Leprosy Elimination: Not as Straightforward as It Seemed

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Leprosy is a unique and enigmatic disease. It is one of the few diseases to have been known in ancient and medieval times, and it was one of the first diseases to be linked to a specific infectious agent, *Mycobacterium leprae* (*M. leprae*), in 1873.[1] Yet even now, the organism cannot be cultured in vitro, and important gaps persist in our understanding of its biology and epidemiology.[2] In particular, although contact with a known case of leprosy is a major risk factor in contracting the disease, scientists are not certain how the organism is transmitted from one individual to another, nor do they know when, throughout the period of incubation and clinical disease, an individual is particularly infectious.[3] These limitations have prevented the development of highly effective leprosy control measures, and there is little evidence that the transmission of the disease has been significantly reduced in recent years, despite efforts made toward that goal.[4]

As a bacterial infection, leprosy is susceptible to treatment with antibiotics; therefore, much has changed in the management of the disease over the last 50 years.[5] The effective treatment of leprosy with chemotherapeutic agents began in the early 1950s with the introduction of dapsone. However, at least 10 years of treatment were required for multibacillary cases, and lifelong treatment was often advised for those individuals with the highest bacillary counts. In the early 1980s, the introduction of multidrug regimens, all of which included the potent bactericidal drug rifampicin, allowed the length of treatment to be cautiously reduced—to a fixed period of 24 months by the early 1990s and to a fixed period of only 12 months by the end of that decade.[6] For the individual patient, multidrug therapy (MDT) meant a relatively rapid and effective cure.

ELIMINATION

Since the introduction of dapsone in the early 1950s, patients have been registered in treatment programs to promote adherence. Numbers of patients on treatment were reported and these data were collated to produce national and global prevalence statistics. Wherever MDT was introduced, a steady decline

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was seen in the number of patients on treatment (the registered prevalence), because the duration of treatment for each case was being shortened. It was soon realized that the widespread introduction of MDT would lead to a dramatic reduction in the registered prevalence of leprosy, and this did in fact occur over the subsequent two decades.[7]

The concept of the "elimination of leprosy as a public health problem" was developed initially in East Asia, where the declining prevalence was noted in various countries in the late 1980s. It was felt that, as the numbers of cases fell to low levels, the workload on the leprosy services would decrease, and so leprosy control activities would be carried out more effectively. It was also assumed that routine use of the rapidly bactericidal drug rifampicin would reduce disease transmission to a certain, although unknown, extent. Together, these elements would lead to a virtuous circle, through which leprosy would gradually die out. A convenient figure for the prevalence level when this virtuous circle would start to operate was put at one case per 10,000 population.[8]

Previous experience in the dapsone era had shown that when the prevalence dropped below this level, leprosy tended to disappear completely. In 1991, the World Health Assembly (WHA) adopted a resolution to eliminate leprosy by the year 2000, using this arbitrary definition of elimination—namely, a registered prevalence of less than one case per 10,000 population.[9] Globally, the registered prevalence did decline rapidly after the introduction of MDT, and by using the global population as the denominator, it was possible to declare the global elimination of leprosy by the year 2000—a remarkable achievement.[10]

By this time, however, attention had turned to the new case detection rate (NCDR) as a proxy for the incidence rate of leprosy.[11] This was felt to be a more accurate reflection of the epidemiologic position than the registered prevalence. It was realized that individuals with incident cases (i.e., new cases, with or without obvious symptoms and signs of leprosy, prior to diagnosis and start of treatment) were the ones actively transmitting the disease to others with whom they had household and social contact; therefore, such incident cases (the NCDR) would be a better indicator of the remaining potential for transmission in the community. In the dapsone era, incidence would have to be extremely low for the prevalence to be as low as one in 10,000, so transmission would be minimal. But with the short duration of MDT, incidence can still be relatively high, even when the prevalence has been reduced to the target level.

In general, the global NCDR has remained fairly static over the last two decades, although there are differences among countries.[4] One of the most widely used proxy indicators of ongoing transmission is the proportion of new cases detected in children younger than 15 years of age, and this rate has also remained very static in recent decades.[12] Thus, there is little evidence that the underlying epidemiology of leprosy has changed since the introduction of MDT. This unexpected failure of leprosy control programs using rifampicin-containing regimens to reduce transmission suggests that, in general, transmission must be occurring early in the course of the disease, before diagnosis and the start of treatment, perhaps even during the later stages of incubation, before the onset of clinical signs and symptoms.[13]

Geographical variations

The earliest accurate data to show a declining NCDR for leprosy came from Norway during the period 1870 to 1920.[14] Similar but more recent declines have been documented in China and other countries in East Asia.[4]

Three factors have been proposed as causes of these declines in incidence. First, the influence of rising living standards, presumably with better hygiene and less overcrowding, is assumed to be significant, although direct evidence for this occurrence is not easy to find.[15] Second, the Bacillus Calmette Guerin (BCG) vaccine (used as a vaccine against tuberculosis in many countries) has been shown in clinical trials to give a variable degree of protection against leprosy. As BCG has been the most widely used vaccine in global terms, it is expected that it will have had some effect on the incidence of leprosy.[16] The third factor is the effect of leprosy control measures—initially, the isolation of people diagnosed with the disease and, more recently, treatment with effective antibiotics.[3]

