up the difference in cumulative incidence (CI) between the blanket (9 new patients in 67,514 person-months (PM) at risk; CI: 0.0090) and the control group (15 new patients in 74,413 PM at risk; CI: 0.0131) was not statistically significant anymore ($P = 0.33$). Effectiveness of blanket treatment was reduced to 57% and the NNT was 244. The relative risk of developing leprosy among persons who took at least one dose of rifampicin under supervision was 0.38 (95% confidence interval: 0.17–0.85) compared with those who did not take rifampicin. This hazard ratio was adjusted for known risk factors in the cohort: being male, living in houses with more than 7 persons, being seropositive and being a household contact of a MB patient.

In this high endemic area for leprosy prophylaxis for spatially defined contacts only did not influence leprosy incidence. Population-based prophylaxis was associated with a reduced leprosy incidence in the first 3 years after implementation, but this reduction was not significant anymore after 6 years.

HANS MOET - RESULTS OF THE COLEP STUDY PERFORMED IN BANGLADESH AFTER 2 YEARS OF FOLLOW-UP

We performed a single-centre, double-blind, cluster-randomized, placebo-controlled trial among 21,711 close contacts of 1,037 newly diagnosed leprosy patients in northern Bangladesh. The intervention consisted of a single dose of rifampicin prophylaxis or placebo given to all contacts in the second month after the treatment of the patient had started. Close contacts that were considered for inclusion were household and compound members, direct neighbours, neighbours of neighbours and close business and social contacts.

19,957 contacts (91.9%) were examined for leprosy during the first follow-up after 2 years. Preliminary analyses showed that in the rifampicin group ($n = 9951$) 29 new patients were detected and in the placebo group ($n = 10,006$) 66 new patients. The reduction in incidence after 2 years by a single dose of rifampicin was 56% and the protection was

strongest among less high risk contact groups (such as neighbours of neighbours and contacts of PB patients). The NNT to prevent a single case of leprosy among contacts was 272.

Whether this is lasting prevention of leprosy or delay of the disease remains to be studied. A second follow up after 4 years is currently under way.

ETIENNE DECLERQ - PRELIMINARY RESULTS OF THE CHEMOPROPHYLACTIC TRIAL IN DFB (DAMIEN FOUNDATION BELGIUM) SUPPORTED PROJECTS IN INDIA AFTER 4–5 YEARS FOLLOW-UP

In nine projects in North and South India a double-blind randomized controlled trial is being executed. A single dose of rifampicin (10 mg/kg) or placebo was given to household contacts of leprosy patients 2–3 months after the start of MDT. Leprosy patients were detected through rapid village surveys (RVS). Contacts of patients detected up to a year after the RVS could still be included. Contacts were annually examined.

Initial results show that after 4–5 years of follow-up incidence per 10,000 person-years was 8.7 in the control group ($n = 3877$) and 2.3 in the intervention group ($n = 3760$), which gives a risk reduction of 74%. The NNT to prevent a single case of leprosy among contacts was 1556.

2. Modelling

EGIL FISCHER - INDIVIDUAL BASED SIMULATION OF LEPROSY, SIMCOLEP

Close contacts of leprosy patients have a higher risk of leprosy than people in the general population. We want to study the epidemiology of leprosy in a population in which people make contact within and between households, and study the effects of control measures in such a population. Therefore, we developed a simulation model with the individual as unit of modelling. Individuals have a simulated life and disease history. Events during the life of an individual are determined by stochastic (i.e. chance-driven) processes. Progression of leprosy is described by unique discrete steps for self-healing and chronic leprosy.

We started our studies with this simulation model with a population subdivided into households, with contact within and between households. We conducted two preliminary scenario analyses. In the first scenario analysis we studied the fraction non-susceptible people in the population and in the second we studied the effect of household size.

The first analysis showed that the prevalence does not change with within-household contact when 90% of the population is non-susceptible. For smaller fractions of the population being non-susceptible the prevalence increased exponentially with contact-rate. In our second analysis, the prevalence was higher when the household size was large. The results of these scenario analyses with SIMCOLEP show that the demographic characteristics of a population and the fraction non-susceptibles have a large impact on the epidemiology of leprosy. If chemoprophylactic treatment of close contacts prevents a fraction of people that were infected within the household of developing leprosy, these simulations show that the effectiveness of such an intervention will differ between populations.

3. Important aspects to be considered

HAN DE NEELING - OVERVIEW OF ANTIBIOTIC RESISTANCE IN *MYCOBACTERIUM LEPRAE*

Dapsone is a folate synthesis inhibitor; it is an analog of para-amino-benzoic acid and inhibits the enzyme dihydro-pterolate synthase early in the synthesis route to folic acid. Resistance to dapsone is due to point mutations in the gene of dihydropterolate synthase (*folPI*). It is relatively easy to select strains resistant to dapsone.

Ofloxacin is a DNA-gyrase inhibitor and belongs to the fluoroquinolone family. Resistance to ofloxacin is due to mutations in *gyrA* of *M.leprae*. Mutations in *gyrA* and *parC*-genes were found in quinolone-resistant *Neisseria gonorrhoeae* and other bacteria.

Rifampicin is a RNA polymerase inhibitor and belongs to the rifamycin family. Resistance to rifampicin for both *M. leprae* and *M. tuberculosis* is due to mutations in the *rpoB* gene.

Minocycline is a protein-synthesis inhibitor and is a tetracycline. Tetracyclines bind to 16S RNA in 30S-subunit of ribosomes. They are mainly bacteriostatic. 27 different tetracycline-resistance genes have been described. No resistance has been detected in *M.leprae*.

In conclusion, for the three main anti-leprosy drugs, dapsone, ofloxacin and rifampicin, resistance is observed. Resistance is due to point mutations in the genes of the enzymes being inhibited. Such mutations are easily detectable by DNA sequencing. Mutations may inhibit the growth rate or the virulence of the bacteria, but secondary mutations may restore their fitness.

Points for discussion:

1. Using an antibiotic for *prophylaxis* will inevitably select resistant bacteria, not only in *M. leprae*, but also in other bacteria (*M. tuberculosis*). 'The more you use it, the more you lose it'.
2. Such resistance may hamper *treatment* of persons who relapsed after prophylaxis as well as their contacts.
3. Only a *small percentage* of healthy carriers would develop leprosy. Nevertheless *all* are treated and experience side effects.
4. Resistance of *M. leprae* and other bacteria such as *M. tuberculosis* should be monitored before as well as after intervention (prophylaxis or treatment).

ERIK VAN KAN - CLINICAL PHARMACOLOGY OF PROPHYLACTIC ANTIMICROBIAL AGENTS IN LEPROSY

Optimal chemoprophylaxis should provide maximum efficacy and minimal risks (adverse effects, resistance). The clinical target is to eradicate *M. leprae* from (presumably) infected contacts, but there are currently no good diagnostic markers for subclinical infection.

Candidate antimicrobial agents for chemoprophylaxis should have: (1) fast oral absorption without gastro-intestinal interactions; (2) fast intracellular penetration into infected tissues; and (3) slow elimination (long half life) to allow prolonged effect and once-only regimens. Adverse reactions are generally a minor issue for (potential) chemoprophylactic agents.

There are a number of antibiotics with proven activity in leprosy, but some of them are less suitable for chemoprophylaxis:

1. Dapsone has favourable pharmacokinetics but will not lead to clearance of inactive *M. leprae* during short-term application.
2. Clofazimine has a slow bactericidal effect and the concentration is too low for once-only application.
3. Quinolones are expensive and not to be used in children and pregnant women.
4. The tetracycline minocycline has a long half-life, but is relatively expensive and not safe in pregnant women.
5. Macrolides (azithromycin, clarithromycin) have a high and fast tissue penetration, but the bactericidal activity on slowly growing mycobacteria is uncertain. Clarithromycin is relatively short acting. Azithromycin has a negative interaction with food (50% lower activity).

This leaves two drug classes which may be suitable for chemoprophylaxis:

6. Rifamycins. Rifampicin is cheap and available. Rifapentin may actually be a better candidate because it has a longer half life than rifampicin of ~ 15 hrs. The third candidate compound, rifabutin, is less suitable for a once-only regimen.
7. R207910 (diarylquinoline) is a new compound with a moderately long elimination half life (± 24 hrs), but one may want to reserve this compound for treatment of leprosy.

In conclusion: there are several candidates with favorable clinical pharmacological properties that would enable once-only regimens, but clinical trials are needed to provide the evidence for their use in leprosy chemoprophylaxis. Costs may be a critical consideration in endemic countries.

WIM VAN BRAKEL - THE OPERATIONAL FEASIBILITY OF CHEMOPROPHYLAXIS

Ideally, if a policy for chemoprophylaxis is implemented, all contacts of a new case should receive prophylactic drug(s). However, in practice this will not be the case, since it will not be possible to reach everyone. Also people may refuse to take part for various reasons. To implement a chemoprophylaxis policy, the following conditions are necessary:

1. An at-risk group can be identified. The most likely target group for chemoprophylaxis is household contacts, but neighbour and social contacts should also be considered. How should potential recipients be identified?
2. The at-risk group can be contacted to inform them about chemoprophylaxis. Ethical issues play a role and need to be considered. Can contacts only be contacted after the index case has given consent? Should people be contacted anonymously with regard to the index case? Should exclusion criteria be used (children, pregnancy, liver failure, suspected TB)? Should people be informed in advance? If so, how and by whom?
3. Loose tablets of the chemoprophylactic drug are available. Loose tablets need to be available to the Leprosy Control Programme. How should quantities be estimated? Should delivery of the chemoprophylaxis to individual members of the target group be recorded and reported? If so, a recording system is needed. This would be particularly important if

the chemoprophylaxis were to be repeated at intervals. In the latter case, a plan for repeat distribution needs to be made in each case.

4. The national programme is prepared to implement the new policy. Use of chemoprophylaxis should become national policy and should be added to the national manual. Staff throughout the programme needs training on how to implement the new policy. This would include drug ordering, selection of contacts, method of screening, etc. In-service training would be a minimum. (Occasional) supervision would be needed.
5. The drugs can be delivered to the target population. How is the chemoprophylactic drug to be administered? Should contacts be invited to come or should it be done by home delivery? Should contacts be screened for leprosy first? Should the intake of the drug be supervised? Should it be a once-only administration or should it be repeated? If repeated administration is used, what should be the frequency and for how long?
6. Procedures for dealing with any (perceived) adverse reactions should be in place.

Although chemoprophylaxis seems simple at first glance, implementation is complicated under routine programme circumstances. At present, the above operational conditions can only be met in more sophisticated leprosy control programmes. Therefore, for the time being, implementation of a chemoprophylaxis policy should be done only as an operational research programme, carefully documenting the lessons learnt.

BAOHONG JI – SOME CONSIDERATIONS ON CHEMOPROPHYLAXIS FOR LEPROSY

Chemoprophylaxis is targeting those subjects with suspected sub-clinical leprosy infection. These subjects do not require and would not accept to be treated as leprosy patients. From an operational point of view, it would be highly desirable if chemoprophylaxis is administered in no more than a single dose. Consequently, the regimen should display powerful bactericidal activity against *M. leprae* by a single dose of treatment. There are four antimicrobial agents, i.e., rifampicin (RIF), rifapentine (RFP), moxifloxacin (MXF) and R207910 (a diarylquinoline), displaying similar but very powerful bactericidal activity, i.e., killing at least 90% of viable *M. leprae*, at a single dose. To date, both R207910 and RFP are not commercially available; both RIF and MXF are commercially available and well tolerated by the patients, but MXF is significantly more expensive than RIF. Therefore, the first choice of the chemoprophylactic regimen would be a single dose of 600 mg RIF, or 10 mg/kg body weight RIF for children. Although the combination of rifampicin-ofloxacin-minocycline, or ROM, has been employed as monthly administered regimen for treatment of leprosy with promising results, a single dose of ROM is no more effective than a single dose of RIF alone; furthermore, addition of ofloxacin and minocycline to RIF will increase the cost and the risk of side-effects. Therefore, ROM should not be employed for prophylactic purpose. Finally, a person with sub-clinical leprosy infection is most likely skin-smear negative, and therefore harbours no more than 10^6 *M. leprae*, or 10^5 viable *M. leprae*, in the body; it is very unlikely that a single RIF-resistant mutant would be included in such bacterial population, therefore the risk of emergence of RIF-resistance by a single dose of RIF monotherapy is probably negligible. On the other hand, if, for whatever reason, the bacterial population size is larger than expected, and even if it includes RIF-resistant mutants, the emergence of rifampicin-resistance is still very unlikely, because a single dose RIF is insufficient to select the resistant mutants, as has been shown in MB patients who relapsed after a single dose of RIF treatment.

4. Summary of discussion

1. CRITICAL REVIEW OF CURRENT EVIDENCE PROVIDED BY TRIALS

A number of remarks were made with regard to the trials presented above:

- Rifampicin showed about the same protective effect as was previously found for dapsone,¹ but dapsone has to be taken for a much longer period of time, making dapsone chemoprophylaxis less applicable in routine control programs.
- It was noted that in the Indonesia trial the efficacy of rifampicin after 6 years would change to 81% (95% Confidence Interval 4–96%) if the single lesion PB patients, including 4 patients that were found in the blanket group, are left out from the analysis.
- Setia *et al.*² showed previously in a meta-analysis that BCG vaccination is 26% effective against leprosy in experimental studies and 61% effective in observational studies, but with a large variation between geographic regions. The COLEP study showed that BCG vaccination provides around 50% protection. Since BCG is widely used, we would like to know the additional effect of rifampicin in BCG vaccinated people. Therefore, analysis should be stratified by BCG status.

It was suggested to perform a meta-analysis using the figures from the different studies to be able to stratify between contact groups and get more detailed information on effects within contact groups. This may lead to the identification of contact groups such as households that are worth intervening in. When using the results of the trials both the absolute value of risk and the risk reduction should be taken into account. The absolute value of risk to develop leprosy (i.e. the incidence) is most important.

There are still a number of fundamental questions with regard to transmission and the diagnosis of sub-clinical leprosy that should be answered first. There is a need for tools for early diagnosis, detection of infection, identification of high risk groups and to understand transmission. These tools are being developed in the framework of IDEAL (Initiative for Diagnostic and Epidemiological Assays for Leprosy).³

The current working hypothesis with regard to the limited success of chemoprophylaxis in high-risk contacts is that the bacterial load at the time of preventive treatment is already too high in a considerable proportion of infected people in this group. These people may need to have another treatment regimen (see point 7).

2. THE WAY FORWARD

The initial reactions on whether we have enough data to recommend a policy varied from (1) the opinion that the evidence was sufficient to start implementation in ongoing leprosy control programmes, but possibly using rifapentin instead of rifampicin as it has better characteristics; (2) cautious views pointing out that after 6 years the effect was less in the Indonesian trial and that we may need to analyse the data from longer follow-up time for all current studies; to (3) more sceptical points of view pointing out that the main effect of chemoprophylaxis may be that incubating (i.e. subclinical) leprosy may be delayed, which may give a wrong idea about the amount of protection and that the trials thus far have not shown a protective effect in the highest risk groups.

There was also doubt whether implementation would be feasible from a practice point of view (logistic and programmatic issues) and about the implications of the use of rifampicin

for TB control. The practical issues surrounding implementation should be studied carefully by people who have experience with leprosy control in the field before chemoprophylaxis can be implemented under routine programme conditions.

3. ANTIBIOTIC RESISTANCE

The main conclusions of the recent (December 2006) WHO meeting on resistance in *M. leprae* were:

- There is not much recent research performed on resistance in *M. leprae*.
- Resistance has been described in relapse cases.
- Secondary rifampicin resistance is seen sporadically and in a few unconfirmed cases also primary resistance (person infected by bacteria that were already resistant).
- PCR-based sequence analysis can be used to assess antibiotic resistance in *M. leprae*.

There is currently virtually no evidence of recognised, operationally important drug resistance in leprosy, a situation which one wants to maintain. In general, there are no serious problems to be expected when rifampicin is given as a once-only treatment, but giving rifampicin as chemoprophylaxis in the control of leprosy increases the availability of rifampicin in a community. Rifampicin is used for other diseases as well, so exposure to rifampicin ('environmental exposure') is higher than only from the leprosy prophylactic treatment.

Rifampicin is one of the mainstay drugs in treatment of tuberculosis (TB). Even though one dose is probably not sufficient to induce resistance in TB, TB control programs may be opposed to the use of rifampicin for leprosy prevention. In most endemic countries there is currently no regular surveillance on rifampicin resistance in TB. This should be established first so that possible effects of widespread leprosy chemoprophylaxis with rifampicin on drug resistance in *M. tuberculosis* can be monitored.

In conclusion, extreme care needs to be taken when using antibiotics for prophylaxis rather than treatment and when implementation of rifampicin prophylaxis would be considered, this needs to be discussed with TB experts and/or control programmes before initiation. It will remain very important to regularly assess resistance of *M. leprae* as well as *M. tuberculosis*.

4. CONTACT VERSUS POPULATION TREATMENT

The target group selection should be sensible and realistic, and the aim should be to define an identifiable high risk group. One should not only look at the percentage reduction of the risk to develop leprosy, but also at the starting risk. The NNT (number needed to treat to prevent one case of leprosy) is a more important measure than relative measures like OR (odds ratio) or RR (relative risk) when considering the operational feasibility of any chemoprophylaxis initiative. The NNT is also a proxy for the (financial) costs of the intervention, but apart from financial implications there are also social and emotional consequences involved in disease prevention.

