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Review Article

Towards Prevention and Eradication of Leprosy : Current Status and Research Needed in Community Health & Immune Dysregulation

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Leprosy, a disease caused by *M. leprae*, mainly affects dermis and peripheral nerve but is feared for its complications, and disabilities. Despite major reduction in leprosy cases after use of multi-drug therapy, blocking the transmission of leprosy is an arduous task due to factors that are possibly involved, these include agent (microbial characteristics), host and environmental factors. These factors including the immune dysregulations may increase the vulnerability towards leprosy, especially in women and children. This review article is aimed at understanding the current knowledge about such factors related to leprosy; and to identify the necessary steps and research needed to eradicate leprosy. A systematic literature search on PubMed, OVID, EMBASE, the Cochrane Library, Scopus, Web of Science, and Science Direct was done with the keywords "leprosy", "immune dysregulation in leprosy", and "risk factors of leprosy" to select published literature for this analysis. Several factors are identified as probable contributors to immune dysregulation/ incapability related to leprosy. These include host factors, health services and environmental factors. Important host related factors and interventions relate to stigma, vaccination, chemoprophylaxis, nutritional status, antenatal care, proper breast feeding. Environmental health factors relate to residential aspects including type of floor, humidity, intensity of sunlight, ventilation, clean water facilities, which may be contributing to persistent transmission. Health services play a role in ending leprosy transmission, both promotive, and rehabilitative treatment. In developing countries like Indonesia, health services suffer huge adverse impact from stigma..Some studies have showed the importance of an immunoprophylaxis strategy with Bacillus Calmette–Guérin (BCG) vaccination, *Mycobacterium w (Mw) or Mycobacterium indicus pranii (MIP)* vaccination and single dose rifampicin chemoprophylaxis, as preventive measures for blocking the leprosy transmission. PEP carboxylase (PPC) is likely to be essential for the intracellular survival of *M. leprae* and since it is absent in humans, it can be a potential target for treatment of leprosy. Studies show that vitamin D receptor (VDR) and vitamin D and role of food in leprosy needs in depth investigation. Pregnant women with poor nutritional status are prone to anaemia and malnutrition; these may be immune dysregulation and may be linked to leprosy infection. Further research is needed to better understand specific roles of said contributors towards immune dysregulation(s), thereby increasing the vulnerability of some person towards leprosy.

Keywords : Leprosy, Immune Dysregulation in Leprosy, Risk Factors of Leprosy

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Introduction

Leprosy, caused by *Mycobacterium leprae and M.lepromatosis* (a newly identified variant) is a curable disease. After major success with WHO recommended MDT, leprosy was declared "eliminated"as a public Health problem (less than 1/10,000) in 2000 in Indonesia and in most parts of world. However, in 2018 there were still around 2 to 3 million people affected by leprosy globally. India has the largest number of leprosy patients, followed by Brazil and Indonesia. The highest number of new leprosy cases is in India with 134,752 cases, followed by Brazil with 33,303 cases and subsequently Indonesia occupies the third position with 16,825 cases and disability rate of 6.82 people per million population (WHO 2018a). The case of new leprosy in Indonesia is relatively stable. The condition is thought to be a result of the failure of the *M. leprae* transmission chain termination (Santos et al 2017).

In 2019, there were 16,186 new reported cases of leprosy in Indonesia. Twenty six provinces has achieved leprosy elimination while 8 provinces have not which include North Sulawesi, South Sulawesi, West Sulawesi, Gorontalo, Maluku, North Maluku, Papua, and West Papua. The prevalence rate and new leprosy cases tend to be static every year after the elimination of leprosy at the national level was reached in 2000. Prevalence rates ranged from 0.6 to 0.9 per 10,000 populations and the number of new case findings ranged from 6-8 per 100,000 population (Ministry of Health 2019).

Children are believed to be an important vulnerable group to leprosy infection due to their immature immunity. The proportion of new leprosy in children is also one indicator of failure on termination of leprosy chain transmission and indirectly reflects the number of undiagnosed cases in the community. WHO has a target to reduce disease transmission and grade II disability, especially in pediatric cases (WHO 2016). However, over the years the proportion of leprosy in children has not improved significantly (De Oliveira & Diniz 2016). Epidemiological data from 150 countries show there were around 16,979 cases of child leprosy in 2017 (Narang & Kumar 2019). Delay in early diagnosis and difficulty in assessing sensory loss in children may contribute to the high leprosy rate in children (Narang & Kumar 2019).

Studies on transmission of leprosy have focused on host and environmental factors (Meima 2002, Joshi 2016, Nath & Chaduvula 2016). Besides the health services, host factors include immunological status, stigma, nutritional status, antenatal care, and interventions such as vaccination/ immunotherapy (Khandapani & Mishra 2010, Rao & John 2012, Jariwala et al 2013, Wagenaar et al 2015, De Oliveira & Diniz 2016, Barreto et al 2017, Oktaria et al 2018, Narang & Kumar 2019). Environmental factors

studied by different investigators pertain to residential aspects, type of floor, humidity, intensity of sunlight, ventilation, and clean water facilities (Matsuoka et al 1999, Kerr-Pontes et al 2006, Lavania et al 2008; Adwan et al 2014, Patmawati & Setiani 2015, Rafiludin et al 2017).

The host's immune system is an important factor for susceptibility/ resistance to any disease. Some immune components that have been identified as having important role in leprosy relate Th1, Th2, Treg, and Th17 (Nath & Chudavala 2016). The dysregulation of these four components has been considered significant in making the host susceptible to leprosy (Ottenhoff 2012, Palermo et al 2012, Bobosha et al 2014, Chaitanya et al 2012, De Sousa et al 2017).

The groups at high risk of leprosy are individuals who have poor living standards, poor nutrition, and poor environmental conditions. These are thought to contribute to dysregulation of the immunity (Cree & Cairns 1998, Ottenhoff 2012, Palermo et al 2012, Bobosha et al 2014 , De Sousa et al 2017) which might facilitate the leprosy transmission (Sadhu & Mitra 2018).

Unfortunately, until now, the factors that have possibly caused the failure in eradicating leprosy are still not well understood. Therefore, it is necessary to conduct studies for analyzing the relationships between various risk factors in community health, including environmental factors, health care factors, and individual health status, with dysregulation of immunity, and its effect on the transmission of leprosy. This review article aims at analyzing the published literature to identify factors associated with transmission, endemicity as well as immune dysregulation in leprosy so that better strategies could be planned to block/ terminate the transmission of *M. leprae* and eradicate it from all parts of world.

Methods

This review has included studies that focus on epidemiology and community health as well as immune dysregulations in leprosy. We have excluded literatures which are not written in English. For this purpose, a search on PubMed, OVID, EMBASE, the Cochrane Library, Scopus, Web of Science and, Science Direct related to immune dysregulation in leprosy with the keywords "leprosy", "immune dysregulation in leprosy" and, "risk factors of leprosy" was done. Besides the original recent and old well cited papers, reviews, popular chapters in standard text books were included in the analysis so that important advances and gap areas could be identified.

Results

1. Health Services

Health services available to patients with leprosy also play a role in stopping the transmission of leprosy. Health services provide not only treatment programs but also from promotional to rehabilitation programs. Unsatisfactory health services influence the surrounding population to be reluctant to seek treatment or to continue treatment that could jeopardize the termination of the transmission chain and increase the loss to follow up cases (Abeje et al 2016).

1.1. Public Health Services in Indonesia : In Indonesia, it is the responsibility of the public health services (PHC) or pusatkesehatanmasyarakat (PUSKESMAS) to control leprosy through a monitoring programme. Approximately 9000 PHCs are led by 530 district health officers to detect new cases, monitor treatment, and evaluate the outcome. A routine and on-time attendance at PHCs is the key to ensure successful therapy (Rachmani et al 2013). Factors of the health services strongly influence the family's ability to care for patients with leprosy. The strength of the family and its involvement increase when a family member needs constant help because of their chronic

health problems, such as in leprosy patients (Nasrudin et al 2018). Public health services in Indonesia are playing their role in early detection of cases in the community and also tracking those (Susanti et al 2018). In addition e-leprosy framework has been tried in a real setting of a leprosy control program in Pekalongan an e-leprosy framework was deployed. A web-based application was developed to send and receive notification messages between the e-leprosy framework and leprosy surveillance officers (LSOs), featuring an automated short message service (SMS). This study showed that low-cost and simple digital health technology is good for disease control programs with long-term leprosy medication (Rachmani et al 2019).

1.2. Stigma Management in Leprosy Patients Related Health Services in Indonesia : Stigma is an intricate social construct. Three interacting levels of stigma have been described (Livingston & Boyd 2010). The first level is the micro-level that includes the three types of stigma displayed by those who are stigmatized: 'anticipated' (or perceived), 'internalized' (or self-stigma) and 'experienced' (or stigma). The second level is the meso-level, also known as social or stigma to the general public. The third level is the macro-level, also known as the institutional or structural stigma. Stigma can have consequences ranging from psychosocial dysfunction, to isolation, rejection, and restriction of participation. Stigma-related risk factors are similar, such as visible impairments, disability, low socio-economic status, low education, and different perceptions of leprosy. Three types of stigma related to leprosy including perceived stigma, enacted stigma, and self stigma have been studied (Adhikari et al 2014). A study in Indonesia observed that 35.5 % (range 18-50%) of patients with leprosy had perceived stigma. Eighteen percent of patients perceived leprosy as causing family problems and 50 % perceived leprosy as causing shame and embarrassment (van Brakel et al 2012). The stigma enacted, also known as discrimination or the stigma experienced, happens when any member of the society, health care provider or surrounding person behaves in a negative way towards the patients with leprosy. The final types are self-stigma, which has also been called internalized stigma. This sort of stigmatization occurs when a person begins to believe what others think and say about him. This could result in a loss of self-esteem and dignity (Adhikari et al 2014).

Health services are having a huge impact from stigma in developing countries like Indonesia (Marahatta et al 2018, van Brakel et al 2012). Starting in 2010 the Stigma Assessment and Impact Reduction Project was conducted in Cirebon, West Java, Indonesia. The aim was to assess the efficacy of various sets of interventions to reduce the stigma associated with leprosy and its consequences, namely: (1) counseling and empowerment of people affected by leprosy, (2) socio-economic development, and (3) community contact with people affected by leprosy; the first two addressed perceived and experienced stigma by those affected; the later addressed community stigma. The project concluded that contact intervention was effective in enhancing knowledge and improving the behavior and attitudes of the public regarding leprosy. Replicating elsewhere is relatively easy, and does not require expensive technology or expertise (WHO 2016).

A study conducted in Cirebon on women showed that they coped with this through acceptance, comfort, trust in God, focus on recovery, friendship or found inspiration in others (Peters et al 2014b).

Stigma can come from leprosy patients not only from their family and friends, but also from health

care workers. The leprosy workers power and influence, and hence also the destructive impact of any stigmatizing behavior on the people they care for from their side. It described as "iatrogenic stigma" or stigma caused by the encounter of a patient with health care workers (Peters et al 2013). The approach to tackling stigma in leprosy has two components: to help those who are actually affected by the stigma, and to prevent future stigmatization of others. Preventing stigmatization will be more satisfactory and effective than trying to reintegrate already dehabilitated patients/ leprosy affected persons. How patients and communities perceive leprosy can be influenced by positive attitudes of health professionals towards leprosy (Rafferty 2005).

Peters et al (2015) observed that contact intervention was one of the ways to reduce stigma associated with leprosy. These methods can be easily replicated and does not require specialized expertise. A study in Cirebon experimenting with three interventions to reduce the stigma associated with leprosy, including counseling (involving peer counselors), socio-economic development (SED), and contact between community members and affected individuals concluded the three types of intervention were successful in reducing the stigma associated with leprosy (Dadun et al 2017).

In Indonesia, a study suggests disability in patients with leprosy can cause some problems. About 60 percent of patients with leprosy reported restrictions on activity and participation, and 36 percent reported the anticipated stigma. As for participation restrictions and stigma, the most frequently reported problems were shame, marriage problems, and employment difficulties (van Brakel et al 2012). Relationship between disabilities and stigma is a known fact since centuries. It has to be addressed in the context of realities of today, attitudes and opportunities.

1.3. Implementation of Nutritional Support for Leprosy Patients in Health Services System : Providing nutrition to leprosy patients as part of the Indonesian health service system is an important thing to note, to consistently improve body resistance toward continuous protein breakdown by leprosy bacteria in addition to meeting normal metabolic needs. The study of Mustamin et al (2010) provided evidence that increasing nutrional intake by giving high calory high protein diet will improve leprosy patients' general health status. Dietary supplement such as vitamins, ferro sulphate, anti-oxidants and neurotropic drugs such as vitamins B1, B6, and B12 should be given to leprosy patients, in addition to multi drugs therapy (MDT) and prednisone (Minister of Health Regulation 2019).

2. Host Related Factors

2.1. Host Immune System : Lot of information is available about host responses to *M.leprae*. Humans respond to leprosy infection at different levels by utilizing mechanisms involving innate immunity, macrophages , natural killer (NK) cell; and adaptive immunity involving lymphocytes and dendritic cells(Rodrigues & Lockwood 2011, Ottenhoff 2012, Scollard 2019). *M.leprae* which enter through skin are believed to encounter dendritic cell (DC) as the host first responder. DC in the epidermis are known as Langerhans cells and in the dermis, as dermal DCs. Langerhans cells in leprosy skin lesions express CD1a as well as langerinand present *M.leprae* antigens to T cells. These cells are reported to be associated with the outcome of reactional episodes in leprosy. The expression of CD1a has been observed in dermal CD123+ cells from both lepromatous and reversal reactional patients. Further quantitative analysis shows a clear predominance of dendritic cells in tuberculoid leprosy, whereas lesions from

patients with the lepromatous pole of thedisease have weak induction of CD1 proteins. In lesions from tuberculoid leprosy patients, dendritic cells have been linked with matrix metalloproteinase (MMP)-12 andare thought to contribute to granuloma formation(Pinheiro et al 2018).

Initially, *M. leprae* entering the host are recognized by toll-like receptors (TLR), which then trigger NF-Kb activation and increase pro-inflammatory cytokines (GM-CSF, IL-1B, TNF-α , IP-α , IP-10, IL-12) and chemokines, such as macrophages, which trigger migration and activation of antigen-presenting cells. This antigen presenting cells (APC) then introduces *M.leprae* to lymphoid T-naive cells. Depending on co-stimulators, inhibitors or other cytokines, naive T cells can develop into Th1, Th2, Treg, and Th17 which will be discussed further in this paper. Several previous studies have demonstrated differences in host response in paucibacillary (PB) and multibacillary (MB) types (Nath & Chaduvula 2016), where PB type leprosy is more dominated by Th1-mediated immune responses. Th1-dominated immune responses are mediated by protective IFN-γ and IL-2 with microbicidal properties. IFN-γ induces macrophage activation resulting in induced synthase of nitric oxide (iNOS) and NO destroying *M.leprae*. Additionally, this immune response also produces IL-1b, IL-6, TGF-β , and IL-23; as later discovered, these cytokines are also involved in Th17 induction (Chaitanya et al 2012). De Sousa et al (2017) has observed that these cytokines could be used to predict protective factors against *M.leprae*. Th1 cells are also largely associated with leprosy reactions, in addition to being associated with PB types. Immune dysregulation causes low levels of Th1-produced cytokines that cause low clearance by activation of APCs, macrophages, and natural killer cells (NKCs). Unlike leprosy of the PB type, MB type leprosy has predominant immune response mediated by Th2. Th2 is mediated by IL-4, which was investigated to have the effect of suppressing macrophage microbicidal response, diminishing Th1 response, and promoting *M.leprae* survival (De Sousa et al 2017). It is noted that these immune aberrations are specific to leprosy bacillus.

Previous studies have shown that in lepromatous leprosy macrophages or macrophage factors suppressed T cell lymphoproliferation and IL-2 production (Bobosha et al 2014). Such factors were nonspecific and consisted of prostaglandins E2, leukotrines and IL-10. This was further supported by the in vitroreversal of this suppression in lepromatous lymphocytes with the use of HLA matched tuberculoid macrophages and soluble factors antagonists. Recently, alternatively activated macrophages (MΦ 2) with immunosuppressive functions have been reported in advanced stages of mycobacterial infections with a shift from Th1 to Th2 phenotype. Phenolic glycolipid (PGL), the specific antigen of the *M.leprae* bacillus has been observed to have a general suppressive effect on peripheral mononuclear blood cells (PBMC) (Saini et al 2017). Implication of these findings is not clear.

The role of regulatory T (Treg) cells in maintaining self-tolerance and balancing immune reactions in autoimmune diseases as well as chronic

infections is well known. Regulatory mechanisms, however, can also lead to an extended survival of pathogens in chronic infections such as leprosy and tuberculosis (TB). Treg are CD4+CD25+ cells that express CXCR4 and CCR5 on their surface, and have FOXP3+ transcription factors that play a role in inflammatory response regulation. One study has shown that CD25 Treg cells play a role in the unresponsiveness of *M.leprae*-Th1 in LL (Bobosha et al 2014). Treg can identify autoantigens that are derived from damaged tissues and thus induce and maintain self-tolerance. Treg regulatory function is performed by inhibiting the activation of effector T cells such as Th1 and Th17; and by activating, proliferating and recruiting other Treg cells at the injury site through intermediaries of inflammatory and chemokine mediators (De Sousa et al 2017).

In leprosy, Treg has a role to play in keeping the balance of Th1 and Th2 responses. Immune dysregulation causes accumulation of Tregs found in MB leprosy which suppresses the immune response and causes the host to experience irresponsiveness to *M.leprae* infections (*M.leprae* specific nonresponsiveness) (Palermo et al 2012, Bobosha et al 2014). Tregs, are considered to be responsible for host immune suppression by producing IL-10 and TGF-β like cytokines. Tarique et al (2017) described the conversion of Tregs into Th1-like and Th17-like cells through STAT-3 signaling using in vitro cytokine therapy in leprosy patients.Th17 (CD4+ Th17), is one of the more recently identified effector T cells in contrast to Th1, Th2, and Treg. The presence of IL-23, IL-6, and TGF-β influences the differentiation of the naive T cells to Th17. Th17, like Th1, is pro-inflammatory, developing IL-17A, IL-17C, IL-17D, IL-17E, and IL-17F (Saini et al 2017). Th17 is thought to have protective properties in leprosy and is found more frequently in PB type leprosy than MB (Nath & Chaduvula 2016). Another study supports this opinion and states thatIL-17 also plays a part in producing inducible Nitric Oxide Synthase (iNOS), to help kill *M.leprae* mediated by reactive oxygen species (De Sousa et al 2017). Macrophages are known to have opposing functions of both killing and promoting *M.leprae* proliferation in the two types of leprosy. While the M1 type of macrophages are pro-inflammatory and promote Th1 cytokine IFN-γ, M2 macrophages have anti-inflammatory properties, being associated with the Th2 cytokines IL-4, IL-10, and IL-13. Monocytes from lepromatous leprosy patients have been shown to be inhibitory for in vitro lymphoproliferation through the release of factors such as PGE2, leukotrienes, and IL-10. Live *M.leprae* infected macrophages of M2 type have been reported to lead to Treg polarization. IL-10 and IL-15 are innate immune cytokines seen in leprosy lesions, shown to be associated with response in lepromatous and tuberculoid types. Though both cytokines enhance CD209 (C-type lectin) expression on monocytes, IL-10 promotes phagocytosis whereas IL-15 induces the vitamin D-dependent microbicidal pathway. The former pathway has been reported to be prominent in the lepromatous type and the latter in the tuberculoid form of the disease (Nath 2016). Nath (2016) have reviewed the role of

macrophages in the immunopathology of leprosy and concluded that macrophages identify pathogens through patternrecognition receptors (PRRs) that recognisepathogen-associated molecular patterns presenton the organisms. TLRs are PRRs on accessorycells which trigger hostimmune responses. TLR2-TLR1 heterodimers are thought to lead to activation of macrophages, DCs, resulting in *M.leprae* death. This antimicrobial effect of TLR is independent of nitric oxide. This has been attributed to IL-15-dependent activation of vitamin D receptors using antimicrobial peptide cathelicidin. Interestingly, the genes encoding the vitamin D pathway are differentially expressed in tuberculoid and lepromatous lesions. miRNA-21 from lepromatous types was shown to down regulate TLR2/1, up-regulate IL-10, and inhibit vitamin D-dependent antimicrobial peptides. *M.leprae* also up regulates expression of tryptophan as partate coat protein (TACO) in macrophages and down regulates TLR2 mediated signalling. TACO has been shown in leprosy lesions as well as in *M.leprae* containing macrophages in vitro (Nath 2016).

While the above recent advances about regulatory mechanisms in leprosy immunity are interesting, there relevance in modulating the immune response at clinical level is yet to studied. Such studies will be important in enhancing the host immunity by vaccines/ immunotherapeutics.

2.2 Vaccines : Prophylaxis/Immunotherapy

To have an effective leprosy vaccine has been the goal immunological research on leprosy. There are currently no specific vaccines for leprosy that have been approved for specific use against this disease. WHO regulations require that all vaccination (immunoprophylaxis) recommendations be formulated by a Strategic Advisory Group of Immunization Experts/SAGE (SAGE 2017).

Currently, evidence suggests that vaccination with BCG (Bacillus Calmette-Guérin) at birth can reduce the risk of leprosy with varying rate from 50% to 80% (WHO 2018).BCG vaccination is thought to have a greater role in inhibiting leprosy development towards MB leprosy of the type MB. Other studies mention the importance of BCG vaccination in contacts with MB due to the increased risk of transmission (De Oliveira & Diniz 2016, Barreto et al 2017).

Approaches are under development to develop safer, more effective BCG-based vaccines; referred to as 'BCG strategies for improvement. 'Several studies have examined the effectiveness of other vaccines and the combination of post-exposure prophylaxis with BCG at birth and/or with BCG revaccination, especially in high-burden countries. Re-vaccination shows mixed responses with some studies showing further protection against leprosy (Karonga Prevention Trial Group 1996), and some studies shows no statistical difference with single BCG vaccination (Cunha et al, 2008). Barreto et al (2017) and Ferreira et al (2017) have opined that immunoprophylaxis strategy with BCG and single dose rifampicin chemoprophylaxis has additive value as preventive measure for blocking the transmission of leprosy.

There are several other mycobacterial vaccines showing similar or slightly less efficacy compared to BCG vaccination interventions such as ICRC, *M. indicus pranii,* and LepVax, however, only the *Mycobacterium w (Mw)* or *Mycobacterium indicus pranii (MIP)* vaccine remains in production. MIP vaccine shows promising results with faster smear negativity, and

histopathological clearance as compared to standard MDT regimen (Katoch et al 2004, Talwar & Gupta 2017,Kamal et al 2017). Its immunotherapeutic effect is faster than BCG (Katoch et al 2004). It is effective as an immunoprophylactic as well (Talwar & Gupta 2017). Vaccination with MIP/Mw has been shown to have more than 60% protective efficacy at 5 years and it has been introduced as pilot project in some districts of India (Talwar & Gupta 2017).The most recently developed leprosy vaccine called LepVax when initially tested on armadillo, shows reduced *M. leprae* infection (Duthie et al 2018). Its development and testing is continuing.

2.3. Chemoprophylaxis

Following the demonstration of its potent bactericidal action against *M.leprae*, and the proven effectiveness of rifampicin in the treatment of leprosy, this has also been considered useful in the prophylaxis of the disease. The use of single dose Rifampicin was shown to reduce 60% risk of developing leprosy when administered as post exposure prophylaxis (Mieras et al 2018,Tiwari et al 2018). This preventative effect increases to around 80% when combined with immune prophylaxis such as BCG vaccine (Ferreira et al 2017). A single center, double-blind, randomized, and placebo-controlled trial in India' has shown protection against leprosy (Moet et al 2008)

With regard to chemoprophylaxis, a study in Bangladesh (the COLEP study) showed that an SDR in contacts with newly diagnosed patients with leprosy reduced the overall incidence of leprosy by 57 % in the first 2 years (Moet et al 2008). This study further showed that the effect of SDR depended on the contact's BCG status (Schuring et al 2009). WHO recently included SDR in its guidelines for the diagnosis, treatment, and prevention of leprosy as a recommendation (WHO 2018b).

During 2014 to 2016 a prospective follow-up study with SDR was conducted in the village of Selaru Island in Lingat, Indonesia. This study showed that with adequate planning and some additional investment, a blanket approach to chemoprophylaxis in a remote island of Indonesia is feasible (Tiwari et al 2018). However, the effect of SDR is not consistent and Lockwood et al (2018) has opined that it is not cost effective intervention. Besides the SDR, other enhanced regimen for PEP is being studied (Meiras et al 2018). It will be fair to conclude that this aspect is rapidly evolving.

2.4. Role of Nutrition in Leprosy

2.4.1. Malnutrition and susceptibility : There are a large number of studies showing the relationship between malnutrition and susceptibility to various infectious diseases. Reduction in proteins has been reported in both types of leprosy (De Oliveira & Diniz 2016), however, causative association/ linkage is yet to be proven. Iron deficiency has also been observed to increase vulnerability to many infectious diseases. Iron deficiency anemia is associated with immune dysregulation (Oktaria et al 2018). Several micronutrients have been found to affect the immune system in a significant way. Zinc plays an important role in the immune response, such as natural killer cells (NKC), macrophage cell phagocytic ability, T helper, and cytotoxic T cells. Deficiency of zinc can cause impaired humoral and cellular immune responses (deficiency of Th1 cells) (Rahfiludin et al 2007, Prabawaningrum et al 2016).

2.4.2. Vitamins, trace elements and leprosy : Interest in finding association between malnutrition and leprosy is old. Sher et al (1981) reported alterations in the trace element status in leprosy. In a study from India on serum levels of vitamins A and E, zinc and iron, a significant lowering in these two fat-soluble vitamins and

also a remarkable hypozincaemia as well significantly lower haemoglobin levels in the lepromatous patients was reported (Rao & John 2012). It has also been hypothesized that selenium supplementation may also contribute to elimination and/or suppression of mycobacterial diseases, by suppressing tumour necrosis factor and its receptors (Partogi et al 2018).

The antioxidant deficiency has been reported in different forms of leprosy; mainly in the lepromatous formand has been associated with the increase of malondialdehyde (MDA) level. The induction of the macrophages in response to *M.leprae* infection might contribute to an increase in MDA levels since phagocytosis is a potential mechanism in reactive oxygen species (ROS) production (Lima et al 2007). Intervention with antioxidant supplementation like vitamin E has been reported to prevent oxidative stress during anti-leprosy chemotherapy (Vijayaraghavan et al 2005). Reduced levels of antioxidants and nutrients have been linked to skin and neurological involvement in *M.leprae* infection (Dwivedi et al 2019).

In another study examining the relationship between leprosy, nutrition and its effect on haemotopoietic process and haematological indices, the anaemia was more common in the patients with lepromatous leprosy (85.7%) than it was in the rest of the group (19%). Findings also suggested the presence of a disordered cytokine-mediated acute phase response in the condition (Lapinsky et al 1992).

One systematic review on the relationship between vitamin D and leprosy severity shows that vitamin D receptors expression in mononuclear cell taken from peripheral blood of leprosy patient are lowered and the patients also have lowered level of blood vitamin D3 as compared to other patient with different infection (Oliveira et al 2017). The differences between immune responses against *M.leprae* compared to TB have been correlated with vitamin D receptor (VDR) polymorphism. Vitamin D receptor gene polymorphisms have shown that the 'tt' genotype is associated with polymorphisms in the vitamin D receptor gene (352 C / T codon) in tuberculoid leprosy, but the 'TT' genotype is associated with LLS leprosy while the resistance in developing leprosy is due to the heterozygous genotype 'Tt.' This data indicates that VDR and vitamin D might play significant roles in TB and leprosy. Lack of vitamin D and its receptor polymorphism may therefore help to predict the clinical evolution and role of food in leprosy (Dwivedi et al 2019). Vitamin D active metabolite, 1α, 25-dihidroxivitamin D3 (1α, 25-(OH)2D3 has been shown topromote the death of the Mycobacterium sp., by inducing the production of antimicrobial peptides in the infected macrophages and neutrophils (Vázquez et al 2014). There are gaps in the knowledge about actual effect of Vitamin D on immunity against leprosy in persons from different genetic and socio-cultural backgrounds.

Iron metabolism also shows particular difference as compared to other infection. In leprosy, iron retention within the host cells tends to perform an important role in inflammation, providing an ideal environment for the growth of the bacillus. A recent study observed increased indexes of hepcidin in the urine of patients with multibacillary leprosy. In lesions from patients with lepromatous leprosy a moderate positive correlation can be observed between the urinary hepcidin and serum IL-1b, as well as between hepcidin expression and the bacilloscopy index (Oliveira et al 2017).

The deficiency of vitamin A is associated with a decrease in phagocytosis, oxidative burst activities of macrophages and a decrease in NK

cells. In an Indonesian study conducted in children with vitamin A deficiency, a decrease in ex-vivo production of IFN-γ was detected. A decrease inserum concentrations of vitamin A, predominantly inlepromatous leprosy (LL) patients was observed , where there was also adepression of the Th1 immune response and replicationof *M.leprae* in macrophages, and a predominance of thehumoral response (Vazquez et al 2014). In a study examining leprosy patient nutritional intake and inflammatory cytokine level which were given vitamin A supplementation showed effect on inflammatory cytokines (Rahfiludin et al 2016). Clearly, there is need for better designed studied to gain better understanding of these mechanisms and usefulness of such interventions.

2.4.3. Differences between *M.leprae* and *M.tuberculosis* on Nutritional Factors that Affect Immune System : *M.leprae* is an intracellular bacterium, thus cell-mediated immunity is the basis of host defence. However, the intracellular metabolism of *M.leprae* is quite distinct from M. tuberculosis. *M.leprae* accesses host cell glucose pools as carbon sources and uses anaplerotic pathways for the synthesis of tricarboxylic acid (TCA)-derived amino acids. Unlike the complex anaplerotic node of *M.tuberculosis* which consists of phosphoenolpyruvate carboxykinase (PEPCK), malic enzyme (MEZ), pyruvate carboxylase (PCA), and pyruvate phosphate dikinase (PPDK); The genome of *M.leprae* codes only two anaplerotic enzymes that link glycolysis to the TCA cycle: PEP carboxylase (PPC) and PEPCK. PPC is probably essential for the intracellular survival of *M.leprae* and since it is absent in humans, it is a potential target for leprosy treatment (Borah et al 2019). This information also needs to be analysed in relation to nutrition.

2.4.4. Antenatal Care : Pregnant women with poor nutritional status are prone to anemia and malnutrition, which is thought to cause immune dysregulation, thereby supporting the leprosy infection (Nagar 2007, Rahfiludin et al 2007, Prabawaningrum et al 2015, Oktaria et al 2018). In depth studies are required to better understand this aspect and translate it into practice.

Women who experience pregnancy in leprosy during and after MDT therapy are at risk of leprosy reactions, impaired nerve function, or eye problems due to leprosy, thus coordinated services from obstetricians / midwives and health workers trained in leprosy are needed. There is no reported teratogenic effect of the MDT drugs based on existing research. It is recommended that the treatment of leprosy in pregnant women must be continued (Butlin & Withington 2019).

2.4.5. Breast Feeding : Breast feeding is an important factor to prevent children from getting malnutrition and infections. Thirty children in this research were given exclusive breastfed for less than 6 months and this contributes to these children's malnutrition. Malnutrition, close contact and length of contact with patients with leprosy are considered as important risk factors for leprosy (Venkatakrishnan 2018). Anti-leprosy drugsare secreted in the breast milk within the safe limits, however, it is recommended not to make close contact in breastfeeding to avoid transmission of infection (Butlin & Withington 2019).

3. Environmental Factors Relevant for Health and Disease

Environmental health addresses all external physical, chemical, biological factors, and all related behavioral factors. It includes assessing and controlling those environmental factors which could potentially affect health. It aims to prevent illness and create a health-supporting environment (WHO 2015).

3.1. Relationship between Environmental Factors and Leprosy

There are reports in the literature showing the presence of *M.leprae* in various ecosystems. Lepra bacillus / its components have ound in various abiotic and biotic substrates. *M.leprae* was found in water and soil near a leprosy centers/ patient's homes, in sphagnum vegetation (Kazda & Pavlik 2009) and in a variety of animals ranging from protozoa to more complex organisms, such as mammals (Valois et al 2015). Thus it would be of paramount to understand factors associated with its presence and survival in the environment and relationship with endemicity of disease.

Environmental factors include biological, physical and social environment. The interactions in the biological environment among humans, plants, animals, bacteria, and othersmutually influence the health of all living beings. Unbalanced interaction between humans and their biological environment will cause humans to become sick. The physical environment, such as water, air, soil, weather, food, housing, heat, light, radiation and others are abiotic. The physical environment includes environmental components that interact constantly with humans throughout time and play an important role in the process of disease occurrence in society. The social environment can be in the form of customs, habits, beliefs, religion, attitudes, standards, lifestyles, work, social life, and socio-political organizations (Siswanti & Wijayanti 2018).

3.1.1. Residential Aspects : Leprosy is often referred to as a social disease, partly because several environmental factors influence the biological vulnerability to leprosy and play a role in the transmission of leprosy (Franco-Paredes & Morales 2016). Dense settlements in leprosy contribute to increased transmission risk because it boosts the intensity of contacts between patients with leprosy and other residents. Overcrowded houses will also affect humidity and temperature (Ratnawati et al 2018). The longer you experience contact, the greater the risk of contracting leprosy (Franco-Paredes & Morales 2016). It is expected that good and less crowded homes will reduce the chances of transmission of leprosy.

Residential aspects, especially the density of the home occupancy, are one factors that determines the quality of the environmental health. The shape, size, and number of rooms must be determined according to the minimum standard number of rooms. Based on the Minister of Health of Indonesia's Decree No. 829 1999 on Housing Health of the Republic of Indonesia established that the minimum sleeping area is $8m^2$ and it is not recommended that more than two people sleep in one bedroom. Buildings that are narrow and not in line with the number of occupants will have the effect of lack of oxygen in the room thus decreasing the resilience of the occupants (Ministry of Health Decree 1999).

Type of Floor

It is suggested that people who have had contact with cases of leprosy with clinical manifestation and/or leprosy seropositivity) should practice prevention against all risk factors for leprosy, in particular reducing the duration of contacts and changing the house flooring if it is still made of soil, because the condition of the floor affects the incidence of leprosy seropositivity (Rahfiludin et al 2017). The result is also supported by Kerr-Pontes et al (2006) study, which showed that living (at least 10 years) in a sand / mud / soil floor house was associated with increased risk of leprosy. The result supported the preceding study viable to *M.leprae* can be detected from homes of people with leprosy in soil samples (Lavania et al 2008). Even though there are not many reports of isolation of *M.leprae* from the environment, it has

been reported that *M.leprae* can remain viable in soil for up to 45 days (Desikan & Sreevatsa 1995). Thus to prevent leprosy and many other diseases the physical conditions like the floor, need attention as well and should be made of proper materials (Nurjanti & Agusni 2002).

Humidity

Building house with inadequate quality, such as: leaky roofs, floors, and walls; not waterproof; and with lack of natural lighting entering the house, cancause high humidity and in turn may have a bad impact on the health of inhabitants. *Mycobacterium leprae* can remainalive at room temperature 32° C with 77.6 percent humidity in a dry nasal secretion rate (Patmawati & Setiani 2015). Rahmah et al (2018) have also observed that high moisture directly increases the risk of leprosy.

Intensity of Sunlight

Home lighting that does not meet the requirements is reported to pose a greater risk of leprosy compared with well-lit rooms (Patmawati & Setiani 2015). Residents living in places with poor lighting, particularly those lacking exposure to direct sunlight, are at greater risk of contracting leprosy. Good ventilation is one of the requirements to ensure the house is not too humid. Sun exposure helps kill *M.leprae* (Rismawati 2014, Joshi 2016).

A recent study in the Semarang City Health Center work arealso demonstrated a significant relationship (p-value = 0.032) between lighting intensity and leprosy. This study concluded that to reduce the risk of leprosy transmission it will be desirable to improve the condition of the house, open the window each morning so that sunlight can enter the house well and increase the effort to create a clean and healthy home environment (Kobis et al 2018).

Ventilation

Good ventilation enabling air circulation as well as entry of ultraviolet rays from sun will help in killing germs including *M.leprae* (Rismawati 2014, Joshi 2016). There is a known relation between the area of ventilation and the leprosy. (Siswanti & Wijayanti, 2018). Patmawati & Setiani (2015) have also found a significant relationship between home ventilation.

Clean Water Facilities

In 1895, Hansen and Looft (1895) made an initial but significant observation about the probability of environmental factors involved in the transmission of leprosy. They indicated that the initial location of cutaneous lesions frequently included locations with direct contact with natural surfaces (e.g. wading in streams and rivers in patients with calves lesions). Subsequently, 27 years after Hansen's explanation of *M.leprae*, Sand suggested that the transmission of leprosy amongst humans would take place indirectly from close contact with environmental sources. He also suggested that perhaps a living organism or soil containing decomposing material would be factors involved in the transmission process (Franco-Paredes & Morales 2016).

In studies from India, viable bacilli present in water and soil may be a significant spreader of leprosy, suggesting extra-human origins of *M.leprae* (Lavania et al 2008). In another recent study from same Ghatampur area of Kanpur (India), it was observed that approximately one quarter of the environmental samples obtained from the patient areas were positive for the 16S ribosomal *M.leprae* RNA genes (Mohanty et al 2016). Another study conducted in the Purulia district, West Bengal, India Turankar et al (2016) has also observedthe presence of *M.leprae* DNA and RNA in environmental samples (Turankar et al 2016). Turankar et al (2018) again reported *M.leprae* 16S rRNA in soil samples and water samples thus showing that leprosy patients discharge or shed viable *M.leprae* into their surrounding environment which remain

alive in soil and water with cohabitation with Acanthoamoeba species and might act as reservoir for *M. leprae.*

De Macedo Arraes et al (2017) and De Holanda et al (2017) in studies from Brazil have also reported the presence of *M.leprae* DNA in water, have emphasized the role of water in leprosy transmission.

In a study from Indonesia, from endemic leprosy areas (East Java Province of Indonesia) *Mycobacterium leprae* DNA has been reported in water (Prakoeswa et al 2017).

All the above studies from India, Brazil and Indonesia show that water as a source/ medium of transmission should be given due attention.

Discussion

This review shows that sufficient evidence exists to consider host and environmental interventions to block the transmission of leprosy in endemic pockets which continue to exist despite major success of MDT in reducing the leprosy burden. These interventions could be nutritional, immunoprophylactic/ immunotherapeutic as well as chemoprophylactic.

Immune dysregulatory diseases including leprosy may be resulting from defects related to the development and/or function of regulatory T cells (Torres et al 2018). The present review shows that there is improvement in our understanding of immune response to *M.leprae* infection. For a long time it is known that patients with lepromatous leprosy (LL) have poor cell mediated responses specifically against *M.leprae* which lead to delayed bacilli clearance. There is also evidence showing that CD25+ Treg cells play a part in *M.leprae* immunity unresponsiveness in leprosy patients (Bobosha et al 2014). Further the role of IL-12 inconverting FoxP3+ Treg cells to Th1 cells (FoxP3+ IFN-T cells) and IL-23 in converting FoxP3+ Treg cells to Th17 cells (FoxP3+IL-17+ Tcells) has been convincingly demonstrated (Kumar et al 2013, Tarique et al 2015). Tariqueet al (2017) have also observed significant decrease in FoxP3+Treg rIL-12 and rIL-23 treatment cells. A study showed that vitamin D receptors (VDR) and vitamin D play important roles in TB and leprosy, so a lack of vitamin D and its receptor polymorphism may help predict the clinical evolution and role of food in leprosy(Borah et al 2019). However, this needs to be proven by actual studiesespecially in the light of other influencing factors.

Health services available to patients with leprosy also play a role in ending leprosy transmission (promotional and rehabilitative treatment programmes) (Abeje et al 2016). Health services in developing countries such as Indonesia suffer enormous impact from stigma (Marahatta et al 2018, van Brakel et al 2012). However, these limitations can be overcome by eGovernance, addition of nutritional support and better sensitization of health care workers as shown in some works from Indonesia. Such approaches have a wider global application subject to local adaptation.

Among different vaccines shown to be useful against leprosy and available in the market BCG and MIP show both prophylactic and therapeutic usefulness (Katoch et al 2004, Kamal et al 2017, Talwar & Gupta 2017). Such strategy of immunomodulation along with MDT has been recommended by others as well (Jariwala et al 2013, Barreto et al 2017, Narang & Kumar 2019). There is enough evidence to consider further research/ research cum intervention using BCG / MIP to boost the immunity of patients and community for therapeutic as well as prophylactic purposes. Newer generation vaccines may be better but that is hypothetical at the moment.

Another possible means of interrupting transmission is prophylactic treatment of

contacts. There is interest in post-exposure prophylaxis (PEP) using single dose of rifampin (SDR) or PEP plus administered to contacts or entire communities (Moet et al 2008, Meiras et al 2018, Scollard 2019). In order for PEP to be effectively implemented, a good contact tracing program for public health must be in place, or developed first. This is a challenge itself and requires resource commitment. However, evidence also suggests that SDR has significant limitations, since the closest contacts receive the least benefit (Lockwood et al 2018, Scollard 2019).

Another important host factor that can influence host susceptibility to leprosy infection is nutritional status. Inadequate and disproportionate nutritional intake suppresses immunity. Failure to improve nutrition statusalso may be increasing the risk of contracting *M.leprae* and facilitates subclinical leprosy development in clinical infections (Khandapani & Mishra 2010, Rao & John 2012, Jariwala et al 2013, Narang & Kumar 2019). Antioxidants (endogens or nutritional) and modulator cytokines are likely to play an important role in balancing the immune response that controls multiplication and protects hosts from tissue-harmful TNF-α species, nitric oxide (NO), and reactive oxygen species (ROS) (Calder & Kew 2002, Khandapani& Mishra 2010, Rao & John 2012, Wagenaar et al 2015, Oktaria et al 2018). Advances in the knowledge are yet be adequately explored for applications at patient or community level in leprosy.

Pregnancy and breastfeeding can also affect host vulnerability against *M.leprae* infection. Pregnant women with poor nutritional status are prone to anemia and nutritional deficiencies which can cause immune dysregulation andmight lead to increased susceptibility to leprosy infection (Rahfiludin et al 2007, Prabawaningrum et al 2016, Wagenaar et al 2015, Oktaria et al 2018).Malnutrition, close contact and length of contact with patients with leprosy have been identified asimportant risk factors for leprosy (Venkatakrisnan 2018) and should be part of future research cum intervention strategies.

Beside host factors, environmental factor such as housing condition, water, and sunlight should also be the primary concern for leprosy transmission control. Long-term exposure to water containing the bacterium *M.leprae* can be a source of transmission, and is one of the reasons for the difficulty in leprosy eradication in endemic leprosy areas (Nurjanti & