Drug Resistance in *Mycobacterium Leprae* in the Context of Zero Leprosy

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* and/or by *Mycobacterium lepromatosis*.[1,2] The disease mainly affects the peripheral nerves, skin, and mucous membranes and if left untreated it may lead to nerve damage and deformity. Use of diamino diphenyl sulphone (DDS), also called dapsone, for treatment of leprosy began in 1945[3] and DDS monotherapy continued till the appearance of primary and secondary DDS resistance during the 1970s.[4,5] Most of these DDS-resistant cases originated from fully treated relapse cases. However, it was noted that low doses of dapsone and irregular treatment were the major causes of relapse.[5] Later when rifampicin, a bactericidal drug, was tried in a mono-therapeutic mode, *M. leprae* developed resistance also to this drug.[6] Considering the above, the multidrug therapy (MDT) approach was adopted like tuberculosis chemotherapy[7] in leprosy elimination by combining DDS with bactericidal drug, rifampicin, and an anti-bacterial drug, clofazimine with anti-inflammatory activity. After finding this MDT combination effective in curing leprosy, it was implemented in 1982 worldwide by the World Health Organization (WHO) for the elimination of leprosy.[8] Because of this robust MDT regimen, the prevalence of leprosy was brought down to <1 case/10,000 population (an elimination figure assigned by WHO) by the year 2002 worldwide.[9] Similarly, in India, the prevalence of leprosy which was 25.9/10,000 in 1991 was brought down to <1/10,000 in 2005 after the introduction of MDT under the elimination program.[10]

During this critical juncture of elimination, WHO has drawn up a strategical road map from the year 2021 to 2030 focussing toward Zero leprosy target.[11] However, at the moment although the prevalence of leprosy has gone down to 0.22/10,000 worldwide[12] and to 0.66/10,000 in India,[13] a total number of 202,185 new cases including 14,981 child cases are appearing in the world.[14] India is still housing 114,451 (57%) of these new cases of the world. These data clearly indicate that despite the continuation of effective chemotherapeutic preventive measures by MDT for more than 4 decades, the transmission of the disease is continuing in the community. Leprosy being a chronic disease with a known long period of incubation (>20 years),[12] a total elimination program with Zero leprosy target by 2030 may be too optimistic.[15] For any elimination/eradication program of an infectious chronic disease such as leprosy, effective chemotherapy with 100% full cure of the disease is one of the most important aspects of a control measure. The disease being dynamic in nature with a range of clinical manifestations exhibited by the host in response to infection has been well classified by Ridley and Jopling[16] based on a bacteriological and immuno-histological scale. However, for making the treatment procedure very handy at the field level, the disease manifestation has been simplified and classified by WHO as paucibacillary (PB = presence of 1–5 skin lesions) and multibacillary (MB = presence of >5 skin lesions) and recommended treatment of the disease with 12 months of MDT for MB and 6 months of MDT for PB cases.[12] Further, as the bacterial index (BI) and the activity of the lesions are not seriously considered at the field level, the patients are considered as cured cases and are released from treatment after the completion of fixed-dose MDT. MB cases harboring a wide range in *M. leprae* population varying between 1+ and 5+ BI receive 12 monthly doses of 600 mg each of the bactericidal drug, rifampicin which has a half-life of only two and half hours.[17] It has been shown that despite full treatment with MDT for 2 or 3 years, *M. leprae* is able to persist as viable bacilli as shown by the growth in mouse footpad (MFP) or by measuring adenosine triphosphate levels using bioluminescence assay.[18-20] Later, the presence of viable *M. leprae* has also been reported from fully treated PB cases also with a history of relapse.[21] In addition, it is also not very uncommon to find defaulters during the course of MDT. The percentage of nonadherence to fixed-dose MDT (defaulters) varied between ≈50% and ≈60% and has been noted predominantly in patients with MB.[22-24] Hence, it was expected that relapses would occur from the pool of defaulters or from fully treated leprosy cases due to the growth of the remaining viable *M. leprae* bacilli which have not been killed by MDT. A recent cohort study conducted by our group in the Leprosy Mission Hospitals in India on MB patients with high BI (≥3+) showed the presence of viable *M. leprae* employing quantitative reverse transcription-polymerase chain reaction for the gene expression level of *hsp18* gene (encoding the heat shock 18 kDa protein) and *esxA* gene (encoding ESAT-6 protein) which were found to correlate with the exponential growth of *M. leprae* in MFP[25] in skin biopsies from fully treated cases (Under publication). The remaining viable bacilli in such fully treated highly bacillated MB cases will be able to grow because in such patients' cell-mediated immunity to *M. leprae* remain suppressed for a long time.[26] If these relapse cases are not diagnosed and treated immediately, they will act as a source of infection and will be responsible for the transmission of the disease in the community.

