SESSION II: PROPHYLAXIS

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Prophylaxis—scope and limitations

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Summary Attempts to prevent leprosy by one or another prophylactic method began with the use of dapsone as a chemoprophylaxis. Following early, small-scale studies, which were promising, large-scale studies with dapsone and acedapsone, both among contacts and in the general population, demonstrated that it is possible to prevent the occurrence of leprosy to a modest extent. With regard to immunoprophylaxis, BCG had long been considered a possibility, particularly in view of its potential to convert the skin test reaction to lepromin. Over the years, major, large-scale field trials of BCG had been carried out in Uganda, Burma, Papua New Guinea and India. All of the studies demonstrated that BCG was capable of preventing leprosy. However, protective efficacy varied from around 20% to greater than 80%. Killed *Mycobacterium leprae* mixed with BCG has also given varying results. Other vaccines based on cultivable mycobacteria have also been tried, and at least one of them appears promising. An approach to prophylaxis must take into account (a) the level of risk addressed and the perception of risk by the community; (b) the level of efficacy of the method of prophylaxis; (c) the possibility of easily identifying high-risk groups; (d) the operational feasibility; and (e) the focus of the prophylaxis, whether the individual or the community, or both. However, in view of the enormous progress being made towards elimination of leprosy by the widespread application of MDT, prophylaxis is becoming less and less relevant and less and less cost-effective, except in very special situations.

Before the advent of modern chemotherapy, leprosy was considered a problem with no solution. The reaction of the community to the disease was one of fear and abhorrence. No wonder that, even before leprosy was understood to be an infectious disease, leprosy patients were driven out of society and isolated. Obviously, society felt that it was the only way to deal with so terrible a problem and protect itself. Isolation of leprosy patients became better organised toward the later part of the nineteenth century, at which time it was rationalized on the basis of evidence that leprosy was infectious and that it was caused by a bacterium, *Mycobacterium leprae*. Many still believe that the disappearance of leprosy from Europe resulted largely from the practice of strict isolation of patients. In any case, isolation of patients in special homes or sanatoria was the first attempt to prevent spread of leprosy in the community. This approach was further extended in some countries to the establishment of preventoria to protect the children of leprosy patients from becoming infected. However, these attempts cannot be considered as specific attempts at disease prevention. The first attempts at specific prophylaxis against leprosy were made only after the advent of dapsone as an anti-leprosy drug and its success in the treatment of leprosy patients. Early workers who tried dapsone as a chemoprophylactic include Figueredo in Bombay, Lew in Korea, Lara in the Philippines, Otsyule in Uganda, and Nhu in South Vietnam. However, these studies were relatively small and not well controlled. Nevertheless, they demonstrated that dapsone was

capable of providing significant but varying protection to contacts of leprosy patients. Two large-scale studies in India, one on contacts and another on the entire population of a community, also demonstrated a significant protective effect of dapsone prophylaxis. In view of the need for the frequent administration of dapsone for a long time, an injectable sulphone formulation, acedapsone, was later tried as a prophylactic in Micronesia and India. Acedapsone also demonstrated a significant protective effect against leprosy, both in contacts and in the population as a whole. More recently, the chemoprophylactic efficacy of rifampicin, administered either alone or in combination with other drugs, has been established.

With regard to immunoprophylaxis, the use of BCG had been considered for a long time, in view of its role in preventing tuberculosis. A number of small-scale studies, beginning from the work of Fernandez in 1939, indicated that BCG was capable of converting the lepromin skin test, and, possibly, of protecting against the disease. Shepard also provided experimental evidence that BCG protects mice against infection in the footpad. All of this evidence led to the organization of large-scale controlled trials in Uganda, Burma and India. In addition, limited information on the protective effect of BCG against leprosy became available from Venezuela and Malawi. In all of the large-scale studies, BCG was found effective in preventing leprosy, although the protective efficacy varied from about 20% in Burma to greater than 80% in Uganda. Overall, the protective efficacy of BCG against leprosy was quite small in Asia, particularly in India. The factors that contributed to the varying levels of protection in different studies are not fully understood.

