

W H O T e c h n i c a l R e p o r t S e r i e s

WHO Expert Committee on Leprosy

Eighth report

*This report contains the collective views of an international group of experts and
does not necessarily represent the decisions or the stated policy of the World Health Organization*



**World Health
Organization**

WHO Library Cataloguing-in-Publication Data

WHO Expert Committee on leprosy: eighth report.

(WHO technical report series ; no. 968)

1. Leprosy - epidemiology. 2. Leprosy - prevention and control. 3. Leprosy - therapy.

I. World Health Organization. II. WHO Expert Committee on Leprosy (2010: Geneva, Switzerland).

III. Series.

ISBN 978 92 4 120968 7

(NLM classification: WC 335)

ISSN 0512-3054

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Printed in Italy

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WHO Expert Committee on Leprosy

Geneva, 12–19 October 2010

Members

Dr Y.A. Al-Qubati, Taiz University School of Medicine, Taiz, Yemen (*Rapporteur*)

Dr M.L.W. de Oliveira, Medical Professor, Rio de Janeiro Federal University, Rio de Janeiro, Brazil

Dr M. De Palma Caldas, Director, National Program for Control of Tuberculosis and Leprosy, Ministry of Health, Luanda, Angola

Professor P.E.M. Fine, Communicable Disease Epidemiology, Infectious and Tropical Disease Department, London School of Hygiene and Tropical Medicine, London, England

Dr M.D. Gupte, Retired Director, National Institute of Epidemiology, Indian Council of Medical Research, Chennai, India¹

Dr H.J.S. Kawuma, Medical Advisor, German Leprosy Relief Association, Kampala, Uganda

Dr T. Mori, Director Emeritus, Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Kiyose, Tokyo, Japan

Dr H. Sansarricq, Former Head, Leprosy Programme, WHO, Geneva, Switzerland

Professor W.C.S. Smith, Head, Department of Public Health, Medical School, University of Aberdeen, Aberdeen, Scotland (*Chairman*)

Professor G. Zhang, Deputy Director, Institute of Dermatology and National Center for Leprosy Control, Nanjing, China

Temporary advisers

Professor P.J. Brennan, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO, USA

Professor S. Cole, Global Health Institute, Department of Immunology, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Professor J.H. Grosset, Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Dr S.K. Noordeen, Former Director, Action Programme for Elimination of Leprosy, WHO, Geneva, Switzerland

¹ Unable to attend.

Mr J. Ramirez Jr., USA Coordinator and Board Member of International Association for Integration, Dignity and Economic Advancement (IDEA) and American Leprosy Missions, Houston, TX, USA

Representatives of other organizations

International Federation of Anti-Leprosy Associations (ILEP)

Mr D. Soutar, General Secretary, International Federation of Anti-Leprosy Associations, London, England

International Leprosy Association (ILA)

Dr M. Virmond, President, International Leprosy Association, Bauru, Brazil

Representative of Mr Y. Sasakawa, WHO Goodwill Ambassador for Leprosy Elimination

Professor K. Kiikuni, Chair, Sasakawa Memorial Health Foundation, Tokyo, Japan

Secretariat

Dr M.T. Htoon, Team Leader, WHO Global Leprosy Programme, WHO Regional Office for South-East Asia, New Delhi, India (*Secretary*)

Dr V. Pannikar, Temporary International Professional, WHO Global Leprosy Programme, WHO Regional Office for South-East Asia, New Delhi, India

Declarations of interest

Members of the WHO Expert Committee on Leprosy reported the following:

Dr Y.A. Al-Qubati reported that he provides supervision to the Leprosy Control Programme of Yemen. For these services, he receives an honorarium from the German Leprosy and TB Relief Association (GLRA), which is a nongovernmental organization.

Professor S. Cole reported that, through his previous employment at Institut Pasteur, he is a named inventor on a patent for antimycobacterial compounds that have antileprosy activity in a murine model. The patent in question has been licensed to the company Alere Technologies GmbH, for whom Professor Cole acts as a consultant, with an annual income of approximately € 20 000. He currently teaches leprosy-related subjects at the Ecole Polytechnique Fédérale de Lausanne.

Professor P.E.M. Fine reported that he is on the Editorial Board of the journal *Leprosy Review*. He also reviews grants related to leprosy research for the Order of Malta, for which he has received an honorarium payment for the past four years.

Professor J.H. Grosset reported that he is a member of the Scientific and Medical Commission of Association Raoul Follereau of France as well of the United States of America/Japan Panel for Leprosy and Tuberculosis Research. He receives no remuneration for either position.

Dr H.J.S. Kawuma reported that he works as a Medical Adviser in Uganda for the German Leprosy and TB Relief Association (GLRA), which is a nongovernmental organization.

Dr S.K. Noordeen reported that he was involved in the preparation of the background documents for this meeting under an Agreement for the Performance of Work (APW) with WHO; this APW expired on 10 October 2010.

Mr J. Ramirez Jr reported that he serves as Managing Editor of *The Star*, an international magazine put together by persons affected by leprosy. He also serves as the United States of America Coordinator for the International Association for Integration, Dignity and Economic Advancement (IDEA), an organization comprising primarily persons affected by leprosy. He receives no remuneration for either position.

Professor W.C.S. Smith reported that he is President of the Leprosy Mission International and Chair of the Technical Commission of the International Federation of Anti-Leprosy Associations. He receives no remuneration for either position.

1. Introduction

The WHO Expert Committee on Leprosy held its eighth meeting in Geneva, Switzerland, from 12 to 19 October 2010. Opening the meeting on behalf of Dr Margaret Chan, WHO Director-General, and Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia Region, which hosts the Global Leprosy Programme (GLP), Dr Hiroki Nakatani, Assistant Director-General, conveyed the appreciation of Dr Chan and Dr Samlee for the gracious support being provided for GLP by WHO partners and experts.

Dr Nakatani noted the progress made towards elimination of leprosy since the Committee's previous (seventh) meeting in 1997. He recounted the catalytic role played by World Health Assembly resolution WHA44.9 (1991) (1) in pushing forward the leprosy agenda. The commitment to eliminate leprosy was reiterated by the World Health Assembly in 1998 through resolution WHA51.15 (2), and the elimination target was reached globally at the end of 2000 (3). Since the introduction of multidrug therapy (MDT) in 1981, an estimated 15 million patients have been cured and disabilities have been prevented in some 2–3 million individuals (4). Such an achievement, Dr Nakatani stated, had been made possible by the unique partnership between governments, communities, WHO, academia, industry and nongovernmental organizations (NGOs). Progress in the elimination of leprosy had been achieved through the synergistic efforts of all the supporting organizations.

It was acknowledged that, despite significant progress in controlling the disease and reducing the disease burden, much still remained to be done to sustain the gains and further reduce the impact of leprosy, especially in terms of its physical, mental and socioeconomic consequences for those affected and for their families.

Five-year initiatives for the elimination of leprosy were set out in WHO publications of 2000 (5) and 2005 (6); the most recent initiative – *Global strategy for further reducing the disease burden due to leprosy 2011–2016* – was published in 2009 (7). The emphasis in these strategies has shifted to reducing the occurrence of impairments and disabilities due to leprosy and to ways of ensuring the sustainability and quality of leprosy services. The strategies have included such specific issues as gender equity and human rights and initiatives to reduce the stigma and discrimination faced by people affected by leprosy and their families.

The purpose of this eighth meeting of the Expert Committee was:

- to analyse the global leprosy situation;
- to review the current status of developments in areas such as the treatment of leprosy and its various complications;

- to consider the results of research and experience in leprosy control since the previous meeting and to review existing indicators of progress in order to determine whether better indicators could be introduced;
- to advise on technical and operational issues relating to efforts aimed at further reducing the burden due to leprosy.

2. Leprosy in the world

Data on leprosy are reported to WHO routinely by most countries, except those of the European Region, and published annually in the *Weekly Epidemiological Record* (WER) (8). While such data are useful in providing a broad picture of leprosy patterns and trends, their interpretation is made difficult by operational differences between different national programmes and the fact that the data cover different time periods.

In the past, the emphasis has been on prevalence data – that is, data on the numbers of cases registered for treatment at the beginning of the year. Because of the long duration of treatment, prevalence was considered an appropriate measure, as it reflected the burden on health services. Starting in the early 1980s, prevalence declined dramatically throughout the world as a consequence of the shortened treatment regimens that followed introduction of MDT (9). Differences in treatment duration between countries, as a result either of different programme policies or of different proportions of multibacillary (MB) cases (which require longer treatment than paucibacillary (PB) cases), have complicated the comparison of prevalence data between countries.

More recently, the emphasis has shifted to case detection, as this provides a more appropriate measure of recent transmission and current epidemiological circumstances. Case-detection statistics are useful for measuring trends over time provided that detection and registration policies remain constant. However, recent aggressive case-finding in many countries with higher leprosy burdens has complicated the interpretation of trends. The fact that data from some low incidence countries may be influenced by an appreciable proportion of cases occurring in immigrants provides a further challenge: these cases do not reflect autochthonous (local) transmission and may or may not be included in national statistics.

Nevertheless, several patterns are clear. The disease remains endemic in all countries of the African and South-East Asia regions and in most countries of the Eastern Mediterranean Region. In the Region of the Americas, autochthonous leprosy is found in all countries with the exceptions of Canada, Chile and several island countries of the Caribbean. In the European Region, although data are not transmitted to WHO, autochthonous leprosy is known to persist at low levels in several southern and eastern European countries but seems to have disappeared from much of the northern and western part of the continent. In the Western Pacific Region, the disease persists in most large countries apart from New Zealand and with the exception of some small island nations. There is some evidence that transmission may have stopped in Japan, although small numbers of autochthonous cases still appear in older individuals (8). Heterogeneity in leprosy frequency and clinical manifestations between populations is a prominent feature of the disease.

2.1 Assessment of global data

Several broad trends over the past 30 years are evident. The first is the tremendous decline in registered prevalence since 1980, in all countries, which reflects the shift from long-term dapsone monotherapy to shorter MDT regimens. This change was initiated by the WHO Study Group recommendation in 1981 (9) and was achieved through aggressive implementation of MDT in all countries during the 1990s. It has resulted in a major decline in the burden of leprosy on health services in endemic communities. The second broad trend relates to incidence. Case-detection numbers and rates have fallen in almost all countries, reflecting both improvements in socioeconomic conditions and the effects of leprosy programmes. It is important to identify and enhance those measures that have been most successful in bringing about these falls. The third trend is more difficult to demonstrate on the basis of available data but relates to the decline in numbers and proportions of cases with disabilities among newly diagnosed patients. There are only rough estimates of the total number of individuals with leprosy-attributable disabilities alive today (4).

2.2 Global leprosy situation in 2010

A total of 141 Member States submitted reports to WHO at the beginning of 2010: 38 countries from the African Region, 36 from the Region of the Americas, 10 from the South-East Asia Region, 22 from the Eastern Mediterranean Region and 35 from the Western Pacific Region (8). These data are shown, by WHO region, in Table 1, which reveals considerable heterogeneity at the regional level, with highest numbers and rates in the South-East Asia Region. At the beginning of 2010, the global registered and reported point prevalence was 211 903 cases; during 2009, 244 796 new cases were detected.

2.3 New case detection

The reported trends in new case detection from 2000 to 2009 are shown in Table 2, by WHO region. Decline was evident in all regions, in particular in the African and South-East Asia regions. These trends were influenced by changes in case-detection policies and aggressive case-detection efforts in some large countries in the early years of this century. Figure 1 shows the case-detection rates reported for 2009 for all countries that provided data to WHO: geographical variation is clear.

2.4 Trends in case detection

Table 2 shows that the global decline in case detection was dramatic (about 58%) during the period 2000–2005 and much more limited (about 18%)

Table 1
Registered prevalence of leprosy and number of new cases detected, as reported by WHO region (excluding the European Region), 2010

WHO region	Registered prevalence ^a (beginning of 2010)	New cases detected ^b during 2009	Grade 2 disabilities during 2009 ^c		
			Among new cases		Rate per 1 000 000 population
			Number	%	
African	30 497 (0.40)	28 935 (3.75)	3 146	10	4.1
Americas	43 370 (0.49)	40 474 (4.58)	2 645	6	3.0
South-East Asia	120 456 (0.68)	166 115 (9.39)	7 286	4	4.1
Eastern Mediterranean	8 495 (0.17)	4 029 (0.70)	608	15	0.11
Western Pacific	8 635 (0.05)	5 243 (0.29)	635	12	0.4
Total	211 903 (0.37)	244 796 (4.27)	14 320	6.7	2.5

^a Prevalence rate is shown in parentheses as the number of cases per 10 000 population.