In general one can envisage two distinct types of strategies, based on the ultimate aim of prophylaxis: to prevent disability in the individual or to prevent transmission at the community level.

1. Household/contact treatment

Individual-based approach for the individual benefit of the contacts/family members of a patient who have an increased risk of developing leprosy. This does not necessarily benefit the population as a whole.

2. Population treatment

Aimed at reducing and ultimately interrupting transmission in the population. This strategy is more controversial as it means more wide-spread and less tightly controlled use of antibiotics. It could be combined with other mass treatment strategies such as those for lymphatic filariasis.

Ad 1: Contact treatment

The household contacts of highly smear positive patients (3 +) have a high attack rate. It therefore seems reasonable to give chemoprophylaxis to household contacts of MB patients. However, the results from the trials in Indonesia and Bangladesh both showed that a single dose of rifampicin seems insufficient to prevent leprosy among (MB) household contacts (or other very high risk groups).

Another issue is that the majority of the new cases come from outside the household contact group.⁴ At low levels of endemicity one can introduce chemoprophylaxis for household contacts, because there is relatively less leprosy among non-household contacts.⁵

Ad 2: Population treatment

Total population treatment should have some impact on transmission, but more research is needed, because this effect is currently still unclear and may be small.

Some participants considered population-wide treatment with rifampicin unacceptable at national level, but others thought it could be introduced in a campaign-like pocket approach for areas where leprosy is clustered. In this case the approach should include tight screening for leprosy and tuberculosis, health education and prophylaxis

5. COUNTRIES/AREAS WHERE PROPHYLAXIS COULD BE INTRODUCED

In first instance the discussion focused on high endemic areas. However, within low endemic countries there are areas with a higher endemicity of leprosy ('pockets') to which one can limit the intervention. Another scenario occurs in Vietnam, where an 'outbreak approach' is practiced for leprosy. Dedicated health workers are sent in for case confirmation when a case of leprosy is diagnosed and all contacts are screened. In this scenario chemoprophylaxis fits better than in routine leprosy control programs or integrated health care programs with only passive case detection and limited (human) resources.

The above example also pointed to another possible division, namely between low and high resource areas. High resource areas are for example Southern Europe and Thailand. It may be more realistic to set up chemoprophylaxis in a high resource setting where all the requirements can be met.

With regard to infrastructure, one has to make a distinction between urban and rural settings. One may expect that giving chemoprophylaxis will be more problematic in urban areas, as populations tend to be less settled and more difficult to reach.

In conclusion, if one wanted to see whether chemoprophylaxis works at all in routine practice, it may be wise to start it in a low-endemic/high-resource area.

6. ACCEPTABILITY AND FEASIBILITY OF CHEMOPROPHYLAXIS IN A ROUTINE SETTING

Acceptability is an issue in any screening or mass treatment program and linked to side effects and perceived benefits. The perception of leprosy *prevention* is important. Prophylaxis will be acceptable as long as the side effects are not too many. From the current evidence it can be concluded that for a long term effect this (post-exposure) chemoprophylaxis would probably need to be repeated every 2–5 years. It will thus be crucial to explain to the persons receiving the drug that prophylaxis gives neither life long nor 100% protection so as to leave them with realistic expectations.

The standing guidelines are to screen contacts, give health education and ask them to return to the clinic if they have signs or symptoms of leprosy. A complicating factor is stigma. Actually, the availability of chemoprophylaxis in combination with community education may help to reduce stigma, but this will require public relations (PR) tools. The fact that the health worker can offer contacts something to reduce the risk of developing leprosy might increase the number of contacts that come for screening, especially in areas where fear of leprosy is highest analogous to the effect caused by the introduction of the ML Flow test, when the availability of a tool led to increased motivation of the health worker AND more enthusiasm of the contacts to come forward for screening.

Anecdotal information from the areas in Indonesia and Bangladesh where the trials are conducted learns that people are now actually asking for prophylactic treatment. However, a good advocacy programme will be crucial: experience from the same area with a mass treatment campaign for lymphatic filariasis learned that in the first year people showed interest, but this became less and less over time.