Apart from BCG, other vaccines based on cultivable mycobacteria, such as the ICRC bacillus and '*Mycobacterium w*', have been tried as immunoprophylactic agents against leprosy. In a recent multi-arm trial in South India, the ICRC bacillus demonstrated a very good protective effect against leprosy, whereas *Mycobacterium w* did not.

With regard to immunoprophylaxis, a major initiative to develop an anti-leprosy vaccine came from the Immunology of Leprosy (IMMLEP) scientific working group, set up by the WHO Special Programme on Research and Training in Tropical Diseases, known as TDR. IMMLEP had focused its attention on developing a vaccine based on killed *M. leprae* obtained from artificially infected armadillos. After obtaining large quantities of *M. leprae*, purifying the organisms, testing the killed, purified *M. leprae* in animals for sensitization and protection, and in a small number of human volunteers, IMMLEP supported large-scale field-trials of a vaccine consisting of a mixture of killed *M. leprae* and BCG in three different geographic settings, in Venezuela, Malawi and India. Whereas the trials in Venezuela and Malawi did not demonstrate protection by the mixture of killed *M. leprae* and live BCG, the trial in India showed considerable protection by this vaccine.

Concerning the main issue of the scope and limitations of prophylaxis in leprosy, whether chemoprophylaxis or immunoprophylaxis, the key issues to be considered are:

- What is the level of risk of leprosy to be addressed through prophylaxis, and how concerned with this risk is the healthy population in the community?
- What is the efficacy of the prophylactic procedures available?
- What is the importance and relevance of identifying high-risk groups, if prophylaxis must be limited to such groups?
- What is the operational feasibility of the procedures, including cost, side-effects and acceptability?
- What is the purpose of the prophylaxis—benefit to the individual, benefit to the public health benefit, or both?

Analysis of all of these factors will help us come to an understanding of the scope and limitation of any prophylaxis.

Level of risk

The level of risk is an important consideration for any prophylaxis. If the risk is very small, it is rational to ignore it and deal with it as and when it materializes into disease, particularly if the disease is a fairly benign one in its early stages and is also easy to detect early. Thus, the level of risk will be an important consideration for making a decision for the use of any prophylactic procedure. As the cost-benefit ratio will be very small in low-risk situations, one way to improve the cost-benefit ratio is to confine the prophylaxis only to high-risk groups. For instance, if the risk of leprosy in the general population is 1:1000, it will be necessary to administer prophylaxis to 1000 persons in order to prevent one case of leprosy. However, if prophylaxis is confined to only a high-risk group, such as household contacts, then it may be sufficient to administer prophylaxis to a much smaller number, probably around 100 people, in order to prevent one case of leprosy.

Efficacy of the prophylactic procedure

Ideally, one would like to have a prophylactic procedure that is close to 100% efficacious. In reality, however, such a degree of efficacy is not easily attained. The maximum achieved in leprosy with one or another prophylactic procedure, whether chemoprophylaxis or immunoprophylaxis, is about 75%. Even this maximum was reached only under the ideal settings of a field study. The same procedures applied under routine conditions are likely to provide a prophylactic efficacy no greater than 50%. The degree of efficacy also has important implications for the number of persons to be treated prophylactically in order to prevent one case of leprosy. In the earlier example of 50% efficacy, the number of persons to be treated prophylactically will be 2000 for a general population and 200 for contacts.

Importance and relevance of high-risk groups

Whereas confining prophylaxis to high-risk groups improves the cost-benefit ratio in terms of benefit to the individual, the cost-benefit ratio in terms of benefit to public health depends entirely upon the proportion of new cases in the population contributed by the high-risk group. In leprosy, there is no way of identifying high-risk groups, other than household contacts. Thus, in the case of leprosy, if one identifies household contacts as a high-risk group, their contribution to the total of new cases in the population is no more than 30%. This is true in areas in which leprosy is highly or moderately endemic; the situation with regard to areas of very low endemicity is not clear. In the example I have given, in which the efficacy under routine conditions is 50%, if we address only 30% of the problem in terms of new cases, then, in terms of the public health, the benefit in any given area will be only about 15%. One way to deal with this is to widen the net to identify additional high-risk groups that would hopefully include a larger proportion of the new cases. Unfortunately, we have no simple, dependable and low-cost means by which to identify additional high-risk groups. The

immunological tests thus far described do not sufficiently meet the requirements of simplicity, dependability and low cost.

Operational feasibility

The operational issues include: (a) the direct cost of the prophylactic preparation; (b) the indirect costs of administering the preparation; (c) the perception and acceptance of the risk of leprosy by the community; and (d) side-effects and incidental risks of the prophylactic procedure. In relation to the direct cost, the situation is likely to be favourable and within the means of many programmes. However, the indirect costs could be very high, depending upon the logistic problems and the need to administer the procedure multiple times. With regard to side-effects and incidental risks, the situation is likely to be more serious with injectable preparations. These risks include local reactions and ulceration and the inadvertent introduction of HIV infection in the field, because of improper sterilization practices. Even with drugs for chemoprophylaxis, the issue of side-effects cannot be ignored. Whereas side-effects may be acceptable as part of the bargain when drugs are administered to diseased individuals, they are relatively unacceptable when they occur in healthy individuals. Lastly, the perception of the risk of disease and its consequences and the need for prevention varies widely among communities, and so much will depend upon creation of community awareness and health education. Whereas this is possible in the ideal setting of a field study, this could be a serious problem in more ordinary settings.

In conclusion, it is clear that, with the current low levels of leprosy endemicity in many countries, and with the small risk, application of any prophylactic procedure as a public health practice is open to question, as there will be a need to treat prophylactically very large numbers of people, in order to prevent the very few cases that are expected to occur. Further, if prophylaxis is confined only to household contacts, it is unlikely to be effective in the public-health context of eliminating or eradicating leprosy. On the other hand, prophylactic procedures may offer individual benefits in situations of exceptionally high risks.

DISCUSSION

Professor Grosset: I wish to congratulate you for your very clear exposition of the advantages and potential disadvantages of vaccination against *M. leprae*. I wish, also, to ask one question. If there were a highly promising vaccine, would you consider a trial of the vaccine justifiable at this time?

Dr Noordeen: I have mentioned the difficulties facing the undertaking of a vaccine trial, and I'm certain Dr Gupte agrees with me. There are now very few field areas suitable, in terms of epidemiological backup, for large-scale trials.

Professor Britton: You stated that the risk of leprosy among household contacts was 30%. I'm certain, however, that this risk varies widely from area to area. Would you summarize the information available with regard to risk in areas of high, medium and low endemicity.

Dr Noordeen: The risk of leprosy among household contacts is four to six times that among non-contacts. However, the important question has to do with the proportion of all new cases of leprosy in the community that is contributed by the contacts. It is clear that, in areas of high and moderate endemicity, no more than 30% of the new cases occur among the

contacts. This is also true for tuberculosis. Only a minority of the new cases occur among household contacts; the remaining, majority of new cases have contracted their infections outside their households. In areas of very low endemicity, the situation is unclear. Thus, the importance of widening the net, to identify others at high risk. This depends upon such things as the availability of easily applied immunological tools. Finally, one should certainly consider the use of prophylactic measures among those at high risk; however, one should not expect public-health benefits, in terms of decreased prevalence, but rather benefits to the individual.

Professor Smith: In identifying household contacts as a high-risk group, you are lumping together the contacts of PB with those of MB patients. Certainly the risk of leprosy is greater among the contacts of MB patients.

Dr Noordeen: This is true, but, because the proportion of PB patients in the community is generally greater than that of MB patients, there are as many patients among contacts of PB as among those of MB patients.