Report of Meeting on Sentinel Surveillance for Drug Resistance in Leprosy

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1. Background

The fight against leprosy has been a great success largely due to the development of multidrug therapy (MDT) in 1981. Resistance to dapsone has been reported since the late 1960s but convincing data supporting the existence of clofazimine-resistant strains of M. leprae have not been reported. . Since rifampicin is the backbone of MDT, it is important to monitor the emergence of rifampicin-resistant mutants.

In addition, several new anti-mycobacterial drugs are either under development or are in the market against other infections. The emergence of drug resistance is a concern and a threat for many disease control programmes, especially when secondary prevention (chemotherapy) is the main component of the control strategy. To meet the challenge of containing the disease and to sustain the declining trend of leprosy in endemic countries, it is essential to keep a vigil on drug sensitivity patterns in leprosy-endemic communities.

2. Objectives

The objectives of the meeting were:

- to review the drug resistance surveillance data;
- to review trends in relapses reported by the national programmes; and
- to discuss recent advances in techniques for diagnosing drug resistance and in therapy for drug resistant cases.

3. Opening session

Opening remarks were made by Dr V. M. Katoch, Director-General, Indian Council of Medical Research (ICMR) and Dr Myo Thet Htoon, Team Leader, WHO Global Leprosy Programme.

Professor Emmanuelle Cambau, Department of Bacteriology and Hygiene, Faculty of Medicine, Paris, France was nominated as chairperson and Dr Vijayalakshmi Valluri from Blue Peter Public Health and Research Centre, Hyderabad, India and Dr Khin Saw Aye, Immunology Research Division, Department of Medical Research (Lower Myanmar) were nominated as rapporteurs.

A total of 40 participants including experts from the sentinel sites (Brazil, China, Colombia, India, Nepal, Mali, Madagascar, Myanmar, Philippines, Viet Nam and Yemen), researchers from the reference laboratories and partner organizations attended the

meeting. The programme and list of participants are provided in Annex 1 and Annex 2 respectively.

4. Updates: 2010 surveillance activities

Dr Myo Thet Htoon updated the surveillance system data. In 2010-2011, there were 14 participating countries: Burkina Faso, Madagascar, Mali and Mozambique for African Region, Brazil and Columbia for American Region, Pakistan and Yemen for Eastern Mediterranean Region, India, Myanmar and Nepal for South-East Asia Region and China, Philippines and Viet Nam for Western Pacific Region. In addition, 10 reference laboratories were involved.

The current surveillance data are based on detecting drug resistant *M. leprae* in relapse cases of leprosy. Dr Myo Thet Htoon recalled the definition of a relapse case which was decided at the previous meetings: (1) the re-occurrence of the disease at any time after completion of a full course with WHO recommended MDT with (2) the appearance of definite new skin lesions and/or an increase in the bacteriological index of two or more units at any single site compared to the same site at a previous examination. The procedure is to seek for mutations in the *rpoB*, *folP* and *gyrA* genes from a skin sample (skin smear or biopsy) from a lesion with a BI of 2+ or above.

In 2010, reports were received from eight countries (China, Colombia, India, Myanmar, Viet Nam, Pakistan, Philippines, and Yemen). A total of 109 MB relapse cases were reported: 80 with a bacteriological index (BI) of 2 and more and 75 cases with new skin lesions. There were no child cases reported and a majority of relapses were among males (84%).

Of these 109 relapse cases, 88 were tested for drug resistance. DNA amplification was reported to be negative for dapsone in 16 and for rifampcin in 17 cases (18%), which is much less that in 2009. Results of resistance associated with gene mutations were the following: nine dapsone resistance cases and one rifampicin resistance. This resulted in 12.5% secondary resistance to dapsone (9/72 results of *folP* sequencing) and 1.4% secondary resistance to rifampicin (1/71results of *rpoB* sequencing). No mutation of the *gyrA* gene associated to ofloxacin resistance was reported.

The definition of relapse was discussed, in order to increase the likelihood of including only “true” relapses and decrease the inclusion of cases of reversal reactions or those with high initial BI, who may remain smear-positive for some time after the completion of treatment with MDT.

5. Country presentations on relapse cases

5.1 Brazil

The source of the data presented by Dr Philip Suffys, was SINAN – National Information System of Communicable Diseases. Dr. Suffys mentioned that there were 1375 relapses reported during 2010. The male to female ratio among relapse cases was 1.82; majority of relapses were reported among MB cases (85%). Only about 1.4% were under the age of 15 years. The bacilloscopy results were available for 63.8% of the cases, of these 38.3% were positive. No resistant cases were observed among the relapse cases in 2010 compared in the period 2007-2008, where four cases with one strain mutated in rpoB only, one strain mutated in folP1 and rpoB and two more strains with SNPs in folP1, rpoB and gyrA were detected as validated by Dr. Matsuoka's laboratory.

5.2 China

Dr Shen Jianping from the National Centre for Leprosy Control mentioned that China is detecting about 1500 new cases and about 150 relapses (after dapsone monotherapy and after MDT) are being reported every year since 1986. During 2010, 1324 new cases were reported. The number of relapses reported for the year was 96 (61 after dapsone monotherapy and 35 after MDT). The number of relapses in 2010 is much smaller than previous years due to efforts to improve the quality of relapse diagnosis and confirmation. Dr Jianping concluded by mentioning that WHO's recommendation of multidrug therapy regime is still effective for the treatment of leprosy. Thus, drug resistance in China may not be a serious problem.

5.3 Madagascar

Drug surveillance data from Madagascar was presented by Dr Ramarolahy Emerantien Benoit. The National Leprosy Programme was initiated in 1992 and the leprosy elimination goal was reached by 2006. The WHO drug surveillance study was initiated in 2011. A stable new case detection and prevalence rate was observed from 2006 to 2010. In 2010, 1521 new cases were detected of which 84% were MB cases. In 2010, eight relapse cases were reported and in the first half of 2011, 10 relapse cases were reported.

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