In most situations contact examination is very difficult in leprosy control and often not practiced. Apart from a few exceptions (like TLM Bangladesh) where contacts are actively traced and visited, in the best case contacts are invited to come to the health centre. It was mentioned that in Indonesia contact examination is practiced in only about 10% of the cases. This will make it very difficult to practice chemoprophylaxis as it is not advisable to give the chemoprophylaxis unsupervised and without appropriate health education.

Even though the argument was raised that, if chemoprophylaxis would be beneficial for household contacts, the control program could aim at empowerment of patients so that they check (and treat) their own family members with proper explanations of benefits, the trial in Indonesia showed that supervised provision of rifampicin gave much better results. This has implications for the set-up of chemoprophylaxis programmes. The overall consensus was that examination of contacts by a health worker is a prerequisite for giving chemoprophylaxis.

The question remains whether national leprosy programs, especially in countries that have reached the elimination goal, would be willing to adopt a leprosy control policy including chemoprophylaxis.

7. CHOICE OF PROPHYLACTIC REGIMEN

From the presentation by Erik van Kan it became clear that rifapentin may actually be a better candidate drug for leprosy chemoprophylaxis than rifampicin, because its activity is enhanced by intake with food and it has a much longer half-life than rifampicin (15 hours vs. 3 hours). The patent on rifapentin has expired, but the situation with regard to licensing of its application was unknown to the participants of the workshop.

Because a single dose chemoprophylaxis seems to be insufficient in household contacts, one could offer a different regimen to direct household contacts compared to other contacts or the total population. If tools for the diagnosis of sub-clinical leprosy would be available, one could decide to treat those people with more than one dose, perhaps standard MDT for PB leprosy or monthly ROM for 6 months; this type of ROM is as effective as standard MDT in treatment studies.

The question was also raised whether people carrying *M. leprae* in the nose as determined by PCR should be treated as people with sub-clinical leprosy. However, most participants felt that since nasal carriage is often transient⁶ and the potential contribution to transmission is uncertain this is not necessary.

The results of the COLEP study in Bangladesh show that BCG vaccination protects about 50% and that the additive effect of rifampicin after BCG is 50% again (total protection 75%). Thus, there is evidence for protective effects from chemoprophylaxis, immunoprophylaxis and both together. In developing countries most children up to 15 have been vaccinated with BCG. In absolute terms one may expect that rifampicin will have the largest effect if given to those who are not yet vaccinated. (Repeated) BCG vaccination of contacts may be another (immuno)prophylactic intervention, which is already practiced in Cuba, Venezuela and Brazil. However, in this case it is necessary to consider HIV, as BCG vaccination should not be given to HIV-infected persons.

8. NEW RESEARCH TOPICS

From the above discussion a number of potential future research topics were identified:

- Based on outcomes from the current trials further important issues are: 1. to look in more detail at the regimen needed for very high risk groups; and 2. to look at the effects of prophylaxis beyond neighbours-from-neighbours (N2) contacts.
- The most important issue, however, remains the development of tools to detect sub-clinical leprosy. Once such tools are available, a trial could study tailor-made prophylactic treatment regimens in which the high exposure group and/or persons with sub-clinical infection are given a ‘heavier’ regimen than one-dose chemoprophylaxis.
- Further operational / health systems research is needed to identify those characteristics of the public health system that are critical for a successful implementation of chemoprophylaxis under routine leprosy control programme conditions.

5. Overall conclusion/recommendations

The results of field trials indicate that there might be a role for chemoprophylaxis in routine leprosy control. However, a number of requirements should be fulfilled. These include:

1. Contacts should be screened by a health worker for leprosy and TB prior to the provision of chemoprophylaxis.
2. Chemoprophylaxis should be provided under direct observation.
3. A system for recording and reporting of prophylaxis distribution should be in place.
4. Health workers need to be informed of such a policy and those directly involved need to be trained in selection and distribution.
5. People receiving chemoprophylaxis should receive proper information about its effects so as to leave them with realistic expectations.
6. A system for antibiotic resistance monitoring should be in place.
7. There is a need for discussion and approval of any such program with the TB (and other infectious disease) authorities.

Some of these requirements are not normally met in leprosy control programmes. For others, practical solutions need to be found. Therefore, before chemoprophylaxis can be implemented in such programmes, careful operational and/or health systems research should be carried to determine the programme conditions required, and to develop practical guidelines for a successful implementation of a chemoprophylaxis policy.

A number of critical issues need further investigation:

1. Practical diagnostic tools to detect sub-clinical leprosy.
2. Prophylactic regimens needed for the highest risk groups.

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