Annex 1

AGENDA: Scientific Working Group on Leprosy

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenter or Organizer</th>
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<tbody>
<tr>
<td>09:00-09:30</td>
<td>Welcome and introductions</td>
<td>C Morel, Director CPE</td>
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<td></td>
<td>Objectives and expected outcomes</td>
<td>H Remme</td>
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<tr>
<td>09:30-10:15</td>
<td>TDR’s research strategy in 2002-2005</td>
<td>C Morel</td>
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<td>10:15-10:30</td>
<td>Discussion</td>
<td>All</td>
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<td>10:30-10:45</td>
<td>Coffee</td>
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<td>10:45-11:15</td>
<td>Leprosy control as seen by the endemic countries</td>
<td>Kyew Nyunt Sein</td>
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<td>11:15-11:45</td>
<td>Leprosy control as seen by ILEP/ILA</td>
<td>WCS Smith</td>
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<td>11:45-12:00</td>
<td>Discussion</td>
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<td>12:00-12:20</td>
<td>Research needs for ensuring leprosy control beyond 2005 as seen by TAG</td>
<td>M Becx</td>
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<td>12:20-12:40</td>
<td>Present strategic directions for leprosy research in TDR</td>
<td>H Engers</td>
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<td>12:40-13:00</td>
<td>Discussion</td>
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<td>13:00-14:00</td>
<td>Lunch</td>
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<td>14:00-14:30</td>
<td>Mycobacterial genomics</td>
<td>S. Cole</td>
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<td>14:30-14:45</td>
<td>Discussion</td>
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<td>14:45-15:15</td>
<td>Chemotherapy and chemoprophylaxis of leprosy</td>
<td>Baohong JI</td>
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<td>15:15-15:30</td>
<td>Discussion</td>
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<td>15:30-15:45</td>
<td>Tea</td>
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<td>15:45-16:15</td>
<td>Leprosy transmission and epidemiological trends</td>
<td>P Klatser</td>
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<td>16:15-16:30</td>
<td>Discussion</td>
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<td>16:30-17:00</td>
<td>Eradication of leprosy? Future research needs</td>
<td>J Krahenbuhl</td>
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<td>17:00-17:30</td>
<td>Discussion</td>
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<td>18:00</td>
<td>Cocktail at WHO</td>
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Day 2 (Wednesday 27 November 2002)

Three break-out groups with presentations/discussion/recommendations (09:00 to 12:30; 14:00 to 17:30)
(each presenter listed after each topic for discussion has 15 minutes to address the “hot” issues and make suggestions/recommendations)

Note: Cross-cutting issues – RCS capacity building needs and research funding challenges – are to be addressed in all three groups

Room 1

Room 2

Room 3

WHO Headquarters, Salle A

Day 3 (Thursday 28 November 2002)

Presentation of group reports; discussion; draft recommendations
Rapporteur’s presentations of the three group reports and discussions:

08:30-09:15 Group 1: Transmission/test for infection/exit strategy
09:15-09:35 Discussion
09:35-10:20 Group 2: Pathogenesis/disability management/prevention
10:20-10:40 Discussion
10:40-11:00 Coffee
11:00-11:45 Group 3: Implementation research/constraints/sustainability
11:45-12:05 Discussion
12:05-12:30 General discussion
12:30-14:00 Lunch

General discussion and summing up; recommendations and action items:
14:30-15:45 General discussion (on points identified by chairpersons/rapporteurs of the three groups)
15:45-16:00 Tea
16:00-17:30 Draft recommendations and action items
17:30 Concluding remarks Chair of meeting
WHO Headquarters, Salle A

**Day 4 (Friday 29 November 2002)**

<table>
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<tr>
<th>Subgroup follow-up</th>
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<tr>
<td>(Dr Marijke Becx-Bleumink, Professor WCS Smith, Dr Douglas B Young)</td>
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<tr>
<th>TDR/TAG subgroup to finalize draft report and brief directors</th>
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<th>Lunch</th>
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<th>SWG meeting concluded</th>
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**Background documents provided to the participants**

- WHO Expert Committee on Leprosy (7th Report)
- Report on Third Meeting of the WHO Technical Advisory Group on Elimination of Leprosy, Brasilia, 1&2 February 2002
- TDR strategy for 2000-2005
- Strategic direction for research on leprosy
- Strategic emphases for tropical diseases research: article and matrix
Annex 2

LIST OF PARTICIPANTS:
Scientific Working Group on Leprosy
Temporary advisers

Dr Jens AAGAARD-HANSEN, Danish Bilharziasis Laboratory, Jaegersborg Allé 1D, DK-2920 Charlottenlund, Denmark.
Tel: +45 77 32 77 84
Fax: +45 77 32 77 33 E-mail: jah@bilharziasis.dk

Dr AO AWE, Department of Public Health, National TBL Control Programme, Federal Ministry of Health, Abuja, Nigeria.
Tel: +234 1 269 3018
Fax: +234 1 68 40 91
E-mail: aweayo@yahoo.co.uk

Dr Jaya Prasad BARAL, Department of Health Services, Ministry of Health, His Majesty’s Government of Nepal, Teku, Kathmandu, Nepal.
Tel: +977 1 262009
Fax: +977 1 248535
E-mail: kncvtbc@kncvtbc.nl

Dr Marijke BECX-BLEUMINK, Royal Netherlands Tuberculosis Association, Riouwstraat 7, PO Box 146, 2501 The Hague, The Netherlands.
Tel: +31 70 416 7222
Fax: +31 70 358 4004
E-mail: knctvbc@knctvbc.nl

Dr Elizabeth BIZUNEH, ALERT, PO Box 165, Addis Ababa, Ethiopia.
Tel: +251 1712552
Fax: +251 1711390
E-mail: leprosytb@telecom.net.et

Professor Patrick J BRENNAN, Department of Microbiology, B116 Microbiology Building, Colorado State University, Fort Collins, CO 80523-1677, USA.
Tel: +1 970 491 6136
Fax: +1 970 491 1815
E-mail: pbrennan@vines.colostate.edu

Dr Stewart Thomas COLE, Institut Pasteur, Unité de Genetique Moleculaire Bactérienne, 28 rue du Docteur Roux, F-75724 Cedex 15.
Tel: +33 1 45 68 84 49
Fax: +33 1 40 61 35 83
E-mail: stcole@pasteur.fr

Dr MJ COLSTON, (deceased) Division of Mycobacterial Research, National Institute for Medical Research, Medical Research Council, The Ridgeway, Mill Hill, GB-London NW7 1AA.
Tel: +44 181 959 3666 (ext. 2353/2354)
Fax: +44 181 913 8528
E-mail: mjc@nimr.mrc.ac.uk

Professor Hazel Marguerite DOCKRELL, London School of Hygiene and Tropical Medicine, Infectious and Tropical Diseases Immunology Unit, Keppel Street, London, United Kingdom. Tel: +44 207 927 2466
Fax: +44 207 637 4314
E-mail: hazel.dockrell@lshtm.ac.uk

Dr Thomas P GILLIS, Molecular Biology Research, National Hansen’s Disease Programs Laboratory, Louisiana State University School of Veterinary Medicine, Skip Bertman Dr, Baton Rouge, LA 70803, United States of America.
Tel: +1 225-578-9836
Fax: +1 225-578-9856
E-mail: tgillis@lsu.edu

Dr Vera Lucia GOMES DE ANDRADE, Rua General Glicério 82/704, Laranjeiras, Rio de Janeiro, CEP 22.245-120, Brésil.
Tel: +55 21 2558 2194
Fax: +55 21 534 3895
E-mail: andradev@bra.ops-oms.org

Dr MD GUPTE, National Institute of Epidemiology, Indian Council of Medical Research, Post Box 2577, Mayor VR Ramanathan Road, Chetpet, Chennai 600 031, India.
Tel: +91 44 8265308 / 8261642
Fax: +91 44 8264963
E-mail: nieicmr@vnsl.com

Professor Baohong JI, Bacteriologie et Hygiene, Faculté de Medicine Pitie-Salpetriere, 91 boulevard de l’Hopital, 75634 Paris, Cedex 13, France.
Tel: +33 140 77 97 46
Fax: +33 145 82 75 77
E-mail: baohong_ji@yahoo.com

Dr Vishwa Mohn KATOCH, Central JALMA Institute for Leprosy (ICMR), PO Box 101, Taj Ganj, Agra-282 001, India.
Tel: +91 562 331 756
Fax: +91 562 331 755
E-mail: jalma@cyberway.com

Dr Paul Richard KLATSER, Royal Tropical Institute, NH Swellengrebel Laboratory of Tropical Hygiene, Meibergdreef 39, Amsterdam, NL-1105, The Netherlands.
Tel: +31 20 566 5441
Fax: +31 20 697 1841
E-mail: p.klatser@kit.nl

Dr James L KRAHENBUHL, Laboratory Research Branch, National Hansen’s Disease Programs Laboratory, Louisiana State University School of Veterinary Medicine, Skip Bertman Dr, Baton Rouge, LA 70803 United States of America.
Tel: +1 225 578 9845
Fax: +1 225 578 9856
E-mail: jkrahe1@lsu.edu
Dr Ashok KUMAR, Directorate of Health Services, Nirman Bhawan, New Delhi 110011, India.
Tel: +91 11 331 7804
Fax: +91 11 331 8607
E-mail: ddgl@nb.nic.in

Dr Diana LOCKWOOD, Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK.
Tel: +44 171 927 2457
Fax: +44 171 637 4314;
E-mail: diana.lockwood@lshtm.ac.uk

Dr Celina Maria Turchi MARTELLI, Federal University of Goias Instituto de Patologia Tropical e Saude Publica, Sala 405, Rua Delenda Rezende de Mello, Goiania, GO, Brazil.
Tel: +55 62 202 0605
Fax: +55 62 261 6389 or 202 3066
E-mail: celina@iptsp.ufg.br

Dr Abraham MEIMA, Erasmus University Rotterdam, Department of Public Health Medical Decision Sciences, PO Box 1738, Rotterdam, NL-3000, The Netherlands.
E-mail: meima@mgz.fgg.eur.nl

Dr Elizabeth MOREIRA DOS SANTOS, DENSIP/ FIOCRUZ, Av. Brasil 4365 Manguinhos, Cx postal 926, CEP 21045-900, Rio de Janeiro, Brazil.
Tel: +55 21 2590 4712
Fax: +55 21 2590 9741
E-mail: endemias@ensp.fiocruz.br

Dr Alcino NDEVE, Ministry of Health, c/o WHO Representative, CP 377, Maputo, Mozambique.
Tel: +258 1 49 90 55
Fax: +258 1 49 19 90
E-mail: solange@oms-mz.org
(unable to attend)

Dr SK NOORDEEN, Leprosy Elimination Alliance, 1-A, KG Valencia, 57-First Main Road, Gandhinagar, Chennai 600020, India (9 Anna Avenue, B. V. Nagar Extension, Chennai 600 020).
Tel: +91 44 4456337
Fax: +91 44 4456338
E-mail: noordeen@eth.net

Dr Kin Than OO, Central Health Education Bureau, Department of Health Planning, Ministry of Health, 27 Pyidaungsu Yeiktha Road, Dagon,Yangon, Union of Myanmar.
Tel: +95 1 29 29 01
Fax: +95 1 29 05 81

Dr Tom HM OTTENHOFF, University Hospital Leiden, Department of Immunohaematology and Bloodbank, PO Box 9600, Leiden, Rijnburgerweg 10, Building 1, E3-Q, NL-2300 RC, The Netherlands.
Tel: +31 71 526 5128
Fax: +31 71 521 6751
E-mail: lhsecr@euromet.nl

Dr Gerson PEREIRA, Ministry of Health, Esplanada dos Ministérios, Bl. G – 5º andar, 70058-900 Brasilia DF, Brazil.
Tel: +55 61 321 1922
Fax: +55 61 312 6550
E-mail: gerson.fernando@saude.gov.br
(unable to attend)

Dr Elisabeth PEREIRA Sampaio, Fundação Oswaldo Cruz, Departamento de Hanseníase, Av. Brasil, 4365 – Manguinhos, 21045-900 Rio de Janeiro, Brasil.
Tel: +55 21 2598-4442
Fax: +55 21 2270-9997
E-mail: esampaio@gene.dbbm.fiocruz.br

Dr Maria Cristina Vidal PESSOLANI, Fundacao Oswaldo Cruz, Hanseniase Leprosy Laboratory, Av. Brasil, 4365 Manguinhos, 21045-900 Caixa postal, 926 Rio de Janeiro, Brasil. Tel: +55 21 2709997
Fax: +55 21 2709997
E-mail: cpessola@ioc.fiocruz.br

Dr Euzenir Nunes SARNO, Research and Technological Development, Oswaldo Cruz Foundation, Ministério da Saúde, Av. Brasil 4365, Manguinhos, Pavilhão Mourisco S.105, 21045-900 Rio de Janeiro, Brazil.
Tel: +55 21 2590 4712
Fax: +55 21 2590 9741
E-mail: euzenir@presidencia.fiocruz.br
(unable to attend)

Dr Kyaw Nyunt SEIN, Leprosy Control Programme, Department of Health, 36 Theinbyu Road, Yangon, Myanmar. c/o WHO Representative Tel: 951 212606;
Fax: +95 1 21 26 05, E-mail: whomm@undp.org or borraa.whomm@undp.org

Professor WCS SMITH, Department of Public Health, Medical School, Polwarth Building, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZD, United Kingdom.
Tel: +44 1224 553802
Fax: +44 1224 662994
E-mail w.c.s.smith@abdn.ac.uk
Dr Douglas B YOUNG, Centre for Molecular Microbiology and Infection, Flowers Building, Imperial College, London SW7 2AZ, United Kingdom.
Tel: +44 20 7594 3962
Fax: +44 20 7594 3095
E-mail: d.young@ic.ac.uk

Observer

Dr Richard SKOLNICK, Director, Center for Global Health, George Washington University, 2175 k. Street, Suite 810, Washington, DC 20037.
Tel: +1 703-264-9063
E-mail: iphrxs@gwumc.edu
(unable to attend)

Secretariat

Dr Carlos Morel, Director, TDR
Mr Erik Blas, Programme Manager, TDR
Dr Howard Engers, Leprosy Research Coordinator, TDR
Dr Gomes Melba, Functional Coordinator (a.i.), Intervention development and implementation research, TDR
Dr Ayo Oduola, Functional Coordinator, Basic and Strategic Research, TDR
Dr Hans Remme, Disease Research Strategy Coordinator, TDR
Dr Rob Ridley, Functional Coordinator, Product Research and Development, TDR
Dr Fabio Zicker, Functional Coordinator, Research Capability Strengthening, TDR
Dr Nevio Zagaria, Coordinator, Strategy Development and Monitoring for Eradication and Elimination, CPE
Dr Denis Daumerie, CPE/CEE (Leprosy group)
Dr Myo Thet Htoon, CPE/CEE (Leprosy group)
Dr Vijaykumar Pannikar, CPE/CEE (Leprosy group)
Dr Clovis Lombardi, PAHO/WHO Regional Advisor for Leprosy
Annex 3

WORKING PAPER: Social, psychological and behavioural research in leprosy
SOCIAL, PSYCHOLOGICAL AND BEHAVIOURAL RESEARCH IN LEPROSY

W Cairns S Smith, Peter G Nicholls
Department of Public Health, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK.

INTRODUCTION

Social, behavioural and psychological aspects of leprosy and its control have been relatively neglected areas in terms of research. However, in the past five years there have been clear signs of a change with more research being undertaken, more publications in the field and a greater emphasis in funding research using these methods. Leprosy Review commissioned a special issue (1) on the topic of social aspects in December 2000. There were workshops, papers, posters and seminars addressing research using social, behavioural and psychological methods throughout the International Leprosy Congress in Brazil, 2002.

The use of social and behavioural research methods is relevant across the spectrum of leprosy control activities and rehabilitation. This research approach is relevant to the issues of information, education and communication, and awareness of first symptoms. The approach is important in addressing help-seeking behaviours and contact with health care providers. There are psychological and behavioural dimensions to communicating the diagnosis and relationships with the family and community. Social behaviour is also relevant to adherence with treatment and prevention of disability and rehabilitation. Recent work is also focusing on issues of stigma and community behaviours and attitudes.

This paper selects areas where social, psychological and behavioural research methods can make a particular contribution: community awareness and attitudes to leprosy, first symptoms, help-seeking behaviour and delay in presentation, adherence with treatment, stigma and stigmatization, and socioeconomic aspects of rehabilitation. The following sections draw attention to what is known from research, highlighting the relevance and importance, and raise questions as to whether more needs to be done in implementing knowledge or further research.

COMMUNITY AWARENESS AND ATTITUDES TO LEPROSY

Information, education and communication (IEC) has been a key part of leprosy control activities for decades. Much of this activity has been conducted on a limited evidence base and there has little robust work on evaluating such interventions. The BBC Marshall Plan of the Mind Trust (MPM) initiatives in the last five years have been important developments that have also been evaluated in depth. The main objective of the evaluation was to gauge the changes in knowledge, attitudes and perceptions of the community regarding leprosy at the end of the year long media campaign. This whole aspect of leprosy control activities is critical to early case detection, early symptom reporting, and for changing community attitudes to leprosy and those affected by leprosy.

Social marketing approaches in leprosy have been developed and demonstrated to be effective in countries such as Sri Lanka (2). The programme encourages people with suspicious skin lesions to seek diagnosis and care, teaches health care providers to recognize leprosy and refer cases for treatment, and helps the general public to understand that leprosy is just a normal disease. The socially marketed product is multidrug therapy. This approach has changed community awareness, attitudes to leprosy, and improved early detection and treatment.

FIRST SYMPTOMS, HELP SEEKING BEHAVIOUR AND DELAY IN PRESENTATION

Over the past five years, a programme of research funded through the International Federation of Anti-leprosy Associations (ILEP) has used qualitative methods to explore delay in presentation, patient pathways to health care, and help-seeking behaviour. This work has included centres in India, Bangladesh, Malawi, Brazil and Paraguay. Similar research has been conducted in Nepal and Nigeria. The work shows important country and regional variations demonstrating that the factors are culture and context specific and that the solutions need to be similarly context specific. The work has lead to the production of guidelines to help leprosy control staff explore delay in presentation and start of treatment, which has consequences for transmission of leprosy and in addressing unacceptably high rates of impairments (3).

Perceived stigma associated with the diagnosis of leprosy may threaten self-esteem, security, identities and life chances, leading to concealment of the diag-
agnosis. In India, Bharath et al (4) have shown an association with psychiatric morbidity. In South Africa, Scott (5) reported that responses to the leprosy diagnosis included feelings of rejection, worthlessness, guilt, confusion, fear, grief and anger, with 11 of 30 patients interviewed reporting suicidal thoughts. In Brazil, De Oliveira (6) reported the response to diagnosis to include fear, disgust, loneliness, grief, aggressiveness, anger, family and social rejection. These reports draw attention to the potential for a significant psychological impact on people affected by leprosy. Is this an area sufficiently recognized or managed? What are the implications? For example, where the disease is suspected or diagnosed, this may restrict help-seeking actions and so contribute to delay.

Angel and Thoits (7) present a framework describing the impact of culture on the process of symptom recognition, labelling and help-seeking behaviour. First they suggest that people inherit from their cultures structured vocabularies of health and illness which limit the possibilities for the interpretation of physical and psychological states and structure help-seeking options. Second, they assert that these concepts of health and illness tend to be “over-learned”, to the extent that they acquire the status of unquestioned objective reality. Finally they suggest that the labels attached to symptoms or illnesses influence their evaluation and determine the actions taken in response to perceived deviations from physical or emotional normality. Thus the response to a disorder may be dependent on prior evaluation concerning its nature, severity, chronicity, cause, contagiousness, personal responsibility, prognosis, futility etc., with the consequence that people may delay seeking treatment for culturally undesirable disorders.

The literature includes many examples suggesting that such processes affect the response to leprosy. Neylan et al in Thailand (8) report that the response to illness differs according to demographic and personal factors, to physical and social factors, and to illness-related factors, specifically pain, disfigurement and stigma. Leprosy was perceived and experienced as a series of acute disorders not necessarily related to one another. The various theories of illness were instrumental in directing treatment choices that included indigenous healing practices. Other authors found similar complexity in responses to leprosy in Nigeria (9), Sierra Leone (10), Pakistan (11), Senegal (12) and Indonesia (13). Becx-Bleumink (14) highlights the implications for Ethiopia. She concluded that delay in presentation was a continuing problem, indicating that there are many undiagnosed patients in the community. Although the programme had been effective with respect to treatment, it had not been effective in regard to case detection.

**Research questions:**

1. What are the IEC and organizational interventions that have proven to be most effective in addressing delay/encouraging early detection? How can genuine community participation, rather than tolerance, be achieved? Where it has been achieved, what difference has it made?
2. Is there a more appropriate indicator than Grade 2 disability to draw attention to delay in presentation – i.e. a direct reflection of delay or a threshold value? Grade 2 disability effectively sanctions delays where there is no visible impairment.
3. What is the extent of the psychological impact of leprosy? Is there sufficient awareness of the social and psychological impact on the affected person? How should this be addressed?

**ADHERENCE WITH TREATMENT**

Social and psychological research and models of behaviour have now been applied to issues of treatment compliance and adherence. This has important implications for treatment completion rates and leprosy control programme quality.

Anandaraj (15) states that default in leprosy treatment is a reflection of underlying emotional, social and cultural resistance which go undetected and hence neglected. Thus the patient continues in a state of ill-health. He/she patient may spread not only the disease but also the negative attitude towards treatment. These factors counter efforts to control the disease and require attention. Anandaraj found that the most common reason stated for default was that individuals were not convinced of their disease (diagnosis). Low levels of awareness were associated with low motivation for cure.

From his work in Indonesia, Elissen (13) recognized that, while many patients presented voluntarily for treatment, there were still causes for concern about their social well-being. He observed a widespread sense of shame and strong self-discrimination, even among those whose symptoms had never been visible. This was illustrated by using different names, by visiting different clinics, and by giving wrong addresses. While accepting the diagnosis of leprosy, they gave their disease a vague and general name. Elissen concluded that something was lacking in the communication between patient and health worker. Treatment should extend beyond prevention...
and cure to alleviation of fear. Mull has similar findings about the inadequacy of the communication between staff and patient in Pakistan.

Heynders (16) reviews published reports finding poorer adherence among women, suggesting problems of access/freedom of movement. However, people who travel long distances from choice are found to be compliant. From her work in Nepal, Heynders found none of the variables assessed at registration to have value as risk factors for default. She did find that late return for the first three return visits was a risk factor for default. She then identified the need for prospective research to explore why some people default after 3-7 visits. What are the experiences that result in their default? She also draws attention to the very short time available to communicate messages that might prevent defaulting. Her conclusion stresses the complexity of compliance. Is the patient able to comply? How does the patient weigh the need to comply with other pressures they face in everyday life? Of basic importance is how the individual understands their disease and its treatment.

STIGMA AND STIGMATIZATION

In 1981, WHO recognized the need for research on stigma because of its significant relationship with transmission and control. The most recent description of stigma and the process of stigmatization in leprosy has been published by Bainson and van den Borne (17). This and other work draws attention to the extent and limitations of current knowledge. Bainson and van den Borne compare the physical and social course of the disease, describing the characteristics of leprosy that contribute to stigmatization and the responses they evoke. They identify five cognitive dimensions of disease that contribute to stigma:

1. Concealability – the ease with which signs of the disease may be hidden.
2. The course of the disease, whether it is progressive, chronic or incurable.
3. The disease’s aesthetic impact or perceived ugliness.
4. The origin, specifically whether responsibility may be attributed to the person affected.
5. The peril dimension, relating to the risk of infection or uncleanness.

They go on to describe how the adverse reactions of the community are expressed in fear, insensitivity and withdrawal, and devalue in the status of the person affected by leprosy. Eventually the affected person loses social status and becomes progressively isolated from society, family and friends. In the worst case, loss of the ability to work and social ostracism lead to dehabilitation, begging and hostility towards society. This reflects the situation described by Goffman (18), where stigmatized and stigmatizer each see the other as a threat.

The suggestion from the literature is that the impact of stigma is not only related to visible impairments. Scambler (19) asserts that where perceived stigma results in successful concealment, the disruption to peoples’ lives may be greater than that of enacted stigma. Rather than a simple relationship between disability and stigma, this suggests a complex relationship in which community attitudes may have an impact on everyone affected by leprosy, not just those individuals with visible signs of disability.

While there are reports suggesting that stigma is reducing, there is little evidence of a complete understanding of the processes of stigmatization. Bainson and Van den Borne call for more information about the relative importance of the cognitive dimensions in engendering stigma. They pose questions about how the characteristics of the individual and their symptoms influence the degree of stigma – the significance of age, sex, personality, and status or role within the community. There is the suggestion that integrated programmes may be more effective in reducing stigma than those treating leprosy as a separate disease. This is reinforced by the recent work reported by Arole (20).

Stigma is known to contribute to the stress of any illness experience and may be a barrier to help-seeking behaviour due to personal shame or fears of the negative attitudes of health workers. Morrison (21), who is primarily concerned with the impact of leprosy on women, affirms that this applies in leprosy. Bainson and Van den Borne recognize that stigma affects all aspects of leprosy control and is a threat to achieving the goal of elimination.

A workshop on stigma and the psychological consequences was held during the International Leprosy Congress in Brazil, August 2002. At this workshop, issues considered included defining the problem, the nature of stigma, the process and consequences of stigmatization, and recent research. A report of the workshop and the recommendations for research will be published shortly.

Current research includes the development of a Participation Scale to assess the extent of participation restrictions experienced by people affected by leprosy. Related qualitative research seeks to develop screening tools to identify people at risk of
participation restrictions and people experiencing restrictions.

Questions:
1. Are the five cognitive dimensions identified by Bainson and van den Borne correct? Do IEC activities address each of these adequately?
2. Are leprosy service providers sufficiently aware of the potential for self-stigmatization? How can self-stigmatization be addressed?

SOCIOECONOMIC ASPECTS OF REHABILITATION

The challenge facing organizations seeking to rehabilitate people affected by leprosy is to find a balanced approach which is caring yet encourages people to manage their own lives in the wider community. The attitudes of family and community present a further challenge in formulating an appropriate response. Arole (22) identified three key principles for rehabilitation work in leprosy:

1. A recognition of the broad impact of leprosy on the individual – physical, psychological, social and economic.
2. Responsiveness to the concerns of individuals affected by leprosy, resulting in an approach that ensures their participation and restores dignity, thereby promoting empowerment and self-respect.
3. Responsiveness and involvement of the families and communities affected by leprosy. Members of the family and the community have an important role to play in rehabilitation.

While local issues and priorities are important, the Arole principles need to be reflected in objectives to restore dignity, reduce stigma, promote social integration and improve economic status. Projects will work for greater community involvement and give more attention to groups with special needs, specifically children, older people and women.

The preferred approach (23) to rehabilitation is participatory, with those directly affected playing a central role. Unless people participate and own the process, they will not be fully committed to it. This extends to people directly affected, their families and communities. Effective rehabilitation requires communication and cooperation between all those providing care. The principle of sustainability requires that activities bring lasting benefit. The principle of integration requires an end to providing independent leprosy rehabilitation services, and the full integration of such services within the compass of community based rehabilitation (CBR). Gender sensitivity and sensitivity to special needs, for example the needs of children, are also a priority. Such programmes encompass an advocacy role. They bring further implications for organizational structure, communication, leadership and decision-making. Guidelines for socioeconomic rehabilitation have recently been published (24) and widely disseminated in a number of languages.

Research priorities focus largely on the need to define best practice. To what extent have current programmes adopted this approach? What are the organizational success factors? What specific difficulties are encountered in this approach? There are broader questions too. What is the extent of the rehabilitation problem? How closely is it associated with disability? What are the specific rehabilitation needs? Are existing CBR programmes ready to extend their services to people affected by leprosy?

CONCLUSIONS

Social behavioural aspects have been under-researched. An increasing volume of work is now being undertaken on socioeconomic rehabilitation. Application of behavioural sciences has much to contribute to leprosy control through work on the effectiveness of models of IEC, symptom recognition and help seeking behaviours, and adherence with treatment. Earlier case detection and more complete treatment will lead to better leprosy control. Quantitative methods can only take us so far; qualitative approaches need to be used to make significant improvements to the quality of leprosy control.

References


Annex 4

WORKING PAPER: Chemotherapy and chemoprophylaxis of leprosy
CHEMOTHERAPY AND CHEMOPROPHYLAXIS OF LEPROSY

Baohong Ji
Bactériologie et Hygiène, Faculté de Médecine Pitié-Salpêtrière, Paris, France

CHEMOTHERAPY

Newer generation MDT regimens

After 2005, which is the new target date for global elimination of leprosy, the disease will still exist and new patients will continue to emerge, but control programmes may be significantly weaker. Under this very complicated situation, newer chemotherapeutic regimens that are more effective and operationally less demanding are required (1). To develop newer generation MDT regimens, powerful bactericidal drugs against M. leprae are needed. Previous experience (2) demonstrated that screening of existing compounds is the only cost-effective way to develop drugs for leprosy, and should be encouraged. The most productive approach is to screen compounds that display powerful activity against either a wide spectrum of gram-positive microorganisms in general or cultivable mycobacterium in particular, or that exhibit pharmacokinetic properties more favourable than those exhibited by the member of the class presently employed for treatment of leprosy (3).

The discovery of a series of new drugs (2) with promising bactericidal activity against M. leprae has made possible the formulation of newer MDT regimens. A highly desirable new regimen is one that would permit all of the components to be administered once monthly under supervision, which would significantly reduce the risk of emergence of rifampicin resistance caused by irregular administration of the daily dapsone-clofazimine component, and would also simplify the treatment. The combination of rifampicin-ofloxacin-minocycline (ROM) is the first fully supervisable, monthly administered regimen (4), and the efficacy of multiple monthly doses for treatment of MB and PB leprosy has been tested in field trials in three different countries (5). Recent findings from mouse experiments indicate that rifapentine and moxifloxacin are significantly more bactericidal, respectively, than rifampicin and ofloxacin, and that the combination rifapentine-moxifloxacin-minocycline (PMM) is far more bactericidal than the ROM combination (3). The efficacy of PMM is currently being compared with that of ROM in a short-term clinical trial among lepromatous leprosy patients.

After the success of single-dose ROM for the treatment of single-lesion PB leprosy (6,7), the possibility of treating multiple-lesion PB leprosy with single-dose ROM is being tested in India (8). To accumulate more reliable information, additional trials are needed and post-treatment follow-up should be longer. If the results of the trials demonstrate that single-dose ROM or PMM display therapeutic results in all PB leprosy similar to those of the standard MDT regimen, this will revolutionize chemotherapy for PB leprosy and save significant resources which can be used in other important activities.

A common regimen for PB and MB leprosy

A common regimen for the treatment of both PB and MB leprosy is desirable. However, because the size of the bacterial populations and the underlying immunological responses are so different between PB and MB leprosy, the requirements for chemotherapy, especially the number of drugs and duration of treatment, are bound to be very different; a common regimen would appear likely to result in over-treatment of PB leprosy or under-treatment of MB leprosy. Recently, the WHO Technical Advisory Group (TAG) on Elimination of Leprosy proposed “implementation of a uniform six-months MB/MDT regimen for all patients” (9). This caused severe criticism from many leprosy workers because there is no information on the five-year relapse rate, which is a key parameter in assessing the long-term efficacy of MDT among MB patients who have received 12-months of MDT. Thus there is no justification to test the possibility of further shortening the duration of MDT for MB leprosy to six months. Currently, a research protocol on a uniform MDT (U-MDT) regimen for all types of leprosy (10) is being widely circulated. The project will involved 2500 MB and 2500 PB patients, who will be examined, clinically only, for evidence of relapse up to five years after completion of treatment. The major weaknesses of the protocol are that:

- Because several million PB cases have already been treated successfully with six-month two-drug MDT, it is not necessary to include PB patients in the trial (half the resources could be saved by not including PB patients).
- The definition of MB leprosy (10) is too broad and includes many cases who are in fact PB leprosy from the bacteriological and chemotherapeutic points of view (11).
- The definition of relapse (10) is too vague and it...
will be difficult to distinguish relapse from leprosy reactions. More important is that, because skin-smear examination, one of the key indicators for diagnosing MB relapse (12,13), is not employed, the quality of diagnosing MB relapse will be compromised.

• Because the average incubation period of MB relapse after treatment with rifampicin-containing regimens is at least five years, patients should be followed up for more than five years after stopping treatment, otherwise only part of the relapse cases will be detected.

The magnitude of MB relapse after MDT is not yet ascertained, and the possible existence of a higher risk subgroup of MB leprosy patients cannot be ruled out. The MB relapse rate has been reported to be very low, about 0.1%, among patients treated with MDT for 24 months or longer in routine programmes (7). Because of the very low relapse rate, post-MDT surveillance (11) was discontinued at the same time as the duration of MDT for MB leprosy was progressively shortened. However, results from the Institut Marchoux (13) in Bamako (Mali) and the Central JALMA Institute (14) in Agra (India), demonstrate the existence of a subgroup of MB patients with a strong tendency to relapse after 24 months of MDT, as high as 4-7 per 100 patient-years among patients with an initial bacterial index (BI) (i.e. the average BI of 4 to 6 sites before MDT) of $\geq 4.0$, far higher than among patients with an initial BI $< 4.0$, suggesting that high initial BI is the most important risk factor for MB relapse. In addition, relapses occurred late, on average at least 5 ±2 years after stopping treatment (12,13). Because there is no easy explanation for the deep disagreements regarding the magnitude of MB relapse after 24-month MDT, and because of the possible existence of a higher risk subgroup of MB patients who are prone to relapse, it is necessary to collect more information from long-term follow-up of MB patients after completion of MDT.

Since 1998, the great majority of MB patients have been treated with MDT for only 12 months (15-17). However, there is no information about the five-year relapse rate. Apparently, determination of the relapse rate after 12-month MDT is highly relevant, and should be considered as a top priority for research.

**Drug resistance**

Emergence of rifampicin resistance would create tremendous difficulty for the treatment of individual patients, and its widespread dissemination would pose a serious threat to achieving the final goal of leprosy control. Previous experience (18) indicates that rifampicin resistance could emerge rather rapidly in a non-negligible proportion of patients whose treatment regimens were inappropriate. Although more than 10 million leprosy patients in the world have completed treatment with MDT, and rifampicin-resistant leprosy has not been reported among these patients (7,17), one must be cautious in interpreting the findings, because:

• post-MDT surveillance for relapse has been discontinued
• during the last decade, rifampicin-susceptibility testing has rarely been carried out, and the results are not always dependable.

Therefore, the current situation regarding rifampicin-resistant leprosy is unclear. Before the problem becomes so frequent that it threatens leprosy control, solid information about its magnitude should be collected from different parts of the world.

Due to administrative, financial and technical reasons, it is no longer feasible to undertake a relatively large-scale survey of rifampicin-resistant leprosy by mouse footpad technique. On the other hand, because the available results of polymerase chain reaction (PCR)-based DNA sequence analysis of the rpoB gene of *M. leprae* were in full concordance with those of the susceptibility testing carried out in the mouse footpad system (19-22), the method could be applied as a cost-effective alternative technique for monitoring rifampicin-resistant leprosy. Although more studies on the association between rifampicin resistance and rpoB mutation, particularly at positions other than Ser531 or His526, should be pursued, it is reasonable to conclude that, based on identification of rpoB mutation with amino acid substitution of Ser531 or His526, this approach may lead to the diagnosis of a good 80% of rifampicin-resistant strains of *M. leprae* (22,23).

Regarding a survey of rifampicin-resistant leprosy, as a first step, this should focus on acquired or secondary rifampicin resistance, which probably exists mostly among MB patients who have relapsed after completion of MDT. Therefore a certain proportion of MB patients should be systematically examined both clinically and bacteriologically after completion of MDT (23). Such a survey may encounter significant difficulties, especially operational difficulties in the field, but it is probably the only way to define the magnitude of the threat to leprosy control presented by rifampicin resistance.

Recently there have been reports of multidrug-resistant *M. leprae* (22,24-26). Besides resistance to rifampicin, the strains were also resistant to at least one
more drug other than dapsone, including ofloxacin (22,25,26) and sparfloxacin (25). Although the number of multidrug-resistant strains remains small, their occurrence is indeed an alarm bell and must be closely scrutinized.

**Accompanied MDT**

Adherence (or compliance) of patients is crucial to the success of treatment. Poor adherence to self-administration of treatment is a common behavioural problem among patients suffering from chronic diseases (27,28), including TB (29-31) and leprosy (32-34). It has been well documented that the treatment behaviour of most patients is unpredictable (35). Among leprosy patients, the magnitude of poor adherence to dapsone self-administration became apparent only when the urinary dapsone/creatinine ratio method (36,37) for monitoring ingestion of dapsone was established and tested in many leprosy control centres. A review of the results of urine testing concluded that only about half of the prescribed dapsone was actually ingested (32).

Furthermore, studies also revealed that mere attendance at the clinic or collection of drugs by leprosy patients was not a reliable indicator of regular drug self-administration (38), as had been observed among TB patients (29). With MDT, only 70% (38) to 80% (39) of patients were found to adhere to self-administration of the daily component of MDT regimens when the monthly component was administered under supervision, suggesting that adherence to the self-administered component of MDT regimens remains poor.

Although a number of alternative means to improve adherence exist (40), supervised (or directly observed) administration is the only proven way to ensure that a patient receives treatment with the correct drugs, in the correct dosage, at the correct intervals (41,42). Based on experience with supervised administration of TB treatment, one of the principles of the MDT regimens recommended by the WHO Study Group on Chemotherapy of Leprosy for Control Programmes was that the monthly component of the regimens – rifampicin alone for PB leprosy and rifampicin plus a supplementary larger dose of clofazimine for MB leprosy – should be administered under the supervision of a health worker (11). By the time of the seventh meeting of the WHO Expert Committee on Leprosy in 1997, more than 8.4 million leprosy patients had completed treatment with MDT in which the monthly component was administered under supervision (7).

However, to accelerate the leprosy elimination process, recently the WHO leprosy programme and its TAG have changed dramatically their position on supervised therapy. They concluded that, after the first dose of MDT, “supervision of the subsequent monthly component of MDT regimens is no longer essential” (9). Further, based on this conclusion, they recommended large-scale implementation of accompanied MDT (AMDT) (9), which refers to a policy that patients are provided the entire supply of MDT drugs – six months of medication for a PB case and 12 months for a MB case – at the time of diagnosis, while choosing someone close to them to accompany them with their treatment (16,17). Some members of TAG even believe that monthly supervision “hampers integration and is not user-friendly”, and that “providing patients with a full course of treatment on their first visit is both patient- and staff-friendly and will improve compliance” (9).

The recommendation to discontinue supervision of monthly drug administration appears to be a simple solution to the difficult problem of implementing supervised therapy, but the solution is obviously wrong. Not only have WHO and its TAG confused the operational difficulties of implementing supervised therapy with the technical justifications for discontinuing its application, and ignored completely the fact of poor adherence of patients to self-administered medication, but, more importantly, the recommendation lacks evidence-based justification. Furthermore, the recommendation also neglects the importance of regular contact between health workers and leprosy patients, which facilitates early detection and management of various complications, crucial for prevention of impairments.

Experience with AMDT has yet to be documented. It is unclear whether this approach has ever been tested in the field and the whole concept of the AMDT policy is extremely vague. For example, it is unclear:

- Whether AMDT is to be applied as a routine or only in special situations.
- Who may be chosen to supervise the patient’s treatment – health workers, community volunteers, or family members of the patients? What is the order of preference? In TB, opinions differ regarding supervision by family members, which is common in DOT programmes; most workers believe that supervision by family members is less reliable and even ineffective (43-45), and some national TB programmes, such as that of India, have clearly defined the DOT supervisor as someone outside the family (45).
- How AMDT “helps” (17) a patient to complete a full course of treatment. Is the person who
accompanies expected to observe the patient swallow each monthly dose of treatment?

- How to train and supervise AMDT by health workers.

Although a number of essential questions about AMDT remain to be answered, AMDT has been rapidly and intensively implemented in the field. In an increasing number of national programmes, the total quantity of MDT blister packs is provided at the time of diagnosis to all patients, including those patients living rather close to treatment centres, but the AMDT supervisor either does not exist or lacks training and supervision. Consequently, one cannot be certain that the MDT drugs are indeed self-administered by the patients. Can so reckless a policy be termed “patient- and staff-friendly”?

In conclusion, with large-scale implementation of AMDT, the quality of treatment is a matter of real concern. Without a guarantee of quality, quantitative achievement or a declaration of leprosy elimination is meaningless. To avoid building the leprosy elimination monument on sand, we must not consider only the short term. Every effort should be made to maintain and improve the basic quality of diagnostics and treatment in the field; these tasks are as important as increasing the accessibility of MDT to the patients. Therefore, it is time to replace wishful thinking with evidence-based practice, and discontinue the implementation of AMDT as a routine in the field.

Defaulter

A defaulter has been defined as a patient who has not collected MDT treatment for 12 consecutive months (15). This is a purely arbitrary decision. It has been recommended that defaulters who cannot be retrieved be removed from the register (15), and that the register should be updated at least annually (15,16). Consequently, removing defaulters from the register has become one of the important mechanisms to reduce the leprosy prevalence rate.

However, a significant proportion of so-called defaulters have not really disappeared from the community, so indiscriminately removing them from the register, as if they never existed, is not a reasonable solution. First of all, every effort should be made to prevent the absentee becoming a defaulter. A serious attempt should be made to trace absentees, beginning at the time of their first absence. Regarding those who have already become defaulters, depending on the reason for default, different actions should be taken. Those who have died or permanently migrated from the country should be removed from the register, whereas those who have moved out of the district or are taking treatment elsewhere should be transferred rather than removed from the register. For the remaining defaulters, whatever the reason for default, as long as they continue to live in the district and have yet to complete the full course of MDT treatment, by definition they are “cases” (15,16) and may continue to be sources of transmission. Instead of being removed from the register, the programme should encourage the health workers, with the assistance of the local community, to actively retrieve all defaulters.

When the defaulter returns to the health centre, the current policy is that a new course of MDT will be given only to those who have active skin lesions, new nerve involvement, or signs of leprosy reaction (15). The justification of such policy is arguable because it is difficult for general health workers to deal with the criteria concerning signs of activity, particularly among MB patients close to the lepromatous end of the spectrum. The policy also creates confusion with regard to the duration of MDT, as if it depends only upon the signs of activity. Because, by definition, a defaulter has not completed MDT treatment, it seems more reasonable that a new course of MDT should be given to every ex-defaulter after retrieve or return.

CHEMOPROPHYLAXIS OF LEPROSY (46)

Recently, because the new case detection rate has not diminished following implementation of MDT, there has been renewed interest in preventive therapy for leprosy.

Regimens for chemoprophylaxis in leprosy

The regimen should be highly effective for treatment of leprosy, relatively non-toxic, low cost, and preferably orally administered. It is important to point out that the target population is healthy and asymptomatic, sub-clinically infected, does not need or accept to be treated as leprosy patients, and may not tolerate side effects of treatment which are normally tolerated by leprosy patients.

Both dapsone (47-49) and acedapsone (51-53) have been found capable of providing significant, about 50%, protective effect against leprosy, but it is unclear whether sulfone may prevent the occurrence of lepromatous, or skin-smear positive, MB leprosy. If today there is a need to apply chemoprophylaxis in leprosy, sulfone is no longer appropriate because dapsone-resistant M. leprae has become a widespread phenomenon since the end of the 1970s.
(11) and also, because the duration of treatment has to be long due to the weak bactericidal activity of dapsone, there would be tremendous operational difficulties, especially poor adherence.

In view of a number of facts and assumptions (46), two principles are proposed in developing newer generation prophylactic regimens:  
- the treatment should be administered in not more than a single dose 
- the regimen should always contain rifampicin.

Two different regimens have recently been tested for chemoprophylaxis: a single dose of the combination rifampicin-ofloxacin-minocycline, or ROM (54), and a single dose of rifampicin, either 25 mg/kg body weight (55) or 10 mg/kg (56). Because a single dose of ROM appears to be no more bactericidal than a single dose of rifampicin alone (4), and furthermore, the small bacterial population in a subclinically infected subject does not require an accompanying drug to prevent selection of rifampicin-resistant mutants, the addition of ofloxacin and minocycline to rifampicin will unnecessarily increase the cost and risk of side effects. Therefore, it seems more reasonable to give a single dose of rifampicin alone for chemoprophylaxis.

In the only published trial of rifampicin chemoprophylaxis, a single dose of rifampicin alone, at a dosage of 25 mg/kg, was tested in Southern Marquesas Island (55). After ten years of follow-up, it was concluded that the protective effect was only 35-40% (55).

Up to now, more than ten million leprosy patients have been treated with MDT containing multiple monthly doses of 600 mg rifampicin, and have tolerated the treatment well. Nevertheless, the effectiveness and tolerance of the two different dosages of rifampicin, i.e. of 1500 mg (approximately 25 mg/kg/dose) versus 600 mg (approximately 10 mg/kg/dose), have not been directly compared in the same clinical trial. Until there is clear evidence that a single 1500 mg dose of rifampicin is more bactericidal than, and as well tolerated as, a 600 mg dose, rifampicin should be administered for chemoprophylaxis in a dose of 600 mg.

With respect to the potential risk for emergence of rifampicin resistance following chemoprophylaxis with a single dose of rifampicin, the small bacterial population of a subclinically infected person is unlikely to include a single rifampicin-resistant mutant, and therefore the risk of rifampicin resistance is probably negligible. On the other hand, if, for whatever reason, the bacterial population size is larger than expected, and even includes rifampicin-resistant mutants, the emergence of rifampicin resistance is still very unlikely because a single dose of rifampicin is insufficient to select resistant mutants, as has been shown by the relapse of MB patients after a single dose of rifampicin (12,18).

**Limitations of chemoprophylaxis in leprosy**

The epidemiological profile of leprosy indicates that, to prevent a single case of leprosy, hundreds or even thousands of subjects need to be treated (50). Whatever regimen is applied, if trying to cover an entire population with chemoprophylaxis, the direct and indirect costs will be prohibitively high with tremendous operational difficulties, whereas the yield will be rather limited (50,54,55), so chemoprophylaxis is unlikely to be applied as a routine method for leprosy control. If chemoprophylaxis is confined only to a high-risk sub-population, i.e. to household contacts of leprosy patients, the benefit will be only 15% (50) because the contribution of household contacts to the total number of new cases in a population is no more than 30% and the efficacy of chemoprophylaxis under routine conditions is 50% (bear in mind that the maximum achieved efficacy of chemoprophylaxis has been no more than 75% in ideal conditions). Thus, from the leprosy control point of view, confining chemoprophylaxis to high-risk sub-populations represents only a very modest contribution. On the other hand, because chemoprophylaxis has shown significant protective effect among high-risk individuals (47-50), it may offer individual benefits in situations of exceptionally high risk. Nevertheless, the effect of chemoprophylaxis will most likely be transitory and, after the effect has waned, the high-risk individual could immediately be re-infected with M. leprae as long as transmission persists. Therefore, the index case and all known leprosy patients in the local community must be covered by chemotherapy before chemoprophylaxis is begun.

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