A diagnostic test to detect *Mycobacterium leprae* and *Mycobacterium lepromatosis* infection among asymptomatic household/familial contacts of leprosy patients to treat them with appropriate prophylactic interventions and prevent the occurrence of overt clinical leprosy.

Epidemiology:

Leprosy continues to be a significant health problem in endemic countries, with approximately 200,000 new cases reported each year from more than 155 WHO member states and territories. The stable incidence in the past 15 years and the fact that approximately 10% of newly detected leprosy cases annually are in children together indicate ongoing transmission of infection. Leprosy is caused by an obligate intracellular bacillus, *Mycobacterium leprae (M. leprae)*. Transmission of leprosy bacilli is poorly understood, and existing evidence suggests that inhalation of aerosols containing *M. leprae* is the main route of transmission. In some circumstances, skin-to-skin contact has also been implicated. To date there is no conclusive evidence that the shedding of bacteria into the environment by an active case can lead to subsequent infection of other individuals.

Owing to the chronicity of *M. leprae* infection, individuals in close contact with the leprosy cases may harbour infection before clinical signs appear. Limited evidence suggests that sub-clinically infected individuals may transmit *M. leprae* to other individuals in close physical contact. Those at highest risk are household and family contacts. Hence, it is vital to detect *M. leprae* infection primarily in the household/familial contacts of leprosy cases to determine individuals that require an enhanced regimen of post-exposure prophylaxis both to prevent subsequent development of disease in those individuals and to prevent onward *M. leprae* transmission.

In addition to *M. leprae*, infection with *Mycobacterium lepromatosis* has been implicated in the manifestation of diffuse lepromatous leprosy. Prevalence was noted in Mexican and Indonesian populations.

In the Neglected Tropical Diseases (NTD) road map 2021–2030, leprosy is targeted for elimination (interruption of *M. leprae* transmission). Guidelines for contact tracing and interrupting transmission with appropriate prophylactic interventions have also been developed. However, the exact, direct mechanisms of action of these interventions has not yet been studied, nor is it known what the long-term consequences of the interventions are.

Public Health Response:

Research and field observations indicate that the risk of developing leprosy is significantly higher among household/familial contacts of leprosy cases when compared to individuals with no known contact with leprosy cases. Given the stable incidence, it is clear that passive case detection and treatment with multi-drug-therapy (MDT) alone cannot interrupt ongoing transmission of infection.

Large-scale clinical trials with single-dose rifampicin (SDR) given as post-exposure prophylaxis (PEP) to contacts of newly diagnosed patients with leprosy have shown a 50–60% reduction of the risk of developing leprosy among these contacts over the following 2 years. Leprosy post-exposure prophylaxis (LPEP) is now being introduced into national programs. In 2018, WHO published guidelines for implementation of contact tracing and PEP. With the view to administer more efficacious PEP against leprosy, the NTD roadmap 2021–2030 has listed “advancing research on new preventative approaches” as a critical action to achieve the 2030 targets. It also lists continuing investment into diagnostics for disease and infection, developing surveillance strategies, systems and guidelines for case finding and treatment, and ensuring resources for validation as critical actions. Tests for confirmatory diagnosis of leprosy (and classification thereof) in individuals with limited clinical signs as well as tests for pre- and post-elimination surveillance to ascertain if transmission has been interrupted, are required.

The WHO guidelines provide information on the importance of active case detection and contact examination, the efficacy of chemoprophylaxis, and feasibility and acceptability of chemoprophylaxis. A diagnostic test that can help identify high risk individuals with *M. leprae* infection who require a more intensive regimen of PEP than just SDR-PEP would be helpful in planning and implementing various

PEP interventions and would materially contribute to interrupting *M. leprae* transmission. SDR-PEP is still advisable for the contacts who are negative as this is a preventative therapy.

Available Diagnostic Tools:

Research has produced many leads in terms of molecular and immunodiagnostics for *M. leprae* infection. Antibodies against *M. leprae* cell wall components have been extensively studied for more than three decades with the goal of developing immunodiagnostics for leprosy. Antibodies against the antigenic part of the *M. leprae*-specific phenolic glycolipid molecule (PGL-I) were detected in many populations endemic to leprosy. Despite the presence of PGL-I antibodies in more than 50% of individuals in hyperendemic areas, the majority of those with a positive antibody titre never develop leprosy as noted from various prospective cohort studies.

Similarly, *M. leprae* nucleic acids were detected with varying sensitivity across multibacillary and paucibacillary leprosy cases and even in household contacts paving a way for the development of more precise molecular detection tools. Many studies identified highly specific and repetitive elements in the genome of *M. leprae* as suitable DNA targets for molecular diagnostics.

To date, only a few leprosy diagnostic assays detecting *M. leprae*, or immune responses to it, possess *in-vitro* diagnostic use authorization and are commercially available. Hain Lifesciences has a test system for the identification of *M. leprae* and its resistance to rifampicin, ofloxacin and dapsone. GenoType Leprae DR is a PCR based DNA strip technology requiring 3 separate instruments, and as such is not suitable for low resource setting. *M. lepromatosis* is currently being detected using molecular diagnostic assays (research use only) and there are no commercially available tests.

Orange life sciences in Brazil, in collaboration with the Infectious Disease Research Institute in Seattle, USA, has developed a qualitative LFA to detect *M. leprae*-specific IgM antibodies against PGL-1 and IgG antibodies to LID-1. CTK Biotech (San Diego, USA) has developed qualitative GOLD-LFA, utilizing the same antigens as Orange life sciences. However, both of these assays are for research use only (RUO) and may no longer be available at this time.

Development and implementation of point-of-care and field-friendly diagnostics to detect *M. leprae* infection requires concerted efforts between technology developers and field/program-level implementing partners.

Diagnostic Technical Advisory Group:

The WHO Department of Control of NTDs manages a diverse portfolio of twenty diseases, each with its own unique epidemiological and diagnostic challenges. The Strategic and Technical Advisory Group (STAG), the principal advisory group to WHO for the control of NTDs, decided that a single WHO working group would help ensure that a unified approach could be used to identify and prioritize diagnostic needs, and to inform WHO strategies and guidance on the subject.

Thus, the Diagnostic Technical Advisory Group (DTAG) was formed as an advisory group to the Department of Control of Neglected Tropical Diseases. The first meeting of the DTAG was held in Geneva, Switzerland, on 30 and 31 October 2019.

DTAG members discussed priorities for the year ahead as well as how to manage the complexity of supporting the diagnostics agenda across the entirety of the WHO NTD portfolio. Recommendations were made, based on the understanding that they would be reviewed at the next meeting, as it had been made clear that all NTDs had diagnostic needs which would have to be addressed in due course.

The diagnostic needs for leprosy, determined by the DTAG are:

- Detection of *M. leprae* infection – to provide prophylaxis to those most at risk
- Screening for potential leprosy cases – to better identify individuals with suggestive signs of leprosy
- Diagnosis of leprosy – to confirm diagnosis of all forms of leprosy (especially indeterminate and PB leprosy)

- Prediction of future disease - to identify those at risk of disability
- Diagnosis of nerve function loss – to recognize early nerve function changes that can lead to sensorimotor neuropathy associated with leprosy

Purpose of the TPP

Prior to attracting developers and companies to invest in producing innovative diagnostics for leprosy, it is essential to have a “target product profile” (TPP) that recognises and documents the gaps, priority areas where diagnostics are needed, use cases, needs statements and requirements for ideal and optimal test characteristics for each of these priority areas.

A point-of-care and a field-friendly diagnostic tool is required to detect *M. leprae* infection among contacts of leprosy cases, especially those who are household or blood-related contacts. Such a diagnostic can detect *M. leprae* infection at subclinical stage enabling programs to intervene with appropriate chemo or immunoprophylactic tools to prevent progressing to clinical leprosy and curb transmission. In the light of the expanding PEP interventions in leprosy endemic countries, it is also important to have a diagnostic as a guiding tool to decide on the individuals needing enhanced PEP interventions as well as to monitor the effect/efficiency of the intervention at an individual level. This TPP will be developed with the view to define ideal and optimal characteristics of the diagnostics that will be used to detect *M. leprae* infection among household/familial contacts of leprosy cases.