Multidrug therapy for leprosy: a game changer on the path to elimination

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Leprosy is present in more than 100 countries, where it remains a major cause of peripheral neuropathy and disability. Attempts to eliminate the disease have faced various obstacles, including characteristics of the causative bacillus *Mycobacterium leprae*: the long incubation period, limited knowledge about its mode of transmission, and its poor growth on culture media. Fortunately, the leprosy bacillus is sensitive to several antibiotics. The first antibiotic to be widely used for leprosy treatment was dapsone in the 1950s, which had to be taken over several years and was associated with increasing bacterial resistance. Therefore, in 1981, WHO recommended that all registered patients with leprosy should receive combination therapy with three antibiotics: rifampicin, clofazimine, and dapsone. Global implementation of this highly effective multidrug therapy took about 15 years. In 1985, 5·3 million patients were receiving multidrug therapy; by 1991, this figure had decreased to 3·1 million (a decrease of 42%) and, by 2000, to 597 232 (a decrease of almost 90%). This reduction in the number of patients registered for treatment was due to shortening of the treatment regimen and achievement of 100% coverage with multidrug therapy. This achievement, which owed much to WHO and the donors of the multidrug therapy components, prompted WHO in 1991 to set a global target of less than one case per 10 000 population by 2000 to eliminate the disease as a public health problem. All but 15 countries achieved this target. Since 2000, about 250 000 new cases of leprosy have been detected every year. We believe an all-out campaign by a global leprosy coalition is needed to bring that figure down to zero.

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Introduction

In 2014, more than 200 000 new cases of leprosy were reported to WHO from 121 countries.[1] This incidence has scarcely changed in the past decade.[1] The consequences of leprosy for the individual patient have also changed very little in the past decade. Leprosy is still one of the most important causes of peripheral neuropathy, and up to a third of patients develop permanent nerve damage that leads to lifelong disability and social stigma.

Leprosy is caused by *Mycobacterium leprae*, a slow-growing bacillus. The incubation period of the infection can be 2–10 years and signs or symptoms of the disease can take up to 20 years to appear, a factor that hampers attempts to eliminate the disease. The mode of transmission of the infection is not fully known but is widely thought to occur through aerosol spread of nasal secretions and direct uptake of the bacillus via nasal or respiratory mucosa. The bacillus is then carried by the bloodstream to peripheral nerves, where it can cause irreversible nerve damage leading to a loss of protective sensation and tissue damage from painless burns and ulcers. Blindness resulting from corneal damage due to facial nerve paralysis, loss of corneal sensation, and iritis can also occur. Additionally, the infection can elicit acute immunological reactions that can cause inflammatory and oedematous skin lesions and also precipitate further impairment of nerve function. Many patients present with a reaction at the time of diagnosis or after starting of multidrug therapy. Those most at risk of reactions and further nerve impairment are patients with multibacillary leprosy (ie, those with six or more skin lesions) and a pre-existing impairment of nerve function.[2] Highly effective chemotherapeutics are available for the treatment of leprosy, which stop transmission of the infection after the first dose—although diagnosis is often established too late to prevent nerve damage.[3]

The dapsone era (1940–81)

M leprae is susceptible to a wide range of antibiotics. One obstacle, however, to finding the best available treatment for leprosy has been the inability to grow *M leprae* on artificial media. In 1960, Charles Shepard[4] showed that *M leprae* could be grown on the footpad of a mouse, a finding that made it possible to measure the potency of a drug and its minimal inhibitory concentration against *M leprae* and also to determine whether a drug's activity was bactericidal or bacteriostatic. In the late 1940s, dapsone, an antibacterial and anti-inflammatory drug, was regarded as the most effective drug against *M leprae*.[5] Additionally, dapsone was inexpensive and readily available worldwide. However, dapsone is only weakly bactericidal and takes several years to cure patients with leprosy, a factor that prevents satisfactory patient compliance. Moreover, by the 1960s,

Key messages

- Dapsone therapy for leprosy, introduced in the 1950s, was associated with increasing bacterial resistance in the 1970s
- In 1981, WHO recommended use of three drugs to treat leprosy: rifampicin, clofazimine, and dapsone
- Uptake of this multidrug therapy was slow and did not reach 100% coverage until 1997
- Global drug donation to provide free multidrug therapy at the point of care was vital to achieving 100% coverage
- The World Health Assembly resolution in 1991 to reduce the prevalence of leprosy to less than one in 10 000 population was a key factor in achieving 100% coverage
- Declaration of achieving this target in 2000 led to a substantial decline in resources for leprosy worldwide
- Use of the shorter multidrug-therapy regimen reduced the prevalence of leprosy by 90% but did not halt transmission
- A global leprosy coalition is needed to achieve zero transmission

evidence of bacterial resistance to dapsone was increasing, thus hampering the prospect of controlling the disease with this drug alone.[6]