Earlier relapses during DDS monotherapy[27-30] associated with the emergence of both primary and secondary drug resistance to DDS[4,5] sufficiently delayed the progress of the leprosy control program till MDT with the bactericidal drug rifampicin was launched in 1982.[8] Now, after more than 4 decades of MDT, relapses are often being noted due to drug resistance against rifampicin. Resistance to

rifampicin and other bactericidal drugs such as ofloxacin has been reported from most of the leprosy endemic countries such as Brazil, China, Colombia, Malaysia, Korea, Myanmar, Indonesia, Philippines, Japan, and India.[31-38] A recent study in Colombia showed a significantly higher percentage of resistance to rifampicin in newly diagnosed cases as compared with treated cases.[39] Considering the gravity of the situation, WHO initiated a multicentric study which continued for 10 years to look for the distribution of drug resistance in the endemic countries of the world. It was noted that of 1143 relapses 58 (5.1%) and of 789 new MB cases, 16 (2%) were resistant to rifampicin.[40] These studies clearly indicated that the rifampicin-resistant strain is transmitting the disease in the community. These results immediately directed WHO to take an account of the background data on antimicrobial resistance (AMR) through a global consultation of the experts of leprosy endemic countries without any data for drug resistance between 2014 and 2020 from India which holds >50% of the world population of leprosy cases.[41] Further, WHO has recently organized a virtual meeting of the global experts and presented AMR surveillance data from all the endemic countries and considered that threat due to AMR is not yet there and hence leprosy elimination program can continue with the first-line drug regimen. However, it was decided that the continuation of AMR surveillance following the WHO guidelines should be continued.[42]

Although relapse in leprosy gathered momentum for search for the occurrence of AMR from cases of relapse and was taken as a probable strong indicator for patients being resistant to MDT, around the same time, there were reports of the occurrence of drug resistance from recurrent reactional cases (both type 1 and type 2) by various tertiary care hospitals.[43-47] Although type 1 reactions may occur in about 20–40% of MB leprosy cases,[48-53] type 2 reactions [or erythema nodosum leprosum (ENL)] have been reported in about 10% of borderline lepromatous[54] and from more than 50% in lepromatous leprosy cases.[55] All these studies strongly indicate that patient manifesting reactions is a very common phenomenon during therapy and after completion of MDT and therefore, reactional patients should be screened for *M. leprae* drug-resistant strains under the leprosy elimination program. Further, a recent retrospective cohort study showed that *M. leprae* drug-resistant strains for all three drugs may also be associated with neuropathy in leprosy.[56]

In the background scenario of the emergence of *M. leprae*-resistant strains during MDT therapy and post-MDT therapy, various research groups are engaged in reducing the transmission of leprosy with a chemotherapeutic approach by administration of single-dose rifampicin (SDR) as a leprosy post-exposure prophylaxis (LPEP) measure to contacts of newly diagnosed leprosy cases.[57] Therefore, in 2008 a cluster-randomized placebo control double-blind trial in Bangladesh named contact transmission and chemoprophylaxis in leprosy was conducted. It was noted that SDR was effective for the first 2 years in reducing the incidence by 57%. However, after 2 years there was no difference in the protective efficacy for leprosy between the SDR and placebo control groups.[58] During the DDS monotherapy era in the 1960s and 1970s, chemoprophylaxis trials were also conducted in Uganda and India with the administration of contact population with dapsone and acedapsone, respectively, for the control of leprosy. These trials although showed about 85% decline in the prevalence of leprosy but ultimately the protective efficacy waned with time as there was no effect of dapsone chemoprophylaxis on the incidence of leprosy. Further, during that time reports on the rise in dapsone resistance cases in the population also did not favor the implementation of dapsone chemoprophylaxis in the control program.[59-65] Although SDR chemoprophylaxis of contacts of newly diagnosed patients did not show any difference in protective efficacy after 2 years between the SDR and placebo group, the SDR chemoprophylaxis was introduced into the program because of its immediate protective effect on the development of leprosy in the newly diagnosed leprosy contact population of the world for ultimate reduction in transmission of infection and consequently in the emergence of new leprosy cases in the world. Initially, a feasibility study conducted for the implementation of SDR to the contacts of newly diagnosed patients under the control program in Brazil, India, Indonesia, Myanmar, Nepal, Sri Lanka, and Tanzania showed that LPEP with SDR is well tolerated and can be easily implemented in the leprosy control program of the endemic countries. Following this, SDR has been implemented under the direction of WHO in the elimination program in 2018 in all endemic countries worldwide.[66]

From the above, it is clear that secondary and primary resistance to rifampicin and ofloxacin are on the rise which has been established by screening relapse and newly diagnosed MB cases from the leprosy endemic countries.[31-40] Further, the annual records also show a gradual rise of relapse cases (from 2844 of 2016 to 3897 of 2019)[14,67,68] under the elimination program. In addition, reports of isolation of rifampicin drug-resistant strains from both type 1 and type ENL cases which are being reported from various research groups are of great concern as this has not been taken up yet in the *M. leprae*-resistant strain surveillance mechanism under the program. As leprosy cases with reactions are difficult to treat under field conditions, these cases are mostly referred to and treated in tertiary care hospitals having indoor facilities. All these findings strongly indicate that both rifampicin and ofloxacin-resistant *M. leprae* strains released from the relapse and reaction cases are slowly spreading infection in the endemic population. Introduction of SDR in such a situation might induce more drug pressure and might help *M. leprae* strain to become more resistant to the

prescribed drugs and could further help in the survival of *M. leprae*-resistant strain in the endemic community for the propagation of infection for a long time to come. Although the problem of AMR is now very focal in distribution, the drug pressure in the community might rather help in further maintenance and propagation of AMR strain in the community.

Therefore, the WHO strategic plan "Toward Zero leprosy by 2030"[11] might direct its priority to monitor both relapses and reactions in leprosy which are occurring due to drug-resistant *M. leprae* to the primary bactericidal drug rifampicin and the second-line drugs, ofloxacin and clarithromycin. Although most of the resistant cases have been reported in patients who have relapsed after MDT indicated the appearance of secondary drug resistance to either rifampicin or ofloxacin or both;[35,36] however, the emergence of primary drug resistance to rifampicin and ofloxacin in an endemic population is an early indication for drug-resistant *M. leprae* strain transmission in the community.[37] It has been often mentioned that the relapse rate in the community is very low and hence it will not have much impact on the leprosy elimination program.[40] However, it may be emphasized that report of relapse and reaction in the community is generally late and mostly the cases land up in tertiary care hospitals because of their need for personalized treatment. Considering the above points mentioned, the journey toward Zero leprosy by 2030 may not be attainable without directing its priority to the establishment of a robust surveillance mechanism for relapse and reactions in leprosy.

Therefore, it is recommended that the following strategy should be adopted immediately to check the transmission of AMR strains of *M. leprae* in the endemic community are as follows:

(i) Establishment of a robust setup for early diagnosis of relapse and reactions in leprosy at the field level and their molecular screening for mutations for drug resistance to DDS, rifampicin, ofloxacin, and clarithromycin.

(ii) Screening of all new MB cases for the presence of molecular mutations for primary drug-resistant strains to DDS, rifampicin, ofloxacin, and clarithromycin.

(iii) Once a drug resistance case to the above drugs is identified, the close contacts in the family should be screened for early detection of transmission of drug-resistant *M. leprae* strains in the family.

(iv) After identification of either primary or secondary drug-resistant cases, the patient should be treated adequately with an alternative regimen for the cure of leprosy.

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