The decline of leprosy in much of Western Europe, however, took place before any of these factors—including a rising standard of living—played a role. Thus, it has been postulated more controversially that over a longer course of time, the rise in infection with *M. tuberculosis* led to increased immunity to *M. leprae* and, therefore, a long-term decline in the incidence of leprosy.[17]

In contrast to those countries with a documented decline in case detection, increases have been documented in Brazil, the country with the second-highest leprosy burden after India. Cunha et al. examined the NCDR in the state of Bahia, Brazil, from 1974 to 1997; almost 20,000 new cases were diagnosed during the period under review. A steadily increasing trend from 0.2 to 1.4 cases per 10,000 population was noted. The

methods of case finding did not change significantly over the period, and the fact that the rate of Grade 2 disability (visible damage or deformity from leprosy) in new cases remained essentially the same suggested that in Bahia, the increase in the NCDR reflected an underlying increase in the incidence of leprosy.[18]

The situation in India is complex, and it is too soon to interpret the most recent trends. Until 2001, the NCDR in India had been reasonably stable, but it has subsequently fallen rapidly.[19] There have been significant operational changes in India's management of its leprosy burden, not the least of which is the integration of leprosy control activities into general health services, with greatly reduced active case-finding activities. More time is required before the underlying trend can be determined.

ERADICATION

The WHA elimination target was defined as a registered prevalence of less than one case per 10,000 population and, as such, was achievable with current tools.[8] The concept of eradication, however, while not strictly defined, is more absolute and suggests at least the complete absence of transmission and new case detection. Thus, for example, leprosy could be described as eradicated from Great Britain, as no indigenous cases have been detected for many decades; in the new cases that have been detected, the individuals were infected while overseas. In Great Britain, a small number of cases are registered each year, MDT is provided, and health and welfare services seek to prevent disability and undertake physical and socioeconomic rehabilitation if needed.[20]

At present, we have neither the knowledge nor the tools to eradicate leprosy, although a successful program was carried out on the small island of Malta.[21] Where eradication has occurred, it has usually been through the interplay of factors beyond our control. One of the most important characteristics of a disease in determining whether it can be eradicated globally is the absence of an animal reservoir—if the disease is present in animals, it is considered impossible to eradicate. If, on the other hand, the disease only exists in humans, as was the case with smallpox, eradication may be possible. The situation regarding leprosy is not entirely clear. It has been found in some animals, such as armadillos in the southern United States, but there is no evidence to suggest that an animal reservoir is important in maintaining the infection in the human population.[22]

Essentially, efforts to eradicate leprosy will depend on the development of new tools, based on a better understanding of transmission. At present, research is focused on three specific areas. First, new diagnostic tools are being developed to detect leprosy infection, and newly developed molecular techniques are being applied to the study of the micro-epidemiology of leprosy.[23] These tools will enable researchers to study the pattern of infection in a community and thus identify appropriate targets for prophylactic interventions.

Second, chemoprophylaxis given to at-risk groups may prevent a majority of potential cases and thus reduce ongoing transmission.[24,25] At present, further trials of chemoprophylaxis in contacts of index cases are ongoing, but the most significant hurdle may be the waning of the protective effect within a few years. In Micronesia, a program of chemoprophylaxis began in 1996, with good short-term results.[26] The NCDR was, however, back to its pre-chemoprophylaxis level by 2005.[19] Longer regimens will incur greater costs and be logistically more demanding; in addition, the promotion of resistance to rifampicin (or any other potent antibiotic that could be used) in other organisms is a risk that may not be acceptable.

Third, vaccine development may allow immunoprophylaxis in either the whole population or an at-risk group, such as people in household contact with infected individuals. An ideal vaccine would be both a therapeutic agent, curing those already incubating leprosy, and a prophylactic agent, conferring a long-lasting immunity to leprosy infection. The development of a new leprosy vaccine has, however, not generally been regarded as a cost-effective venture.[27]

CONCLUSION

While the elimination target has been reached in most countries, and substantial benefits (including the universal availability of MDT without charge to the patient) have occurred through the World Health Organization Leprosy Elimination Program, the available evidence suggests that the underlying trends in incidence of the disease have been only minimally affected. It is also apparent that trends in incidence differ significantly in different parts of the world, for reasons that are not understood.

Further progress toward eradicating leprosy is dependent on a better understanding of the transmission of the disease and new tools with which to interrupt it. The tools being developed at present include (*1*) new diagnostic and epidemiologic tools that will be able to show which individuals in contact with the disease have been infected and the origin of the infection; (*2*) better chemoprophylactic regimens, although long-term efficacy may be an elusive goal; and

(*3*) effective immunotherapeutic/immunoprophylactic agents, which, although more costly to develop and deploy, may overcome some of the potential obstacles to a successful chemoprophylactic regimen.

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