In the mid-1960s, two other antibiotics were found to have activity against *M leprae*: clofazimine, a weakly bactericidal drug, and rifampicin, a potent bactericidal drug. A period of uncertainty followed, during which these and other drugs were tested singly in clinical trials[6,7] in several countries. By the late 1970s, no conclusive results about monotherapy regimens had emerged from these studies. In 1981, a WHO study group[6] recommended that patients with leprosy should be treated with combination therapy of three drugs (rifampicin, clofazimine, and dapsone), with rifampicin, the most potent drug, as the backbone of this multidrug therapy.

Implementation of multidrug therapy (1982–2000)

It took about 15 years after the WHO call for universal implementation for multidrug therapy to attain worldwide coverage of all registered patients. Many patients continued to receive dapsone alone.[8,9] Rapid adoption of multidrug therapy faced several hurdles: the cost of multidrug therapy was substantially greater than that of dapsone monotherapy; the availability of the three drugs, especially clofazimine, was limited; and agreement among experts about the optimal therapeutic regimen for multidrug therapy was not unanimous.[9] Furthermore, concerns were raised about the effectiveness and putative adverse effects associated with intermittent use of rifampicin. Additionally, in some countries, the slowness of the bureaucratic process for approval of multidrug-therapy deployment thwarted its early adoption.[9]

Some countries encountered other hurdles. Most African countries, for example, found it difficult to switch to multidrug therapy after their long-standing use of dapsone monotherapy. Dapsone and other antibiotics were being administered in Africa with little regard to standardised regimens. The drugs were often administered by mobile teams of paramedical workers based in leprosaria or by semi-autonomous treatment programmes that were dependent on non-governmental organisations (NGOs) for the necessary funds and supplies. Also, switching from often lifelong dapsone monotherapy to the 2 year regimen recommended for multidrug therapy called for a reconfiguration of deeply ingrained habits. The backdrop to all these impediments in Africa was an almost total absence of political commitment to leprosy in general and to multidrug therapy in particular. However, most African countries with leprosy cases adopted the new therapy after elaborate pilot multidrug therapy projects done between 1982 (when multidrug therapy was introduced) and 1997 (when all registered patients were receiving multidrug therapy).[10–15]

Brazil, which has long been among the top-five countries with the highest prevalence of leprosy, faced a different set of obstacles to early adoption of multidrug therapy. In particular, health authorities hesitated at implementing a new regimen: they questioned its efficacy and possible risk of side-effects, and expressed fears that clofazimine would cause changes in skin pigmentation that would lead to stigmatisation.

Several countries adopted multidrug therapy relatively early, largely because of the growing evidence of *M leprae* resistance to dapsone. Some early adopters used a regimen that differed somewhat from the regimen recommended by WHO, to which they subsequently adhered. India, for example, which had a high level of political commitment to leprosy, responded almost immediately to WHO's call for universal implementation of multidrug therapy.[16] By the end of 2000, the estimated number of leprosy cases in India had decreased from 3·9 million before adoption of multidrug therapy to 384 240 after adoption, despite the difficulties experienced by health-care providers in many Indian districts associated with introduction of multidrug therapy.[17]

By 1991, the number of patients with leprosy receiving multidrug therapy had decreased globally to 3·1 million from 5·3 million in 1985.[18] This achievement prompted the World Health Assembly to pass a resolution in 1991 to eliminate leprosy as a public health problem by 2000. Elimination was defined as a global prevalence rate of leprosy of less than one case per 10 000 population.[19] By May, 2001, WHO and its partners announced that the global elimination target had been reached. However, 15 countries (Angola, Brazil, Central African Republic, Côte d'Ivoire, Democratic Republic of the Congo, Guinea, India, Liberia, Madagascar, Mozambique, Myanmar, Nepal, Niger, Paraguay, and Tanzania) had still to meet the target.[17]

Effect on epidemiology

The two main epidemiological measures of leprosy are the number of new cases detected over a given period, which serves as a proxy measure of incidence, and the number of patients on treatment at a given time, which serves as a proxy measure of prevalence. In 1977, 4 years before the advent of multidrug therapy, more than 12 million patients with leprosy were estimated to be receiving treatment.[20] Most of these patients remained on treatment for 4–10 years and, in some cases, for life. The duration of multidrug therapy for patients with multibacillary leprosy was substantially shortened from 24 months in 1990 to 12 months in 1998. Over the next two decades, the number of patients receiving treatment decreased from 12 million in 1977 to about 600 000 in 2000, the target date given by WHO for elimination of leprosy as a public health problem.[21,17]

Shortening of the treatment duration was clearly a pivotal factor in achieving the elimination target set by WHO. Another was the 1991 call by WHO for all patients with leprosy worldwide to receive multidrug therapy. Between 1985 and 2000, the number of new cases detected each year remained at around 600 000–700 000. However, in the 6 years after WHO announced its elimination

target, the new case detection level decreased to 260 000 and remained close to that level over the subsequent decade.[22] This rapid decrease in the detection of new cases could be attributed to a decline in transmission of the infection due to a reduced load of *M leprae* in the community as a result of multidrug therapy. However, the long incubation period of *M leprae* would not be consistent with such a rapid decrease in incidence. Two observations suggest that leprosy transmission is continuing unabated: the fact that at least 9% of new cases detected over the past decade have been in children and the persistently high rate of disability in new cases in several countries, which reflects a delay in diagnosis and treatment that would be consistent with ongoing transmission of the infection.[1] This argument is supported by modelling studies[23–25] suggesting that delayed detection of leprosy is likely to have a greater effect on transmission than will the type of chemotherapy used. Perhaps the most plausible, if discomforting, explanation for the decrease in detection of new cases is that attainment of the WHO elimination target around the turn of the century led many health professionals and policy makers in the leprosy community to equate elimination of leprosy as a public health problem with eradication and, as a result, to scale back or abandon their efforts to stop *M leprae* transmission.[26]

However, many factors other than multidrug therapy are known to affect leprosy transmission. These factors include socioeconomic and educational improvements, increased access to clean water and sanitation, and reduced overcrowding. Moreover, robust evidence supports the possibility of leprosy being a zoonotic infection, a factor that would clearly affect disease transmission and efforts to curtail it.[27] Evidence also points to the BCG vaccine as being able to prevent leprosy.[28] Finally, rifampicin, a component of the multidrug therapy regimen, has been shown to be effective for preventing leprosy in the contacts of patients with leprosy,[29] a finding that offers a new way to reduce the incidence of leprosy.

Effect on disability

The advent of multidrug therapy offered a unique opportunity to attenuate the burden of disability in patients with leprosy by offering so-called multidrug-therapy services. These services go beyond administration of multidrug therapy, not only in efforts to prevent disability but also in establishing a relationship with patients that fosters access to early diagnosis, compliance with treatment, prevention of disability, self-care, and other forms of care and counselling.

There is a scarcity of evidence that multidrug therapy can reduce the disability rate associated with leprosy. One study[30] in India reported a reduction in the disability rate of patients treated with multidrug therapy from 6·15% to 1·50% over 3 years. In 1995, a WHO analysis[31] estimated that mutidrug therapy has prevented 1–2 million people from developing disabilities caused by leprosy since its introduction in 1982.

Future challenges

The answer to the question of whether leprosy still exists is sadly yes; leprosy remains part of the public health landscape in more than 100 low-income countries. Leprosy is newly diagnosed in more than 200 000 people each year, many of whom will suffer from physical, mental, and social impairment.[1] Additionally, 2–3 million people are estimated to be living with physical disability and stigmatisation as a result of the disease.[31] These figures are particularly disheartening because of the existence of a highly effective treatment, free at the point of care, that can prevent the suffering of these patients, a fact that raises two obvious questions: if the treatment is so effective, what is stopping it from reaching people with leprosy and why are people still being infected? The answer to the first question is that leprosy occurs mainly in hard-to-reach communities that have poor access to health care and where health-care systems lack the means to find and treat patients with leprosy. The answer to the second question is that infected, untreated people living in these communities are still spreading the infection and will continue to do so until transmission of the leprosy bacillus is halted.

How to stop *M leprae* transmission remains a subject of debate, fuelled by the absence of solid data about an appropriate evidence-based strategy. One reason for this absence is the lack of a clear understanding about the pathogenesis of *M leprae* infection, its mode of transmission, its interaction with the immunological responses it elicits in infected individuals, the mechanisms underlying the transition from infection to disease, and other unknown factors. Definition of a robust strategy is also hindered by the extremely long incubation period of the infection.

Despite these obstacles, use of multidrug therapy to treat this inadequately understood disease has been associated with substantial achievements. The development and global deployment of multidrug therapy in the early 1980s rescued leprosy treatment from growing antibiotic resistance to drugs used in the pre-multidrug therapy era and spared patients with leprosy from years of treatment with these drugs.[5] Multidrug therapy has been used to treat more than 16 million patients with leprosy during the past 20 years and has brought the global leprosy prevalence down by 96%, from more than 5 million cases in the mid-1980s to less than 200 000 by 2015. After more than 30 years since the global implementation of multidrug therapy, the relapse rate in patients remains extremely low, with only 1312 cases being reported in 2015.[1] The indisputable efficacy of multidrug therapy has gained the support of two donor institutions, the Nippon Foundation and the pharmaceutical company Novartis, who at different times ensured availability of the three drug components of the multidrug therapy at no cost to the patients (panel).

The final battle, however, has yet to be fought. A final strategy needs to interrupt the transmission of leprosy,

Panel: The crucial role of drug donations

Implementation of multidrug therapy was a monumental task, not only because of the huge number of doses required to treat a worldwide population of patients with leprosy of more than 5 million, but also because of the complex logistics and management needed to ensure that the drugs would reach the patients. Unsurprisingly, there were major problems. For example, many countries with endemic leprosy and various other public health needs were unable to find the funds needed to operate a national multidrug-therapy programme. Moreover, the global multidrug-therapy programme encountered frequent drug shortages as it progressed.

Two institutions came to the rescue by providing the drugs for multidrug therapy free of charge, which were then distributed by WHO to leprosy-endemic countries. The Nippon Foundation funded the donation from 1994 to 1999, and Novartis, the company that had developed two of the drugs (clofazimine and rifampicin), continued to donate all three drugs from 2000. These donations had a vital role in demystifying leprosy and paved the way to full integration of multidrug therapy into the general-health services of more than 100 countries. In 1992, Novartis began supplying the drugs for multidrug therapy in monthly calendar blister packs, which greatly simplified inventory control and drug distribution under sometimes difficult field conditions.

Without these donations, fewer of the world's leprosy-endemic countries would have reached the WHO's target of elimination of leprosy as a public health problem by the end of 2000. These donations, believed to be the first ever to be made in support of a disease-control effort, had a crucial role in enabling multidrug therapy to reach 100% global coverage by 1997. Over the years, the usefulness of these donations prompted WHO to undertake similar agreements with pharmaceutical firms for the drug-based treatment of other diseases, including human African trypanosomiasis, Chagas disease, visceral leishmaniasis, schistosomiasis, trachoma, onchocerciasis, and lymphatic filariasis.

Search strategy and selection criteria

We identified references for this Review through searches of PubMed for articles published up to Dec 31, 2015, by use of the terms "leprosy", "multidrug therapy", and "chemotherapy". We identified relevant articles through searches (Jan 1, 1970, to Dec 31, 2015) of WHO and Infolep websites, as well as our personal files. We reviewed articles obtained from these searches and relevant references cited in those articles. We included only articles published in English.

not through an attack on the prevalence of the disease, as has been the case until now (with global elimination of leprosy as a public health problem), but on the incidence of the disease, with an aim of zero detection of new cases. The linchpin of this zero-case strategy should be, as WHO stresses in its 2016 global leprosy strategy,[32] early diagnosis and prompt treatment of patients. Implementing this strategy will call for research aimed at accelerating the diagnosis of leprosy. Furthermore, its implementation will require sensitive and specific point-of-care tests to achieve early diagnosis of infection and disease; deployment of measures to prevent infection in patient contacts; and efficient, action-oriented surveillance systems to detect the remaining foci of *M leprae* transmission. For this strategy to succeed, increased social awareness to reduce the burden of stigma that is still prevalent in many communities is required. One analysis sums up the overarching tasks facing the leprosy community: "the challenge is to tackle the research gaps through novel collaborations, to improve operational collaborations with multiple players in all [neglected tropical diseases], and to incorporate new approaches in community engagement that would enhance public health at the community level. The leprosy world, including WHO, national governments, NGOs, the research community, and industry, together with people affected by leprosy, must respond to this situation that, if left unaddressed, could see all the past achievements in leprosy control reversed."[26] A preliminary meeting of all potential stakeholders, including national programme managers, WHO, non-governmental agencies, people affected by leprosy, and donors, was held during the 19th International Leprosy Congress in Beijing during September, 2016. Work has begun in 2017 to explore and develop a global leprosy coalition.

Contributors
AA developed the concept of the paper. AA and CSS prepared the initial draft and final paper. Specific reviews were drafted about the history and background of multidrug therapy (PS); leprosy in Africa (JK), Brazil (MV), and Asia (CSS); leprosy-associated disability (MV); the role of WHO, drug supply, and goals (EK); and epidemiology (CSS). All authors contributed to the discussion and approved the final draft.

Declaration of interests
We declare no competing interests.

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