^b Case-detection rate is shown in parentheses as the number of cases per 100 000 population.

^c New-case grade 2 disability rate per 1 000 000 population.

during the period 2006–2009. It shows also that the dramatic decline observed during 2000–2005 was largely the result of the 67% reduction in detected cases in the South-East Asia Region over that period; during 2006–2009 the reduction – as in other WHO regions – was 18%. Because of the numerous operational changes that have occurred at country and regional levels during the past 10 years, it is impossible to determine which factors were responsible for the observed dramatic decline in case-detection rate or to assess the epidemiological significance of the decline.

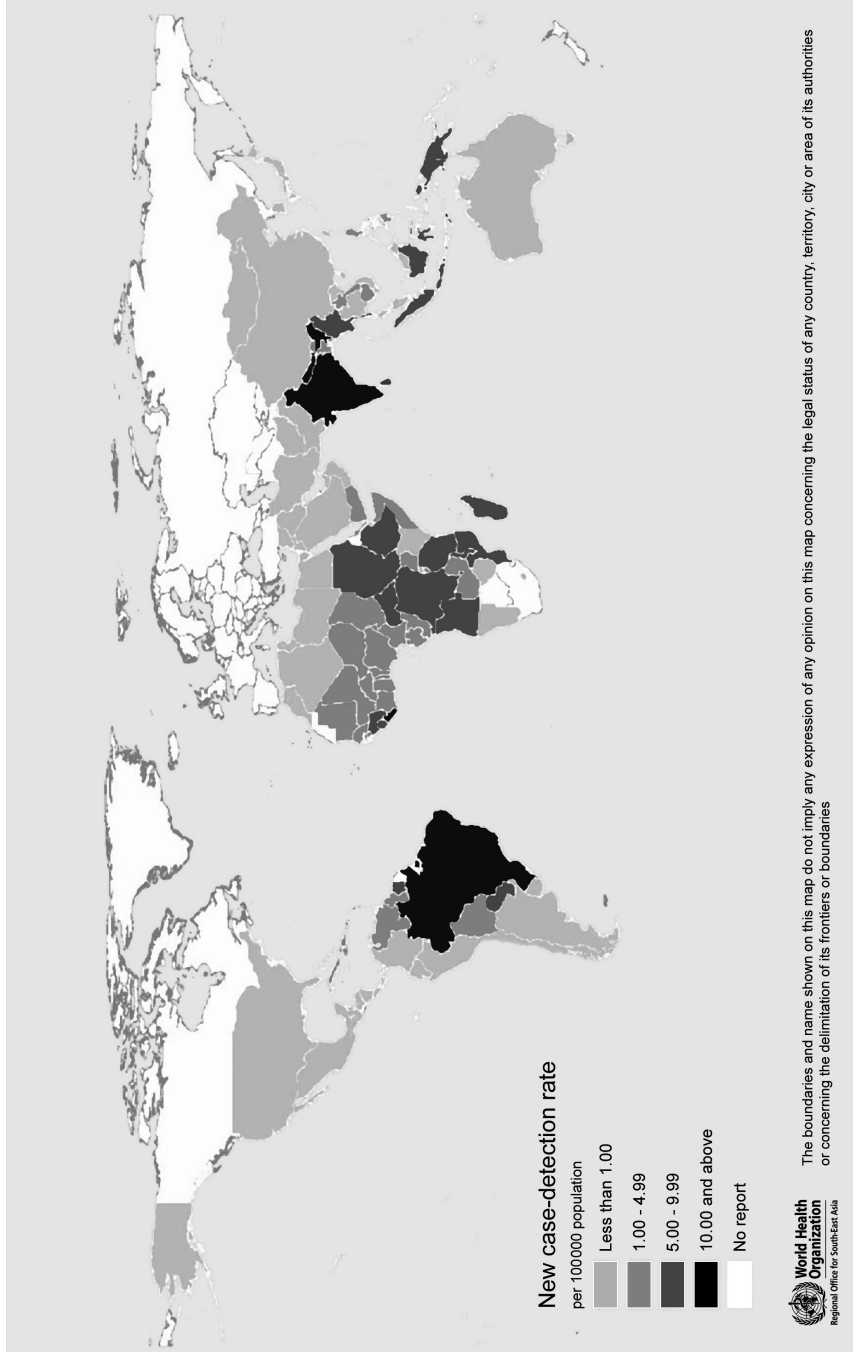
The steady fall in case detection has not been uniform, either among countries or over the years, and fluctuations have occurred as a result of operational factors, particularly during special case-detection campaigns organized in certain countries (8).

Comparison of peak case-detection figures reached between 1992 and 2009 with the figures for 2009 in the top 16 countries (i.e. those accounting for 93% of the global disease burden) reveals two very different trends. Detailed analysis identifies two groups of countries – one group of eight showing considerable decline, and another group of eight showing a very modest decline.

Table 2
Number of leprosy cases detected annually, by WHO region (excluding the European Region), 2000–2009

WHO region	Annual case detection									
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
African	54 602	39 612	48 248	47 006	46 918	45 179	34 480	34 468	29 814	28 935
Americas	44 786	42 830	39 939	52 435	52 662	41 952	47 612	42 135	41 891	40 474
South-East Asia	606 703	668 658	520 632	405 147	298 603	201 635	174 118	171 576	167 505	166 115
Eastern Mediterranean	5 565	4 758	4 665	3 940	3 392	3 133	3 261	4 091	3 938	4 029
Western Pacific	7 563	7 404	7 154	6 190	6 216	7 137	6 190	5 863	5 859	5 243
Total	719 219	763 262	620 638	514 718	407 791	299 036	265 661	258 133	249 007	244 796

Figure 1
Case-detection rates reported for 2009



In the 16 top countries there was a decline (from peak case-detection rate to case detection in 2009) of 71.7% over a mean period of 9.2 years, indicating an annual geometric decline of 12.9%.

In 8 of those 16 top countries, accounting for 64% of the global burden of cases, the decline over a mean period of 9.2 years was 78% – an annual geometric decline of 15.2%. In the other 8 countries, with 29% of the global burden of cases, the decline over a mean period of 9.9 years was only 27.7% – an annual geometric decline of 3.2%.

2.5 Profiles of new cases

Statistics on age, sex, classification, disability status and relapse are collected routinely by many countries and reported to WHO. Though potentially of considerable interest for monitoring trends, these statistics vary considerably between countries for reasons that include operational factors such as coverage and case-finding methods, which makes comparisons difficult.

Age is traditionally broken down in terms of child (under age 15) versus adult cases; the proportion of cases among children would be expected to decrease as transmission declines. In the past, age patterns have been influenced by BCG (bacille Calmette–Guérin) vaccination, which should reduce cases among children, and by school surveys, which selectively increase case detection among children. The proportion of child cases in 2009 varied between 0.6% in Argentina and 32% in the Comoros Islands.

Data reported by sex should give some evidence of gender equity in populations, but are complicated by the fact that males have a greater tendency to MB disease and the proportion of MB disease varies between populations. The reported proportion for females in 2009 varied from 6.5% in Ethiopia to 60% in the Central African Republic. Classification statistics have been influenced by repeated changes in criteria for classification over the past 20 years; new cases reported in 2009 ranged from 32% MB in the Comoros to 95% MB in the Philippines.

Statistics on grade 2 disability (G2D) are of particular interest as they provide a potential indicator both of programme quality (a programme with early case detection should be associated with a low proportion of G2D) and of the morbidity burden attributable to leprosy (8). The fact that the proportion of new cases with G2D ranged from 1.5% (Liberia) to 23% (China) indicates that countries may differ considerably in terms of how disabilities are detected and reported as well as in the predominant clinical manifestations of the disease.

These differences in patient profiles between countries highlight ethnic and cultural differences between populations and differences in national leprosy control programmes. They could be valuable indicators of practices and trends within countries and are thus important to national programme managers (see section 6.13 on monitoring and evaluation).

Table 3

Detection trend of leprosy in 16 countries reporting ≥1000 new cases during 1992–2000

Country	Number of new cases detected									
	1992	1993	1994	1995	1996	1997	1998	1999	2000	
Bangladesh	7 307	6 943	7 983	8 782	11 225	11 320	12 351	14 336	12 135	
Brazil	30 094	34 235	32 515	32 724	39 792	43 933	–	42 055	43 175	
China	3 755	3 755	2 096	2 109	1 845	1 854	2 051	2 051	1 595	
Democratic Rep. of Congo	3 247	3 927	4 195	4 344	5 526	3 781	–	4 221	3 103	
Ethiopia	1 936	4 090	4 790	5 160	4 747	4 444	4 457	4 457	4 931	
India	517 000	456 000	414 894	391 760	415 302	519 952	634 901	537 956	474 286	
Indonesia	13 219	12 638	17 255	13 492	15 071	15 337	18 367	17 477	13 539	
Madagascar	2 050	740	4 701	4 676	3 921	11 555	8 957	8 704	7 689	
Mozambique	1 732	1 930	2 583	3 430	4 225	4 195	3 764	5 488	6 617	
Myanmar	9 816	12 018	8 303	6 577	6 935	9 086	14 357	30 479	10 262	
Nepal	5 953	6 152	6 169	4 783	6 602	7 446	6 570	18 693	6 661	
Nigeria	4 381	4 381	7 827	7 147	6 871	7 176	7 230	7 918	7 918	
Philippines	7 169	3 442	4 450	3 988	4 051	4 942	3 490	3 390	2 596	
Sri Lanka	–	944	1 059	1 897	1 528	776	1 376	1 757	1 700	
Sudan	1 980	1 489	3 100	1 765	2 126	2 633	2 077	2 426	2 045	
United Rep. of Tanzania	–	2 731	2 596	2 596	2 747	2 798	3 535	5 081	4 640	
Total	609 639	555 415	524 516	495 230	532 514	651 288	723 483	706 489	602 892	

Table 3 (continued)
Detection trend of leprosy in 16 countries reporting ≥1000 new cases during 2001–2009

Country	Number of new cases detected								
	2001	2002	2003	2004	2005	2006	2007	2008	2009
Bangladesh	10 740	9 844	8 712	8 242	7 882	6 280	5 357	5 249	5 239
Brazil	41 070	38 365	49 206	49 384	38 410	44 436	39 125	38 914	37 610
China	1 726	1 646	1 404	1 499	1 658	1 506	1 526	1 614	1 597
Democratic Rep. of Congo	4 980	5 037	7 165	11 781	10 737	8 257	8 820	6 114	5 062
Ethiopia	4 523	4 632	5 193	4 787	4 698	4 092	4 187	4 170	4 417
India	617 993	473 658	367 143	260 063	169 709	139 252	137 685	134 184	133 717
Indonesia	13 286	12 377	14 641	16 549	19 695	17 682	17 723	17 441	17 260
Madagascar	8 599	5 482	5 104	3 710	2 709	1 536	1 521	1 763	1 572
Mozambique	5 713	5 830	5 907	4 266	5 371	3 637	2 510	1 313	1 191
Myanmar	9 684	7 386	3 808	3 748	3 571	3 721	3 637	3 365	3 147
Nepal	13 830	13 830	8 046	6 958	6 150	4 235	4 436	4 708	4 394
Nigeria	5 981	5 078	4 799	5 276	5 024	3 544	4 665	4 899	4 219
Philippines	2 669	2 479	2 397	2 254	3 130	2 517	2 514	2 373	1 795
Sri Lanka	2 309	2 214	1 925	1 995	1 924	1 993	2 024	1 979	1 875
Sudan	1 299	1 361	906	722	782	884	1 706	1 901	2 100
United Rep. of Tanzania	4 656	6 497	5 279	5 190	4 237	3 450	3 105	3 276	2 654
Total	749 058	595 716	491 635	386 424	285 687	247 022	240 541	233 263	227 849

3. Epidemiology

3.1 Definition of a leprosy case

The presence of classical clinical signs plays a major role in the diagnosis of leprosy, although demonstration of the causative organism by slit-skin smears, histopathology or polymerase chain reaction (PCR) is sometimes used to support the diagnosis. Since the availability of laboratory facilities for slit-skin smear or histopathology is restricted in many endemic countries, and the current PCR technology is still not adequately reliable, diagnosis of most cases of leprosy in the field will continue to be based on clinical evidence, at least for the time being. However, this situation may not be ideal when disease incidence is declining and where more sensitive diagnostic tools and procedures may be needed to ensure that all cases that need treatment are diagnosed and cured (10).

Leprosy should be suspected in people with any of the following symptoms or signs:

- pale or reddish patches on the skin;
- loss, or decrease, of feeling in the skin patches;
- numbness or tingling of the hands or feet;
- weakness of the hands, feet or eyelids;
- painful or tender nerves;
- swelling of or lumps in the face or earlobes;
- painless wounds or burns on the hands or feet.

Although most leprosy patients have skin lesions that are visible, experienced field workers are aware that a great variety of skin lesions are manifest in cases of the disease. Some are very diffused and difficult to distinguish from the normal skin. In these cases, the other symptoms and signs become important for diagnosis.

Leprosy is diagnosed when at least one of the following cardinal signs is manifested:

- definite loss of sensation in a pale (hypopigmented) or reddish skin patch;
- a thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve;
- the presence of acid-fast bacilli in a slit-skin smear.

The quality of diagnosis should be monitored as part of regular technical supervision. If there are indications of substantial over-diagnosis, a validation exercise on a representative sample of cases can be conducted to determine the magnitude of the problem.

3.2 Classification

Leprosy is a classic “spectral disease”, being manifest in a variety of clinical forms related to the type and strength of the immune response. A strong cellular immune response is effective in curtailing the multiplication of *M. leprae* and is thus associated with PB disease. A weak cellular response allows bacilli to replicate freely in the body, leading to MB disease forms.

In 1981, the WHO Study Group on Chemotherapy of Leprosy for Control Programmes classified leprosy as MB and PB according to the degree of skin-smear positivity (9). This was an essentially operational classification, intended to serve as the basis for chemotherapy. Multibacillary leprosy included polar lepromatous (LL), borderline lepromatous (BL), and mid-borderline (BB) cases in the Ridley–Jopling classification, with a bacteriological index of 2+ or more at any site in the initial skin smears. Paucibacillary leprosy included indeterminate (I), polar tuberculoid (TT) and borderline tuberculoid (BT) cases in the Ridley–Jopling classification, with a bacteriological index of <2 at all sites in the initial skin smears.

At its sixth meeting in 1987, the Expert Committee on Leprosy endorsed the principles upon which this classification is based but specified that all smear-positive cases should be classified as MB leprosy for the purposes of MDT programmes (10). In 1993, the Second WHO Study Group on Chemotherapy of Leprosy concluded that approaches based on clinical classification may be required where reliable facilities for the bacteriological examination of skin smears are unavailable; it recommended that, when classification is in doubt, the patient should be treated as having MB leprosy (12).

Where skin smears are not available, cases can be classified on the basis of clinical examination as either PB leprosy (one to five skin lesions) or MB leprosy (six or more skin lesions).

3.3 Transmission, infection and incubation period

Although mice, armadillos and certain primates can be infected with *M. leprae* under laboratory conditions, it has long been thought that *M. leprae* infects only human beings in nature and that humans, in particular those with MB leprosy, are the only important source of infection for other humans. Contacts of MB cases are 5–10 times, and contacts of PB cases 2–3 times, more likely to contract clinical leprosy than individuals in endemic communities but with no known close contact with recognized cases. This is consistent with the observation of nasal lesions in an appreciable proportion of MB cases.

In the 1970s, natural *M. leprae* infection was recognized in wild nine-banded armadillos (*Dasypus novemcinctus*) in the southern USA, in a region known to have autochthonous leprosy. There is now evidence that leprosy is a zoonosis in this area. The extent of endemic *M. leprae* infection in nine-banded

and other armadillo species, and its precise contribution to leprosy in the Americas, is unknown and is a topic for research (13).

Infection is thought to occur primarily by the respiratory route but there is also evidence that it may occur through injured skin (14). The mechanism of dissemination from the primary site to the final location in the skin and nerves is unclear. The incubation period from infection to clinical manifestations is variable, but appears to be shorter for PB disease (in the order of 2–5 years) than for MB (in the order of 5–10 years and sometimes much longer) (15).

3.4 Infectiousness of leprosy

The infectiousness of leprosy patients is related to the size of the bacillary population in the body. It has been shown that a single dose of rifampicin reduces the load of viable bacilli to such low levels that it is no longer possible to cultivate the organism in an animal model. In public health terms, it is reasonable to conclude that infectiousness becomes negligible after the start of MDT (16).

3.5 Risk factors

Leprosy cases occur at all ages in endemic populations, although the disease is rare among the very young because of the long incubation period before the appearance of clinical manifestations. Cases are more commonly reported in males than females in most populations. While this may be the result of biased case ascertainment or selective hiding of the disease in females in some populations, the prevalence of MB disease is higher among males than females in all populations, which may reflect a gender difference in immune response or exposure. Contact with a known (especially MB) case is recognized as a risk factor in all populations, as is the absence of a history of BCG vaccination. Low socioeconomic status is likewise associated with leprosy in all populations, for reasons that remain unclear. Although there is evidence that certain genetic factors may be associated with leprosy, the population-attributable risk is small and leprosy should therefore not be considered a “genetic” disease. Family clustering is determined predominantly by contact, not by shared genes. It is useful to recollect that leprosy extended north of the Arctic Circle in the nineteenth century and is thus compatible with cold as well as warm climates. The gradual disappearance of the disease from high latitudes over the past century is thought to be attributable largely to socioeconomic factors.

3.6 Interaction between HIV infection and leprosy

In the 1980s it was feared that the HIV pandemic might have the same effect on leprosy as it has on tuberculosis. It was predicted that patients with leprosy and HIV coinfection would be at increased risk of lepromatous disease and faster

clinical evolution, and that leprosy would be more difficult to treat. None of these fears has been realized, and the interaction between HIV and *M. leprae* is known to be far more subtle than that between HIV and *M. tuberculosis*. Most of the recent epidemiological, clinical and pathological studies show neither an increased HIV prevalence among leprosy cases nor an alteration in the clinical spectrum of leprosy among coinfecting patients. On the other hand, there is some evidence that immune-mediated reactions (particularly Type 1) occur more often in coinfecting patients (17).

There are several reports of leprosy presenting as an immune reconstitution disease among patients starting highly active antiretroviral treatment (HAART), probably as a result of the unmasking of an existing subclinical infection or incubating disease (18). Histopathological observations reveal a normal spectrum of appearance in biopsies of leprosy lesions from coinfecting patients. Although no data indicate whether HIV infection exacerbates nerve damage in leprosy, it may alter the immune response to *M. leprae* in nerves because of its neuropathic effect. Leprosy-HIV coinfecting patients respond equally well to MDT and experience similar side-effect profiles. Some studies showed that patients with lepromatous disease and HIV coinfection were at a higher risk of reversal reactions and neuritis but responded as expected to steroid therapy.

In considering the relationship of HIV and leprosy it is also important to recognize that HIV coinfection may influence health-seeking behaviour and this in turn may affect the chance of leprosy being diagnosed (19).

3.7 Geographical variations

Geographical variations are a striking feature of leprosy at every level. As shown in Figure 1, there are considerable differences between countries: among the 141 countries reporting, just 7 countries accounted for 85% of all new cases detected in 2009.

Geographical variations are also prominent within countries. In India in 2009, for example, 12 out of 35 states (with 79% of the population) accounted for 94% of all new leprosy cases. In Brazil from 2005 to 2007, 10 population clusters with 17% of the population contributed 53% of all cases in that country. In Indonesia, in 2007, 14 out of 33 provinces (with 60% of the population) accounted for 83% of cases. In China, in 2009, 3 out of 31 provinces (with 12.4% of the population) had 54.5% of cases. These regional patterns have long been recognized, but their mechanism remains unclear.

Even at the local level, leprosy cases are often reported to be far more common in certain villages or valleys than in others. In some circumstances this may be the result of biased case ascertainment – selective searching and a high diagnostic suspicion in certain areas – but the observation is so common

in leprosy-endemic populations that it is more likely to reflect important risk factors that are not yet understood.

These variations have two important implications. First, they indicate the importance of risk factors that remain to be elucidated and whose recognition could be useful in control of the disease. Second, they allow targeting of leprosy control activities, which improves the cost-effectiveness of control programmes. However, while targeting may be good policy in some circumstances, the very wide distribution of the disease, often at very low frequency, needs to be kept in mind if appropriate services are to be provided to all cases.

4. Chemotherapy and management

4.1 Chemotherapy

4.1.1 Standard MDT regimens

Three standard first-line drugs – rifampicin, clofazimine and dapsone – are available for use in multidrug regimens of fixed duration, none of which should be used as monotherapy.

■ *Multibacillary leprosy*

The standard adult treatment regimen for MB leprosy is:

- rifampicin: 600 mg once a month
- clofazimine: 300 mg once a month, and 50 mg daily
- dapsone: 100 mg daily

Duration: 12 months.

The standard child treatment regimen for MB leprosy is:

- rifampicin: 450 mg once a month
- clofazimine: 150 mg once a month, and 50 mg every other day
- dapsone: 50 mg daily

Duration: 12 months.

■ *Paucibacillary leprosy*

The standard adult treatment regimen for PB leprosy is:

- rifampicin: 600 mg once a month
- dapsone: 100 mg daily

Duration: 6 months.

The standard child treatment regimen for PB leprosy is:

- rifampicin: 450 mg once a month
- dapsone: 50 mg daily

Duration: 6 months.

Note: Children under 10 years of age should receive appropriately reduced doses of drugs, such as

- rifampicin: 10 mg/kg body weight once a month
- dapsone: 2 mg/kg body weight per day
- clofazimine: 1 mg/kg body weight to be given on alternate days, depending on the dosage.

There may be occasional cases of dapsone hypersensitivity although the drug is relatively non-toxic in the doses used. In the event of hypersensitivity, dapsone must be stopped immediately and the adverse reaction reported (dapsone syndrome).

4.1.2 Existing second-line antileprosy drugs

Since the mid-1980s, the bactericidal activities of the new fluoroquinolones (pefloxacin and ofloxacin), a new macrolide (clarithromycin) and a tetracycline (minocycline) have been demonstrated (20–23). In the limited experimental tests carried out in mouse models, all these drugs were able to render the mouse inoculums non-infective after only 1 month of treatment. The new drugs showed greater bactericidal activity than dapsone and clofazimine. In the nude mouse model of leprosy, a single dose of a minocycline+clarithromycin combination killed 96% of viable *M. leprae* and a single dose of a minocycline+clarithromycin+ofloxacin combination killed 98.4% – a bactericidal effect close to the 99.5% killing effect of a single dose of rifampicin (24).

These drugs were also tested in humans with MB leprosy. Ofloxacin, given at a daily dose of 400 mg, killed more than 99.99% of the viable *M. leprae* after only 4 weeks of therapy (25–27). Similar bactericidal activities were demonstrated with minocycline and clarithromycin (28). The bactericidal activity of a single dose of minocycline+clarithromycin+ofloxacin was tested in patients with MB leprosy against a single dose of rifampicin alone and 4 weeks of standard MDT. Although the bactericidal effect of the three-drug combination was similar to that observed in the mouse model, the severe gastrointestinal side-effects related to the use of clarithromycin were sufficient to preclude the routine use of this drug in the field (29). A single dose of ofloxacin 400 mg + minocycline 100 mg killed 68–98% of viable *M. leprae* and a single dose of rifampicin 600 mg + ofloxacin 400 mg + minocycline 100 mg killed more than 99%.

Ofloxacin

Of the many fluoroquinolones that have been developed, ofloxacin was the first of interest for leprosy. The results of clinical trials have indicated that its optimal dosage for the treatment of leprosy is 400 mg daily. While a single dose of ofloxacin displayed a modest bactericidal effect, 22 doses killed 99.99% of the viable *M. leprae* in lepromatous patients. Side-effects include nausea, diarrhoea and other gastrointestinal complaints, and a variety of central nervous system complaints including insomnia, headaches, dizziness, nervousness and hallucinations. Most side-effects do not require discontinuation of ofloxacin treatment, and serious problems are rare (26).

Minocycline

Minocycline, a member of the tetracycline group of antibiotics, has significant bactericidal activity against *M. leprae* – greater than that of clarithromycin although much less than that of rifampicin. The standard dose of 100 mg daily gives a peak serum level that exceeds the minimum inhibitory concentration (MIC) of minocycline against *M. leprae* by a factor of 10–20 and has shown promising bactericidal activity in lepromatous patients. The side-effects of minocycline include discolouration of teeth during their period of formation, and the drug should therefore not be given during pregnancy or to infants and children. Other side-effects include occasional pigmentation of the skin and mucous membranes, various gastrointestinal symptoms and central nervous system complaints, including dizziness and unsteadiness. Minocycline is most commonly used for the long-term treatment of acne, indicating that it is generally well tolerated; however, some rare but serious side-effects such as autoimmune hepatitis and lupus erythematosus-like syndrome have been reported recently (30).

Clarithromycin

Clarithromycin is a member of the macrolide group of antibiotics and displays significant bactericidal effect against *M. leprae* in mice and in humans (27, 28). In lepromatous patients, a daily dose of 500 mg of clarithromycin kills 99% of viable *M. leprae* within 28 days and >99.9% in 56 days. The most common side-effect is gastrointestinal irritation (including nausea, vomiting and diarrhoea), which is particularly frequent when clarithromycin is given at a dose of 2000 mg.

4.1.3 Promising new antileprosy drugs

In recent years moxifloxacin (a fluoroquinolone) and rifapentine (a long-acting rifamycin derivative) have been identified as having highly promising antimycobacterial activities.

Moxifloxacin

Moxifloxacin is a fourth-generation synthetic fluoroquinolone with broad-spectrum antibiotic activity against both Gram-positive and Gram-negative bacteria. Like other fluoroquinolones it functions by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV – enzymes that are required for bacterial DNA replication, transcription and repair – and thus inhibits cell replication.

Moxifloxacin has shown potent bactericidal activity against *M. leprae* in mice and humans. Given at 150 mg/kg in mice (equivalent to 400 mg in humans), it is as active as rifampicin. A single dose of moxifloxacin 150 mg/kg

killed five times more *M. leprae* than a single dose of ofloxacin 150 mg/kg. In humans, given at a dose of 400 mg daily, it killed more than 99% *M. leprae* within 7 days, and no viable bacilli were demonstrated from day 28 onwards. It is more potent than ofloxacin, minocycline and clarithromycin (31, 32).

Rifapentine

Rifapentine is a semi-synthetic rifamycin derivative with a prolonged action (serum half-life 15 hours) compared with rifamycin (half-life 3 hours). Because of its long half-life, rifapentine was investigated in the 1980s and 1990s in combination with other medications for the once-weekly treatment of tuberculosis.

Like all rifamycin derivatives, rifapentine targets DNA-dependent RNA polymerase, which is necessary for RNA synthesis and thus for production of proteins. This process is different in human (eukaryotic) cells and bacteria, and all rifamycin derivatives, including rifapentine, affect the process only in bacteria. Resistance to rifapentine can develop during tuberculosis treatment by selection of pre-existing rifamycin-resistant mutants within large populations of tubercle bacilli. If resistance develops to one rifamycin-type drug, the bacteria become resistant to all rifamycin derivatives.

Rifapentine can cause some body fluids such as saliva, urine, breast milk, tears and sweat to become orange-red in colour. The skin, teeth and tongue may also change colour and dentures and contact lenses can be permanently stained. Rifapentine may reduce the effectiveness of contraceptive pills, and other forms of contraception should therefore be used during treatment with this drug.

In leprosy treatment, rifapentine exhibited more potent bactericidal activity than rifampicin in both in mice and humans. In the mouse foot-pad model, a single rifapentine dose of 10 mg/kg killed 20 times more *M. leprae* than a single rifampicin dose of 10 mg/kg. A single dose of a rifapentine+moxifloxacin+minocycline combination killed 50 times more *M. leprae* than a single dose of rifampicin+ofloxacin+minocycline (32).

Diarylquinoline (R207910)

Diarylquinoline offers a new mechanism of antituberculosis action by inhibiting mycobacterial adenosine triphosphate (ATP) synthase. The drug potently inhibits drug-sensitive and drug-resistant *M. tuberculosis* in vitro and shows bactericidal activity both in patients with drug-susceptible pulmonary tuberculosis and in those with multidrug-resistant (MDR) pulmonary tuberculosis (33–36).

Against *M. leprae* in mice, a single dose of 25 mg/kg is bactericidal. The drug is as active as rifampicin, rifapentine and moxifloxacin and more active than minocycline. In mice, multiple doses of 1 mg/kg five times a week were as

active as a single dose of 25 mg/kg. Similarly, a dose of 25 mg/kg once a month was as active as the same dose given five times a week. Diarylquinoline has a long half-life (1 week in humans). The drug may be used to replace minocycline in the new combined regimens for once-a-month treatment for leprosy.

Other new drugs active against Mycobacterium tuberculosis complex

The activities of PA-824 (a nitroimidazopyran) and linezolid (an oxazolidinone) against *M. leprae* are rather modest (37). A single 100 mg/kg dose of PA-824 showed no significant bactericidal activity; after five consecutive days of treatment the bactericidal effect was significantly weaker than that of a single dose of diarylquinoline or of moxifloxacin. Thus, PA-824 has a narrow spectrum of activity, limited primarily to the *M. tuberculosis* complex (37). Neither PA-824 nor linezolid – which yielded similar results – is a promising drug for the treatment of leprosy.

4.1.4 Study on the uniform multidrug therapy regimen

In order to shorten the duration of treatment and simplify drug supply logistics, a multicentre study has been launched to assess the efficacy of the WHO-recommended 6-month MDT regimen for MB leprosy in new cases of all types of leprosy, both MB and PB. Patients are to be actively followed for a minimum period of 8 years after completion of treatment to monitor reactions and relapses. This study aims to recruit a total of 5000 newly detected, previously untreated patients (2500 PB and 2500 MB). It is designed as a multicentre, open field study; some 3400 patients have been recruited so far and about 2000 patients have completed their treatment. The preliminary report is favourable (38), but no conclusions can yet be drawn.

4.1.5 Combined therapy with four weeks of daily ofloxacin and rifampicin

The possibility of further shortening the duration of MDT was evaluated in a rifampicin–ofloxacin field trial. This was a multicentre, double-blind trial organized by the Steering Committee on Chemotherapy of Mycobacterial Diseases (THEMYC), a component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Multibacillary leprosy patients were randomized into four groups and treated with:

- 24 months of standard WHO-MDT for MB leprosy (as positive control);
- 12 months of WHO-MDT for MB leprosy;
- 12 months of WHO-MDT for MB leprosy with rifampicin 600 mg plus ofloxacin 400 mg daily during the initial 4 weeks; and
- rifampicin 600 mg plus ofloxacin 400 mg daily for 4 weeks.

The published results (39) showed that the trial regimen of daily rifampicin and ofloxacin for 4 weeks resulted in an unacceptable relapse rate of 13%. Thus, daily treatment with rifampicin and ofloxacin for 4 weeks is not a viable option.

4.1.6 Treatment regimens for special situations

Patients who cannot take rifampicin

Special treatment regimens are required for individual patients who cannot take rifampicin because of side-effects or intercurrent diseases, such as chronic hepatitis, or who have been infected with rifampicin-resistant *M. leprae*. The following 24-month regimen is recommended:

- Daily administration of 50 mg clofazimine, together with two of the following drugs – 400 mg ofloxacin, 100 mg minocycline or 500 mg clarithromycin – for 6 months, followed by daily administration of 50 mg clofazimine, together with 100 mg minocycline or 400 mg ofloxacin for an additional 18 months (40). If available, ofloxacin may be replaced by moxifloxacin 400 mg, which has stronger bactericidal activity against *M. leprae*.

Patients who cannot take rifampicin

Multibacillary leprosy patients who refuse to take clofazimine because of skin discolouration also need a safe and effective alternative treatment. In such patients, clofazimine in the normal 12-month MDT may be replaced by ofloxacin, 400 mg daily, or by minocycline, 100 mg daily, for 12 months. Similarly, ofloxacin may be replaced by moxifloxacin, 400 mg.

In 1997, the WHO Expert Committee on Leprosy (41) also recommended the following alternative 24-month regimen for adult MB leprosy patients who refuse to take clofazimine: rifampicin, 600 mg once a month, ofloxacin, 400 mg once a month, and minocycline, 100 mg once a month, for 24 months.

Patients who cannot take dapsone

If dapsone produces severe toxic effects in any PB or MB leprosy patient, it must be stopped immediately. No further modification of the regimen is required for patients with MB leprosy. For PB leprosy, however, clofazimine – in the dosage used in the standard MDT for MB leprosy – should be substituted for dapsone in the 6-month treatment regimen.

4.1.7 Relapses after multidrug therapy

Relapse after MDT remains low, even after almost 30 years of widespread use. Some reports suggest that the risk of relapse is higher in a subset of patients

with a pre-MDT average bacterial index (BI) of 4 or more. Recently published WHO operational guidelines recommend that it may be advisable to treat an MB patient with high BI for more than 12 months, taking careful consideration of the clinical and bacteriological evidence. A number of studies have reported that retreatment of relapses following dapsone monotherapy or MDT with another course of standard MDT regimens is highly successful (41–43).

Although demonstration of organisms resistant to dapsone is relatively common, probably because of pre-existing dapsone-resistant strains, there are reports on organisms resistant to rifampicin, clofazimine or quinolones after completion of treatment with MDT. Most investigators consider that a relapse after MDT is most likely to be due to persisters and only rarely to resistance. This is borne out by the results of molecular tests on biopsies from a small number of relapsed cases.

Several risk factors for relapses in leprosy have been suggested, including persisters, re-infection, drug resistance, inadequate/irregular therapy, use of monotherapy, high initial BI, number of skin lesions and lepromin negativity. The risk of relapse in patients coinfectd with HIV is a possibility and needs further investigation. Currently, diagnosis of relapse is based mainly on clinical features such as appearance of a new lesion and a significantly increased BI. Some studies have demonstrated the utility of histopathological changes and simple serological tests in confirming the diagnosis of relapse. There is a possibility of developing molecular tests based on PCR for early identification of relapses (44).

4.2 Management of leprosy reactions and neuritis

4.2.1 Neuritis and nerve function impairment

Nerve function impairment (NFI) results from a variety of pathological and immunological processes taking place in the peripheral nerves. The presence of longstanding NFI at the time of registration and MB classification are the main risk factors for subsequent development of serious nerve damage in leprosy. The proportion of new cases with NFI at diagnosis may be as high as 20%.

Leprosy reactions, particularly Type 1 or reversal reactions, are regarded as the leading cause of NFI. Most patients, particularly those with MB disease, develop NFI events and reactions during the first 6 months after starting treatment: these events diminish over time (including time after MDT) and very few patients develop such events after the second year following completion of MDT. However, nerves can be functionally impaired in the absence of any obvious signs or symptoms of reactions (silent neuropathy) (45, 46).

4.2.2 Leprosy reactions

Together, the two major clinical types of leprosy reactions – Type 1 or reversal reaction, and Type 2 or erythema nodosum leprosum (ENL) reaction – may

affect 30–50% of all MB leprosy patients (47). Because *M. leprae* infects peripheral nerves, the inflammation associated with reactions is a medical emergency: severe nerve injury may develop rapidly, with subsequent loss of sensation, paralysis and deformity (48). No clinical or laboratory tests are available that can accurately predict either which patients are the most likely to develop a reaction or when such a reaction might occur.

Type 1 reactions are recognized by swelling and redness of skin patches and are regarded as severe when associated with loss of nerve function (loss of sensation or muscle weakness), pain or tenderness in one or more nerves, when the red swollen skin patches are on the face or overlying another major nerve trunk, when skin lesion anywhere becomes ulcerated and when there is marked oedema of the hands, feet or face. Type 1 reactions occur across the whole leprosy spectrum.

Type 2 or ENL reactions are characterized by the appearance of tender, erythematous nodules in MB patients. They are regarded as severe when numerous ENL nodules occur in association with high fever and neuritis or become ulcerated and when other organs (e.g. eyes, testes, lymph nodes and joints) are involved. A severe ENL reaction can be recurrent and chronic and may vary in its presentation.

Promising new markers to identify patients at high risk of developing reactions have been demonstrated but additional studies are needed to determine their sensitivity and specificity (49).

4.2.3 Treatment of leprosy reactions

The mainstay of treatment of both types of reaction is corticosteroids because of their anti-inflammatory effects. Some studies have demonstrated better results when steroids are administered for longer than 12 weeks, particularly in the treatment of neuritis. To ensure that due attention is given to the risk of serious side-effects of long-term use of steroids, such as weight gain, peptic ulcer, diabetes, hypertension, reactivation of tuberculosis, osteoporosis and psychiatric disorders, these drugs should be prescribed only by someone properly trained in their use. Trials of prophylactic steroids have demonstrated only a short-term effect on prevention of NFI. Several studies have indicated that NFI improves to some extent without steroid therapy, which may be attributable to MDT (45).

Cyclosporine has been used to treat Type 2, or ENL, reactions with mixed results (50). Azathioprine and methotrexate have been used in combination with prednisolone for treatment of Type 2 reactions and may offer a steroid-sparing regimen for treatment (51). Pentoxifylline, a TNF-alpha inhibitor, has shown no significant benefit. Inhibition of lymphocyte proliferation by several potent antimetabolites has had little or no consistent effect in the treatment of

either type of leprosy reaction. Similarly, clinical inhibitors of TNF-alpha, IL-2, and other cytokines have had minimal effects on reactions (52, 53).

Although several studies have demonstrated the usefulness of thalidomide in the treatment of acute ENL reactions, its use is restricted because of its teratogenic effects and of ethical and legal considerations. In addition, thalidomide availability is limited by restrictions on its import and supply in many endemic countries. WHO therefore recommends its use only under strict medical supervision in specialized referral facilities.

It is important to educate all patients about the signs and symptoms of reactions and NFI and to encourage them to return to health centres immediately in case of such events – even those that occur after completion of MDT.

National leprosy programmes should continue to ensure that an efficient referral system exists within the general health services to allow timely nerve function assessment and diagnosis and treatment of patients experiencing reactions, neuritis and related complications such as iritis. Regular availability of antireaction drugs should be ensured.

Guidelines for the management of severe reactions

- Severe Type 1 or reversal reaction

Severe reversal (Type1) reactions should be treated with a course of steroids usually lasting 3–6 months. Patients still on antileprosy treatment should continue the standard course of MDT.

- Severe Type 2 or ENL reaction

Severe ENL reaction should be treated with a standard course of prednisolone (daily dosage not exceeding 1 mg/kg body weight) for 12 weeks. Patients who experience reactions while still on MDT should continue the standard treatment with MDT. If MDT has been completed, the management of ENL should not include restarting of MDT. Adequate doses of analgesics to control fever and pain should be prescribed.

A combination of clofazimine and corticosteroids is indicated for management of patients with severe ENL who are not responding satisfactorily to treatment with corticosteroids alone or for whom the risk of corticosteroid toxicity is high. Prednisolone should be given in daily dosage not exceeding 1 mg/kg body weight. Treatment with clofazimine should start with 100 mg three times a day for a maximum of 12 weeks, with the dose then tapering to 100 mg twice a day for 12 weeks and to 100 mg once a day for 12–24 weeks.

Management of ENL reaction with clofazimine alone is indicated in cases of severe ENL when the use of corticosteroids is

contraindicated. Treatment with clofazimine should follow the same guidelines as when it is used in combination with prednisolone. However, the total duration of treatment with high-dose clofazimine should not exceed 12 months.

It should be noted that it takes about 4–6 weeks for clofazimine to take full effect in controlling ENL. Management of severe ENL reaction is complex and should be undertaken only by physicians at referral facilities, who will adjust the dose and duration of anti-reaction drugs according to patients' individual needs.

4.3 Disability and rehabilitation

Disability – in new patients as well as in people who have completed treatment – remains a challenge. Addressing the problem of disability falls within the broad scope of public health but requires support from social services, the community and the voluntary sector.

4.3.1 Magnitude of the problem

Currently there is no robust information on the numbers of people affected by disability due to leprosy at either global or national level. While information on G2D among new cases is regularly collected, only limited information is available on disability among people who have completed MDT.

For planning and implementation of rehabilitation measures for people with leprosy-related disabilities, it is important to estimate the total prevalence of G2D in the population. It would therefore be useful to include, in all national programmes, a new measure of total prevalence of G2D in the population as one of the main indicators for monitoring further reduction in disease burden. As well as information on total prevalence of G2D, more detailed information will be needed at the local level on the specific rehabilitation needs, including physical, social and economic needs, of leprosy-affected communities.

4.3.2 Disability grading for leprosy

The three-grade WHO disability grading system (0, 1, 2) has been in use for several years and has proved to be a good basis for measuring the magnitude of the problem and organizing physical rehabilitation activities at both individual and community levels.

4.3.3 Prevention, limitation and management of disabilities

Prevention of disabilities begins with early diagnosis of leprosy, recognition and treatment of complications such as neuritis and reactions, identification of patients at risk of developing secondary disability, and timely intervention.

Although for programme purposes statistics are compiled only for G2D, it is important that information on grade 1 disability is also made available at the clinic level so that such patients are supported by preventive measures such as provision of footwear and protective devices and advice on self-care. These preventive measures are equally relevant for individuals who are cured and do not normally present themselves at clinics except as part of an active follow-up. Management of disabilities should be an integral part of routine treatment services at the clinic level and should also cover people who have been cured. Available services should include the provision of aids and appliances, specialist medical care, and surgical reconstruction and rehabilitation facilities.

4.3.4 Self-care

Sustaining the prevention and management of disabilities requires greater emphasis on self-care and self-help through counselling of those in need, as well as of their families and community members. Self-care measures should include care of dry, denervated skin of palms and soles in order to prevent wounds, ulcers and skin cracks. Prevention of occupational injuries, such as burns caused by handling hot objects, should be an important aspect of the counselling of individuals with sensory loss in the limbs, as should care of the eyes where indicated.

4.3.5 Community-based rehabilitation

Following the Declaration of Alma-Ata (1978), stating that health is a fundamental human right, and in consideration of the constraints of scope, expertise and resources imposed on specialized medical rehabilitation services, WHO introduced the strategy of community-based rehabilitation (CBR). This was intended to enhance the quality of life for people with disabilities through community initiatives, promoting the concept of the “inclusive community” and using local resources to support the rehabilitation of people with disabilities within their own communities. However, stigma and lack of knowledge meant that specialized rehabilitation services and many CBR programmes failed to recognize people with leprosy-related disabilities as equal members of the community requiring rehabilitation.

In recent years there has been a change in attitude towards leprosy. Stigma has lessened in many countries and people affected by leprosy now more often remain within their families and communities. As a result, involvement of family and community members is now seen as critical for empowering people affected by leprosy, encouraging them to play an active role in their rehabilitation and further reducing the stigma of the disease. The central strategy of CBR is to facilitate community action to ensure that people with disabilities – including those disabled by leprosy – have the same rights

and opportunities as all other community members, including, for example, equal access to health care, education, skills training, employment, family life, social mobility and political empowerment. Thus CBR has become a legitimate strategy for meeting the needs of people affected by leprosy and enhancing their quality of life.

Community-based rehabilitation calls for a comprehensive, rights-based approach, involving sectors other than health. The recently published *WHO/ILEP Technical guide on community-based rehabilitation and leprosy: meeting the rehabilitation needs of people affected by leprosy and promoting quality of life* (54) highlights the importance of the CBR approach, and the WHO/UNESCO/ILO/IDDC *Community-based rehabilitation: CBR guidelines* (55) includes a supplementary section on leprosy and CBR that further promotes the inclusion of leprosy-affected persons in broader CBR and development programmes.

5. Social issues

The Seventh Meeting of the Expert Committee on Leprosy did not address social issues except in reference to the meeting held in 1952 (40), which recommended that the issue of human rights be acknowledged, especially with regard to the particularly negative impact of leprosy on women.

In June 2010, WHO hosted a meeting of regional managers, individuals affected by leprosy and various experts with the aim of developing guidelines for increasing the participation of leprosy-affected persons in leprosy control activities (56). The meeting identified several areas, with corresponding strategies, for enhancing the empowerment of those affected. The empowerment strategies aim to increase the inclusion of persons affected by leprosy in different aspects of community life, including health, housing, social welfare, education and decision-making, as well as in socioeconomic activities. The result of this enhanced participation and empowerment is threefold: greater willingness of individuals affected by leprosy to seek diagnosis; completion of the prescribed treatment plans; and improved quality of life.

5.1 Equity, social justice and human rights

The principle of equity is based on the premise that disparities or inequalities in the levels of health enjoyed by different populations are unnecessary, avoidable and unjust. It is the right of individuals enshrined in the Universal Declaration of Human Rights (57). In 2008, the United Nations Convention on the Rights of People with Disabilities came into force. This Convention represents a major new international legal instrument and, with its greater focus on inclusivity in development, is of critical importance in protecting the rights of all persons with disabilities, including those affected by leprosy.

Further potential for improving the condition of persons affected by leprosy and promote their rights to quality of life was enshrined in the United Nations Human Rights Council resolution on the “Elimination of discrimination against persons affected by leprosy and their family members”, which received unanimous approval in June 2008 (58). This has been further strengthened with the adoption by the Human Rights Council in September 2010 of a set of principles and guidelines on the elimination of discrimination against persons affected by leprosy and their families (59).

Equity, social justice and human rights in the world of leprosy are difficult to attain without continually challenging those who label this population in pejorative terms; consistent respect for those affected is essential.

5.2 Gender

The sociocultural norms in many societies discriminate against girls and women, often consigning them to a lower status and value and placing them at

considerable disadvantage in terms of access to resources and goods, decision-making power, and choices and opportunities in all spheres of life. Since women appear to suffer more negative health consequences of leprosy than men (60), the topic of women in the world of leprosy is a cross-cutting issue.

Health systems need to give greater emphasis to gender in the training of health professionals and health-care workers in order to improve awareness of and sensitivity to gender concerns and disparities (61).

Programmes need to identify patterns of service use, levels of participation in decision-making and perceptions of quality of care. When defining priorities in leprosy control services, it is critical to increase women's involvement in health action at all levels. There is evidence that integration of leprosy services into general health services, coupled with decentralization, has improved the accessibility of services for all population groups in general and for the female population in particular (62).

5.3 **Enhancing the involvement of affected persons**

Persons affected by leprosy have a major role to play in leprosy services, especially in the areas of advocacy, awareness, rehabilitation and case-finding. Organized efforts by these individuals are vital to promoting a positive public perception of and attitude to the disease; to effecting change in any legal measures that are discriminatory in nature; and to ensuring that leprosy control continues to occupy an important place in the health policy framework of the country.

Persons affected by leprosy also have a clear role and responsibility in the area of community involvement for social action. Their involvement can lead to country-specific definitions of the quality of service to be provided, as well as help the programme in setting the standard for quality. They can provide regular information – to programme managers, supervisors or sponsors – on the quality of services. Their participation in research and evaluation can assist in identifying needs, particularly with respect to the accessibility and quality of services being provided. They can contribute to reforming leprosy services and provide a focus on issues of discrimination and stigma. As role models, they are the major contributors to cultivating positive attitudes.

5.4 **Stigma and stigmatization**

Leprosy has a strong social and psychological impact on all individuals affected by the disease (including family members) and the societies in which they live. The disease carries significant stigma: communities respond with fear, rejection, insensitivity, use of pejorative terms, and general devaluation of the status of affected persons – who, in turn, feel threatened by the rest of society. Socioeconomic rehabilitation of affected people can play a major role in

improving their quality of life, increasing their social integration and reducing leprosy-related stigma. Some reports suggest that stigmatization is in decline, particularly where integrated programmes are functioning. Although stigma may change in nature – from overt rejection of those affected by leprosy to the individual's fear of what might happen as a result of having leprosy (63–65) – it often persists long after the disease has ceased to be a public health problem.

The response of the programme should be twofold. It is important to address the community, responding to unanswered questions, dispelling misunderstandings and myths, and helping people to acknowledge and accept those affected by leprosy without prejudice. It is equally important to empower persons affected by leprosy to deal with the daily challenges of misunderstanding and miscommunication.

The treatment programme should also include counselling as an important management strategy, and should introduce guidelines and protocols for building the competence of health professionals in three important areas: transforming knowledge into information that is easily understandable by persons affected by leprosy; managing people and tasks; and communication skills. A well-trained health person should be able to advise, support, guide, share information and empower others.

5.5 Counselling

The purpose of counselling is to provide support to individuals in emotional distress in order to lessen their distress and allow them to function optimally in their everyday lives. Counselling by trained and experienced professionals is a critical resource that should be available to all persons affected by leprosy and that should often be extended to their family members. It should be community-based and initiated at the time of diagnosis.

When provided by individuals who are familiar with the community, knowledgeable about the emotional impact of leprosy and professionally trained can have a positive impact on the social issues discussed in sections 4.1–4.4.

5.6 Residential care

Persons newly diagnosed with leprosy should not be admitted for long-term institutional care. The consequence of such institutionalization is often significant difficulty in returning to independent living – and in the event of institutions closing there is the problem of finding suitable alternative accommodation for inpatients.

6. Leprosy control and prevention

Elimination of leprosy as a public health problem – defined, in terms of prevalence, as fewer than 1 leprosy case registered for treatment per 10 000 population – was achieved at the global level at the end of 2000. More recent approaches, however, have focused on monitoring new case detection and working to reduce the burden of disease. Eradication of leprosy is not considered to be feasible since there is no test for infection and the incubation is very long; moreover, many aspects of the natural history of the disease (such as subclinical infection and the role of carrier states) are unknown (for example, there is at least one animal reservoir – the armadillo – of *M. leprae*). The current approach targets reduction in disability in new cases based on early case detection, treatment with MDT, and good-quality services that include prevention of disability to reduce the burden of disease.

6.1 Improving the quality of leprosy services

Improving the quality of care not only enables all the needs of the patient to be met but also makes it possible to attract more people to come for examination, which results in improved case detection. The elements of good-quality care include:

- easy accessibility of health care;
- availability of MDT;
- management of complications and side-effects;
- disability care and prevention of disability (POD);
- CBR;
- respect for individual rights of patients; and
- elimination of stigma and gender bias.

These elements can be ensured by improving:

- the capacity of peripheral health services to deal with essential tasks (diagnosis, classification, MDT, need for referral, etc.);
- availability of appropriate tools/protocols, resources and the necessary competence at referral points;
- the counselling of patients and their families; and
- community awareness.

Patients should be reviewed at the end of MDT treatment to confirm the completion of treatment and to assess any new nerve function impairments

that may have developed during treatment. Patients should be counselled at this point on the risks of future reactions and relapses and on recommended actions. Self-care should be re-emphasized and advice given on prevention of disability.

6.2 Integrating leprosy control into general health services

The need to integrate leprosy control into general health services is based largely on the principles of equity and sustainability. In addition, integration allows issues of stigma and discrimination against persons affected by leprosy and their families (66, 67) to be more effectively addressed. In an integrated programme, leprosy control activities should be conducted in multipurpose settings by health workers within the general health services. However, integration does not mean that specialized personnel no longer have a role. They *must* be a part of the integrated programme at the national level; may also be available at the intermediate (regional or provincial) or even district level; and are expected to play a vital part in coordination, planning and technical support and in monitoring of progress in leprosy control (68). Almost all endemic countries have already involved general health workers, to a varying extent, in antileprosy activities.

The key issue is that of improving the performance of the integrated programme, which may be achieved by:

- raising community awareness of the main features of leprosy – its curability and the availability of free treatment – and increasing community participation in case-finding, case-holding, MDT delivery and POD;
- building capacity within general health services;
- ensuring regular supervision and technical support by workers from higher levels of the general health system and by specialized leprosy workers;
- ensuring adequate referral services;
- ensuring availability of the necessary quantities of MDT drugs, of other medical supplies and of materials for handling complications and care at the peripheral level.

6.3 Referral system

An ideal referral system ensures that patients can receive appropriate, high-quality care for their condition in the closest possible facility and at the lowest cost given the resources available to the health system (69). Improving the effective functioning of referral systems requires progress in three areas: referral

system design, facilitation of the transfer of both patients and information between levels, and effective referral discipline.

Improving the design of the referral system requires identification of the services that can appropriately be provided at each level of care in both rural and urban settings, including community- and home-based care and primary health care at district, secondary and tertiary levels and in specialized hospitals (70).

The development of effective transportation arrangements is critical to ensure that patients from remote areas have a fair chance of being referred to specialists. When the patient's treatment has finished at the higher-level facility, back-referral to the original facility must include information regarding treatment, investigations already done and follow-up expected at the lower level.

The bypassing of lower-level services by patients is a common problem that leads to overcrowding of higher-level facilities. Effective referral discipline demands improvements in the quality of care at lower levels and in the availability of resources in order to strengthen primary health care services, giving them greater credibility and making them more attractive to patients. A referral system will function effectively if all services providers adhere to the referral discipline, referring appropriately and following the agreed protocols of care (71).

The referral system has a crucial role in defining the quality of care that a programme can provide to persons affected by leprosy; it should include identification of the primary-, secondary- and tertiary-level services that are available to meet a whole range of needs (72). An integrated leprosy control programme thus needs the support of an efficient referral system to be effective. Currently, the referral system in most programmes is either non-existent or is very weak as regards meeting programme needs. Strengthening existing referral facilities and, where necessary, establishing an adequate number of such facilities to form the national referral network should be one of the key priorities for integrated leprosy control programmes.

The referral system should include a network of individuals and institutions capable of providing services. Their tasks and responsibilities should be clearly defined, along with procedures and protocols for good, standardized clinical practices, including protocols for the flow of patients and information to and from different levels. The system should build partnerships, coordinating the work of all care providers to maximize care and reduce cost. An effective referral system requires good communication and coordination between levels of care: a range of options are available for effective communication and transfer of information, including personal visits, telephone, post, e-mail, and telemedicine). It is also important to ensure that persons affected by leprosy are provided with support for travel from remote areas when needed.

Besides direct patient care, referral hospitals has other roles within the health system, such as teaching and research, as well as technical support and quality assurance to lower levels of health services (70). They may also be closely involved in other public health interventions such as disease-specific health promotion and education activities.

6.4 **Building and maintaining national capacity**

Capacity building assumes greater importance against the backdrop of a declining disease burden, shrinking resources, competing interests and priorities and, most importantly, loss of clinical expertise in leprosy. The Enhanced Global Strategy envisages a two-pronged approach, designed to develop a global strategic capacity-building plan and to maintain national reference/training centres at different levels in endemic countries (72).

Global, regional and national action should be directed at identifying suitable institutions and establishing training programmes for national-level experts, including dermatologists and trainers, with appropriate training modules and materials being developed for different categories of health personnel. In most endemic countries, the expert knowledge of dermatologists provides significant support to the programme, particularly in urban areas, and will be an important resource for national efforts to sustain clinical expertise in leprosy.

6.5 **Community awareness and education**

6.5.1 **Community awareness**

Low levels of community awareness may be due to a lack of health education and to provider-centred policies rather than community-centred social action. Collaboration with community groups, including persons affected by leprosy, public agencies and professional organizations, is thus essential to the successful implementation of activities and to building programme resilience. Efforts to demonstrate the benefits of educational interventions should become an integral part of a leprosy control service.

Means of improving community awareness include: identifying and involving specific groups from the community; identifying the most useful forms for relaying messages; designing core messages; suggesting delivery options (campaigns or community networks), activities and tools; establishing criteria for measuring success; and finding ways to link such activities to other initiatives. The programme should be able to make optimum use of all available media to disseminate information as effectively as possible. While the mass media are useful for the widespread dissemination of information, changes in attitudes and behaviour can be brought about only through interpersonal communication.

The purpose of such activities is to improve levels of understanding about the disease and the control programme and of the implications for the community in terms of benefits and responsibilities (73), and to encourage community members to accept an active role in leprosy services by encouraging their use, promoting treatment adherence, etc. The expected outcome is an increase in the rate of self-referral and a positive attitude of society towards persons affected by leprosy (74).

6.5.2 Information, education and communication

A lack of proper understanding of leprosy and the unconstrained propagation of traditional myths and beliefs have led to the development of negative social attitudes, resulting in social discrimination and stigma against persons affected by leprosy and their families. While discrimination refers to the unjust or prejudicial treatment of people, especially on the grounds of being affected by leprosy, stigma is an ugly act of labelling, rejection or overt fear of a person affected by leprosy (75).

Although information, education and communication (IEC) activities have been a key part of leprosy control activities for decades, they have often been conducted on a limited evidence base, and there has been little effort to evaluate the effectiveness of such interventions. The IEC activities are important in early detection, in early reporting of symptom/signs and in changing community attitudes to leprosy and those affected by leprosy.

In some countries, social marketing approaches have been developed to improve early self-reporting and diagnosis and to change the community view of leprosy (76).

Public information and education in the field of leprosy control is aimed at building people's awareness by:

- improving their understanding of the disease and the programme;
- stimulating concern about the quality – and use by patients – of the available leprosy services;
- increasing the demand and support for health services;
- dispelling myths and refuting misconceptions;
- making stigma and discrimination unacceptable;
- developing a sense of community ownership of the leprosy programme;
- enabling the community to develop the positive attitudes and behaviour needed to underpin social action;
- helping those affected by leprosy to overcome the barriers that prevent them from discharging their social responsibilities.

6.6 Improving case detection

6.6.1 Case-finding and case-holding

There are a number of possibilities for improving case detection but not all are easily implemented. Active case-finding under vertical leprosy programmes produced reasonably good results in the past, when leprosy was much more common, but it is no longer feasible or even advisable except in very special situations such as in highly endemic, underserved communities where leprosy appears to be a neglected problem. Thus the best possibility for improvement is to promote passive case detection by creating increased awareness in the community and among peripheral health workers. Ultimately, the key to improving case detection is ensuring a strong political commitment at all levels and a sincere desire to reduce the burden of leprosy. In addition, improving the quality of care would ensure that leprosy services are more acceptable to patients, resulting in better compliance with MDT and treatment completion.

An important – and cost-effective – method of achieving major reductions in leprosy would be a focused approach that takes advantage of the very uneven distribution of the disease within countries and among population groups. Such an approach, combined with intensive and innovative case-detection efforts, is likely to accelerate the reduction in disease burden. It calls for detailed mapping of the disease, by population groups and using geographical information systems.

6.6.2 Delay in diagnosis

Studies show that the factors influencing delays in diagnosis are culture- and context-specific. Currently, the delay between onset of the disease and the start of effective chemotherapy is estimated to average about 2 years but to range from a few months to 20 years (77). In a situation where there are few new cases, the delay in detection is likely to increase further, resulting in a rise in MB disease and in the number of disabled individuals among new cases (78).

6.7 Special areas and populations

6.7.1 Areas with a high disease burden

Within countries there may be geographical areas or population groups with high numbers of untreated/hidden new cases or a high proportion of new cases with grade 2 disabilities. These cases call for priority attention – particularly if the affected individuals are children. Significant delays in diagnosis in such a situation result in extended transmission within the community, and may be the result of one or more of the following factors:

- inadequate skills for correct diagnosis among health staff;
- high degree of stigma in the community, leading to concealment of cases;

- poor case-finding efforts by the programme;
- ineffective or inappropriate IEC activities in the area;
- services not easily accessible or affordable by the community;
- limited community participation and involvement.

The primary response must be to establish a sustainable leprosy control programme that can offer treatment and supportive services to new cases for as long as they appear in a particular population. The leprosy control programme will have to rely on voluntary reporting or referral following dissemination of information on disease and programme objectives. Once a case has been diagnosed, identification and examination of household contacts, on a voluntary basis, is essential to rule out the existence of any further cases. In special situations, a rapid screening of the population may be conducted to find any undetected new cases.

6.7.2 Areas with a low disease burden

As has been observed in several previously highly endemic countries, a reduced disease burden in terms of the number of new cases is likely to define the nature of leprosy in the future. It then becomes important for national programmes to reassess the situation and to allocate resources and services accordingly. It will be difficult and prohibitively expensive to sustain a wide range of services and professional expertise to manage a small number of new cases across a large number of peripheral health facilities: some peripheral health facilities may not see a single new case of leprosy in a year.

A focused, needs-based strategy will also be required for other activities, such as building the capacity of different categories of health staff. Training will have to be restricted to workers from facilities that are likely to have leprosy-affected individuals in their catchment areas rather than being made available to all health workers in all facilities. At the same time, however, it is important to ensure that service points are strategically located for easy accessibility. Consideration must also be given to maintaining and establishing the optimal number of leprosy referral centres at regional and national levels, in order to ensure the availability of treatment expertise in endemic countries for as long as is necessary.

6.7.3 Underserved population groups

The most crucial element of any leprosy control programme is to reach all individuals who are in need, including persons affected by leprosy who live in special situations – in difficult-to-access areas or in underserved and marginalized population groups. These individuals may face geographical,

social, economic or cultural barriers that limit access to health services or hinder the provision of services (79).

Such special situations pose complex management challenges: innovative and practical strategies involving mainly operational solutions need to be developed if services are to be provided for these individuals and communities. The strategy adopted should emphasize strengthening and sustaining health services at the community level. The population groups, the range of services available and any gaps in providing for needs should be identified. A plan can then be developed that focuses on building partnerships and the capacity of local health workers.

6.7.4 Urban areas

In 2007, the global population became predominantly urban for the first time, with a third of the world's estimated 3 billion current urban residents living in slums (80). Over the next 30 years, almost all of the world's population growth will occur in urban areas in low- and middle-income countries.

Urban populations pose challenges for health service management, including social, cultural and economic inequalities and constraints that leave vulnerable sectors of the population unaware of or unable to access services. This situation is further complicated by rapid industrialization, by the increasing density of migrant populations in slums and by the multiplicity of, and lack of coordination among, health-care providers.

Within urban areas, the major focus should be on improving services for the people living in slums. The United Nations has operationally defined slums as those communities that are characterized by insecure residential status, poor structural quality of housing, overcrowding, and inadequate access to safe water, sanitation and other infrastructure (81). Many health outcomes are worse in slums than in neighbouring urban areas or even rural areas. Moreover, the formal health sector encounters slum residents only when they develop late-stage complications of preventable chronic diseases. This situation takes a heavy toll on these neglected communities and on already-limited health-care resources.

Inequalities in health among sections of the population in urban settings reflect the inherent inequalities in economic, social and living conditions. Integrated approaches are needed to promote changes in health-care practices, particularly among marginalized populations living in slums, and may require the following actions:

- making health care, including leprosy control, an integral part of urban health plans;
- promoting local ownership, i.e. involving local leaders and persons affected by leprosy in coordination and decision-making;

- expanding public–private partnerships with government, the private sector, NGOs, community-based organizations (clubs, associations, unions, etc.), dermatologists and representatives of persons affected by leprosy;
- facilitating targeted messaging – disseminating information to target groups using appropriate media network;
- ensuring access to referral services for specialist care.

6.8 Contact surveillance

Since human beings are the major known reservoir of *M. leprae*, another focused approach would be case detection among household contacts, with or without the additional intervention element of chemoprophylaxis. The increased risk of leprosy among contacts does not mean that they would necessarily contribute to a major share of new cases in the community. Nevertheless, contacts are an easily identifiable target group who are likely to be well motivated to accept examination and possibly chemoprophylaxis. Thus, as well as clearly identifying highly endemic areas and populations, an intensified approach calls for examination of household contacts of known cases, at least at the time of registration of such cases.

Most investigations of contacts with leprosy have focused on households since they form easily recognizable groups of individuals living in close proximity to one another. The associated risk reflects the intimacy of contact within the home as well as other factors shared by household members, such as genetic traits, behaviour, diet, intercurrent infections, and physical features of the home or its surroundings (82).

The risk of leprosy for individuals living in households with MB patients is 5–10 times greater, and with PB patients 2–3 times greater, than the risk for individuals not living in such households. However, it is possible that a household with PB cases may have, or have had, transient or indirect contact with MB cases. Unrecognized or unrecorded MB cases or subclinical infections are likely to be responsible for increased risk among contacts. The risk is higher for younger than for older contacts and higher for male than for female contacts.

Household contacts may contribute a significant proportion of all new cases in situations of relatively low or moderate endemicity; in areas of relatively high endemicity, the distinction between contacts and non-contacts may be less clear. On detection of a new case, the patient's household contacts should be examined for evidence of leprosy. They should then be educated about the early signs of the disease and their significance, and asked to report on a voluntary basis if any suspect skin, motor or sensory lesions occur. National programmes may include the offer of a single dose of rifampicin to household

contacts following treatment of the index case and examination of each contact to exclude active leprosy and tuberculosis.

6.9 Treatment adherence

Non-adherence to prescribed treatment, irregularity of drug intake, and premature cessation of treatment are common observations worldwide in all types of patients suffering from conditions requiring treatment of long duration. To improve treatment adherence, patients need the support of the health services, their families and their community (83). It is therefore essential that the health service has an organized network to facilitate treatment adherence.

For example, as soon as a treatment appointment is missed, action should be taken to find out why the patient has not attended the clinic and, if necessary, to remind him or her of the importance of taking treatment regularly and completing the full course of MDT. If this action proves insufficient, a home visit by a local community worker should be arranged to find out why the patient has stopped visiting the clinic and, if necessary, motivate him or her to resume treatment. Other persons affected by leprosy who are recognized by the community as advocates can play a valuable role in emphasizing the importance of compliance with the treatment plan.

6.9.1 Flexible treatment

Every leprosy patient should be able to benefit from MDT. The delivery of treatment must therefore be adapted to the needs of patients and populations living in difficult-to-access areas or in situations where regular contact with health services is impossible. If a patient has difficulty in attending the clinic, it may help if several blister packs can be provided at once, so that visits to the clinics can be less frequent. In such a case it is advisable to recruit another responsible person (a community volunteer, family member or neighbour) to supervise the treatment and to help the patient to continue the treatment properly at home; this arrangement is called “accompanied MDT” or A-MDT. Counselling and information about the importance of regular drug intake are essential, and patients should also be advised to report to the clinic in case of any problem. Patients should be assessed at the end of treatment (84).

6.10 Supply management for multidrug therapy

Early case detection and treatment with MDT will remain the key elements of leprosy control strategy in the foreseeable future. The provision of an uninterrupted supply of high-quality MDT drugs in blister packs, free of charge, to all patients, including those living in difficult-to-access areas, is essential. The consequences of poor MDT supply management can be harmful for patients and for the credibility of local health services.

As the numbers of patients requiring treatment with MDT decline steadily, logistical support for effective distribution of drugs will need to be adjusted appropriately. To ensure the availability and proper distribution of MDT drugs, coordination mechanisms among governments, WHO and donor agencies at the country level should continue (85–87).

6.11 Disease prevention

As noted earlier, the decline in leprosy prevalence in many populations since the early 1980s has been largely the result of the shorter, WHO-recommended MDT regimens. Reductions in incidence, reflected in case detection, have also been evident and are more revealing of changes in underlying *M. leprae* transmission. Several historical analyses have shown a link between these reductions and improved socioeconomic conditions. There is strong circumstantial evidence that both BCG vaccination, and case-finding and treatment have contributed to the decline in the incidence of the disease.

The contribution of case-finding and treatment to reductions in leprosy incidence has been difficult to quantify. Gradual declines in incidence have been observed for decades in many countries, both before and since the introduction of modern chemotherapy. While it is reasonable to presume that the killing of *M. leprae* associated with finding and treating cases reduces transmission, there are at least two reasons why this may be difficult to quantify. First, by the time any case is identified and treatment started, there has already been a lengthy period during which the patient could have infected many close contacts. The fact that onset of disease is insidious, particularly in the case of MB leprosy, supports this argument. The second reason is that there may be sources of infection that have yet to be recognized. For example, several studies have provided evidence for silent carriage of *M. leprae* in the nasal cavity of healthy individuals (89, 90), which might represent an additional source of transmission.

Another approach to leprosy prevention may be based upon targeting contacts of known leprosy cases, as such individuals are known to be at high risk of the disease; the risk of leprosy for contacts of MB cases is 5–10 times, and for contacts of PB cases 2–3 times, greater than the risk for individuals with no such contacts. These high-risk individuals are identifiable and can therefore be targeted for specific preventive measures, either immunoprophylaxis with BCG, or chemoprophylaxis with one or another antimycobacterial drug.

6.11.1 Primary BCG immunization

There is now a large body of literature on the relationship between BCG and leprosy. All studies have shown protection against both MB and PB disease, and recent studies in Brazil have shown that this protection can last for decades. The observed protection has varied between studies and populations, from 20% to

80%, for reasons that are not understood; however, the variations are reminiscent of those observed in the protection provided by BCG against tuberculosis (88, 89). Given that BCG has been, and continues to be, very widely used around the world and in almost all leprosy-endemic countries (approximately 85% of the world's infants now receive BCG in the first year of life), the vaccine must be making a substantial contribution to global leprosy reduction. Measurement of the precise impact is more difficult – historical analyses are confounded by improvements in socioeconomic conditions that have coincided with the increased use of BCG vaccine.

6.11.2 Immunoprophylaxis of contacts

Vaccination of contacts with BCG has been a policy in several countries in Latin America (Brazil, Cuba and the Bolivarian Republic of Venezuela), and there is evidence for its effectiveness in reducing leprosy incidence in the populations of these countries (90, 91). However, the evidence is complicated by several factors: the observed heterogeneity in protection between populations, the fact that a high proportion of most contacts will have received BCG in infancy, and the fact that repeat BCG vaccination has been found effective in some populations (e.g. Malawi) but not in others (e.g. Brazil) (92). In addition, there is some evidence that BCG vaccination may precipitate the clinical onset of leprosy; this is rare but needs to be considered given the low absolute risk of leprosy even among contacts.

6.11.3 Chemoprophylaxis of contacts

Chemoprophylaxis of contacts, or of total populations, has been evaluated in several controlled trials, and there is now much evidence for its effectiveness in various circumstances (93, 94). The first studies were carried out with dapsone, or injectable long-acting acedapsone, and a recent study has shown the effectiveness of a single dose of rifampicin in contacts in Bangladesh. However, the protection afforded by chemoprophylaxis is time-limited, reducing incidence among treated individuals for 2 or 3 years. In addition, there is evidence that such protection may be lower among intimate contacts of patients than among contacts who are less close.

Both of these contact-based approaches to leprosy prevention can be supported by evidence. Decisions on whether to implement such interventions will depend upon several factors:

- resources: training and supervision of field staff, and appropriate budget support;
- concerns over contraindications: BCG vaccination, for example, should not be given to HIV-positive individuals, and single-dose

rifampicin should not be given to tuberculosis cases or individuals with liver disease, and both of these contraindications require screening of the target contact population;

- adverse reactions: both BCG vaccination and single-dose rifampicin are relatively safe but neither is entirely risk-free; and
- ethics/confidentiality: some cases may not wish their diagnosis to be known to contacts.

6.11.4 Next steps – prophylaxis strategy

Given the high risk for contacts, it is important at least to examine them, and most programmes should be able to do this. Well-resourced programmes may be able to consider immunoprophylaxis or chemoprophylaxis of identified contacts, but such decisions need to take into consideration the full complexities of these interventions, as mentioned above. The impact of these policies on overall leprosy incidence will depend upon several factors, in particular the proportion of all new cases that arise in identifiable contact populations. Further research on the logistics of implementation and the cost-effectiveness of such policies is of high priority.

6.12 Surveillance for drug resistance

The current treatment, based on WHO-recommended MDT for MB and PB leprosy, is unlikely to be subject to any major, immediate changes. However, the emergence and transmission of rifampicin-resistant strains of *M. leprae* is the most serious of the various problems that may hinder ongoing efforts to further reduce the disease burden in leprosy-endemic countries. The limited availability of the mouse foot-pad inoculation technique means that, until recently, there has been very little information on drug resistance. With the development of DNA sequencing methods, however, several reports of rifampicin, dapsone and ofloxacin resistance have been published, which underscore the potential importance of this phenomenon (95). Regardless of whether the drug resistance problem is or is not serious at present, it is important that data are collected more systematically and trends carefully monitored so that timely and effective measures to combat the problem can be developed (96).

At a time when very few laboratories in the world are able to perform phenotypic testing of drug susceptibility in the mouse foot-pad model or its equivalent, the new molecular methods offer an attractive alternative. In general, there is excellent concordance between the results obtained by phenotypic and genotypic drug susceptibility tests. However, the molecular tests are more rapid and cost-effective and can therefore process considerably more specimens.

6.13 Monitoring and evaluation

6.13.1 Indicators for monitoring

The main purpose of monitoring the progress towards further reduction of the disease burden is to enable timely corrective steps to be taken. The indicators for measuring progress can be broadly grouped as follows:

- (a) main indicators requiring minimum amounts of data;
- (b) other indicators (some that require only limited data and others that provide important insights and require more detailed information); and
- (c) indicators for evaluating the quality of services.

(a) Main indicators for monitoring progress

Case detection is the best indicator of transmission of infection in the recent past; it also indicates the current disease burden. The earlier use of prevalence as an indicator of disease burden is less relevant now because of the small backlog of undetected cases and the shorter duration of treatment. In terms of new case detection, there are some problems with regard to specificity of diagnosis as a result of several operational factors that may vary with time and with geographical location. A more reliable indicator is therefore needed, with high specificity (even if sensitivity is quite low), mainly for studying trends and evaluating the impact of antileprosy activities, particularly in relation to timely detection of cases. The “new cases with G2D (visible disabilities) per 1 million population” is such an indicator. It is valuable not only for monitoring the overall leprosy situation but also as an indicator for timely diagnosis and for efforts made to prevent disabilities. The proportion of new cases with G2D can be used together with rate per 1 million.

In most programmes, the rate of treatment completion is currently 75–90%, which needs to be improved through continued monitoring. The main difficulty here is collecting information based on cohort analysis, even though it is possible to get a rough idea of treatment completion by looking at the number of cases completing treatment in any year and relating it to the number of cases detected in the previous year. Every effort should be made to collect information based on cohort analysis. The main indicators are:

- number and rate of new cases detected per 100 000 population per year;
- number and rate of new cases with G2D detected per million population per year;
- treatment completion/cure rate for MB and PB cases.

These indicators are used primarily to monitor progress within individual countries over time; they can also be used for comparisons between countries.

(b) Other indicators for monitoring progress

Many other indicators are already in use for monitoring progress:

- number and rate of new cases detected per year among persons less than 15 years of age per 100 000 population under 15 years of age;
- proportion of G2D cases among new cases;
- proportion of females among new cases;
- proportion of MB cases among new cases;
- proportion of household contact cases among new cases.

(c) Indicators for evaluating the quality of services, including diagnosis, treatment and disability care

The indicators of quality of services are:

- prevalence of G2D per million population (G2D in new patients and in those who have completed MDT);
- proportion of patients who develop new G2D during MDT;
- proportion of new cases verified as correctly diagnosed;
- prevalence:detection ratio;
- number of relapses among those who have completed MDT;
- number of patients assessed at completion of treatment.

The prevalence of G2D per million population gives an estimate of the total burden of leprosy in both new cases and those who have completed MDT. The prevalence:detection ratio gives an indirect indication of treatment completion, but may be high in countries using longer treatment than is recommended.

These quantitative indicators can be supplemented by qualitative methods that include patient participation through exit interviews and focus groups. Use of patient interviews to estimate delay in detection can identify obstacles to early diagnosis. Information on staff training and supervision can contribute to assessment of the quality of services.

As monitoring aims to measure the disease situation using the various indicators, the information system for recording and reporting should be able to provide the necessary data to calculate the various rates, and most importantly to calculate the main indicators listed under (a) above. Data necessary to

calculate the other indicators listed under (b) and (c), while important, may not always be available; every effort should be made to collect the data needed to calculate the other indicators as well.

6.13.2 Independent evaluation of leprosy programmes

Apart from routine monitoring, the structure, process and outcomes of leprosy programmes need periodic independent evaluation to provide an objective picture that enables corrections and adjustments to be made in strategies and activities, particularly at the local level. These exercises, which can be carried out by trained independent evaluators, even from within the country concerned, should be quick and cost-effective. It is very useful if such exercises are undertaken in collaboration with national programmes working with WHO, participating partner NGO agencies and representatives of people affected by leprosy. Checking the validity of the available information should be part of the exercise. It is useful if the evaluations are based on uniform guidelines, such as a simplified Leprosy Elimination Monitoring (LEM) exercise, which takes account of all the main indicators and of as many of the other indicators as possible, including process indicators for coverage, accessibility and diagnostic delay, and structural aspects of staffing levels, training and supervision.

7. Strategy for further reducing the disease burden due to leprosy – setting targets

7.1 Elimination of leprosy as a public health problem

The global target for elimination of leprosy as a public health problem, set by World Health Assembly resolution WHA44.9 in 1991 (1), was defined as reducing the prevalence to below 1 per 10 000 population at the global level by the year 2000. It was highly successful in providing a focus for leprosy programmes and in securing political and financial commitment. The strategy for achieving this target also resulted in important improvements in leprosy activities, such as simplification of diagnosis and treatment using MDT blister packs made available free to all new patients. The result was a dramatic reduction in prevalence of more than 90%, and the global target was reached by the end of the year 2000 – a major public health achievement.

7.2 New targets based on case detection and disability prevention

National leprosy programme managers recognize the importance of targets in providing a focus and direction for programmes and in securing political and financial commitment. Targets must be set carefully if programmes are to achieve early case detection and treatment and prevention of disabilities, and avoid any perverse incentives to engage in inappropriate activities. The possibility of developing and using targets based on case detection and disability has been extensively discussed and supported by national programme managers, partners and people affected by leprosy (97). The use of the G2D index in newly detected cases, as a rate per million population, is proposed as a more robust indicator than case detection alone because the diagnosis is more specific; the indicator addresses both case detection and the issue of disability.

A target of 35% reduction in G2D in new cases per million population from 2011 to 2015 has been agreed and can be used to evaluate progress towards the longer-term goal of reducing G2D in new cases to less than 1 in 1 million at the global level by 2020. A major review of progress should be conducted in 2015. This gives every country an incentive to improve case detection, treatment and disability prevention, and their achievements will be an essential contribution to the global goal. The goal of 1 G2D in new cases per million population is recommended at the global rather than at the national level. Countries are then urged to contribute to the global target by achieving a proportional reduction in the G2D rate per million population.

8. Research priorities

In the past decade, leprosy research has benefited from the availability of the genome sequences of several strains of *M. leprae* and its human host. An international consortium, IDEAL (Initiative for Diagnosis and Epidemiological Assays for Leprosy), has been established to exploit these new opportunities; it comprises more than 40 laboratories worldwide and includes many partners in endemic countries. Several reviews of research priorities for leprosy have been undertaken by WHO, ILEP and the International Leprosy Association. The following key areas – in no particular order of priority – have been highlighted:

- Molecular tools are available for genotyping *M. leprae* and assessing the emergence of drug resistance. These tools should be used to provide an understanding of the basis of transmission and to monitor the success of the control programme. Research is also required to improve the sensitivity and robustness of these new tools in order to make them suitable for use in regional centres and ultimately in the field. The use of molecular tools could also provide an insight into possible non-human sources of infection, including the role of the armadillo in transmitting leprosy in the Region of the Americas, and into related conditions such as Lucio's phenomenon, which may result from infection with *M. lepromatosis*.
- It is important to develop and improve diagnostic tests to identify individuals with disease or those who are at high risk of developing leprosy. Efforts to find species-specific antigens and use them in developing immunodiagnostic tests, involving cell-based immunity and/or serology, should be intensified. The discovery of biomarkers that could predict infection with *M. leprae*, reactional states or cure is particularly desirable; these biomarkers could form the basis of a much needed biomedical tool with sensitivity suitable for early-stage leprosy and for PB disease.
- The efficacy and duration of MDT could be improved. Good progress has been made in developing new drugs for tuberculosis and other conditions, and the efficacy of combinations of these drugs against *M. leprae* should be established in the laboratory and then in clinical trials. New immunomodulatory agents may also find application in the management of reactional states and may provide an alternative to the current therapies if they offer improved potency that could lead to shorter treatments.

- More research is needed in the area of prevention and management of nerve function impairment (NFI) and the underlying reactions. In particular, it is important to study the molecular, cellular and immunopathological basis of NFI in order to improve the treatment of neurological conditions and to prevent disabilities.
- Chemoprophylactic and immunoprophylactic tools for prevention of leprosy need to be developed. For example, studies in chemoprophylaxis could be undertaken using single-dose rifampicin, equivalent drugs such as rifapentine, or any new tuberculosis drugs that become available. Likewise, further research could be undertaken to measure the impact of BCG as an immunoprophylactic agent, possibly in combination with rifamycin or a similarly potent drug.
- Operational, epidemiological and implementation research is important to improve the sustainability and quality of leprosy services, including prevention of disability and community-based rehabilitation. Here, in order to reduce stigma, community education, empowerment of persons affected by leprosy, social awareness and counselling are paramount.

9. Conclusions and recommendations

The major conclusions and recommendations of the Committee are summarized below according to the four specific purposes of the Expert Committee meeting.

The global leprosy situation

1. The global leprosy situation is now best described by the patterns and trends in new case detection; however, caution is needed in interpreting these data and efforts are needed to continuously improve their quality.
2. Globally, and in most countries, there has been a steady decline in new case detection; the rate of decline varies between countries.
3. The age, sex, classification and disability of new cases vary considerably between countries for reasons that include epidemiological and operational factors.

Current status with regard to developments

4. The current strategy for leprosy control is based on early case detection and MDT treatment.
5. The uneven distribution of leprosy within countries represents an opportunity to focus on areas of higher endemicity as well as on underserved communities.
6. Surveillance of contacts through examination and education, with or without chemoprophylaxis, is increasingly important as the numbers of new cases decline.
7. Integration of leprosy activities into general health services, supported by referral systems including supervision, is vital to further reduction in the burden of leprosy.
8. Standard MDT regimens remain the mainstay of leprosy chemotherapy, although there are second-line and promising new antileprosy drugs.
9. The relapse rates after MDT completion remain very low, but some rifampicin-resistant strains of *M. leprae* have been identified; a surveillance programme for drug resistance is therefore required.
10. Trials of treatment regimens using new drugs are recommended.
11. It is essential that WHO-funded drug trials in leprosy be reported in timely fashion and in peer-reviewed journals.
12. To further reduce the burden of leprosy, research based on new molecular tools, improved diagnostics tests, improved MDT, studies of subclinical infection, and trials of prevention and treatment of reactions and nerve function impairment are recommended.

13. Support for operational, social and implementation research should continue because of its potential to improve the quality of leprosy services, particularly in community-based rehabilitation.
14. The focus on issues of equity, social justice, human rights, stigma and gender, together with the increasing contribution from people affected by leprosy, is recommended.

Latest evidence and existing indicators

15. The main indicators to be used for monitoring progress relate to case detection, disability assessment and treatment completion, and these indicators are to be interpreted together.
16. The new indicator of grade 2 disability in new cases detected per million population is recommended as it focuses attention on early case detection, treatment and disability prevention; however, more operational experience is required in the use of this indicator.
17. The current treatment completion indicator based on MDT provision needs to be revised to reflect adherence to treatment through an end-of-treatment review.

Further reducing the burden of leprosy

18. Maintaining high levels of BCG immunization in newborns is important in the prevention of leprosy.
19. Adoption by individual countries of the target to reduce grade 2 disability in new cases per million population by 35% between 2011 and 2015 will help to maintain commitment to further reducing the burden of leprosy.
20. A global goal of reducing the burden of leprosy to 1 new G2D case per million population by 2020 is recommended to maintain long-term commitment through partnerships with governments, NGOs, communities, WHO, academia, industry and people affected by leprosy. This is to be a global, rather than a national, goal.

Acknowledgements

The Committee acknowledged the valuable contributions made to its discussions by the following WHO staff members: Dr H. Nakatani, Assistant Director-General, HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases, WHO, Geneva, Switzerland; and Mr M. Tuler, Programme Manager, Knowledge Management and Sharing, WHO, Geneva, Switzerland.

The Committee also wished to acknowledge the valuable administrative and secretarial support provided by the following WHO staff members : Mrs E. Aimé-McDonald, Assistant to Director, Department of Control of Neglected Tropical Diseases, WHO, Geneva, Switzerland; Mrs L. Manful, Assistant to Assistant Director-General, HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases, WHO, Geneva, Switzerland; Mrs A. Mathew, Administrative Assistant, Global Leprosy Programme, WHO Regional Office for South-East Asia, New Delhi, India; Mr A. Singh, National Professional Officer-Editor, Reports and Document Unit, WHO Regional Office for South-East Asia, New Delhi, India; and Mr K. Surendranathan, Administrative Officer, Regional Director's Office, WHO Regional Office for South-East Asia, New Delhi, India.

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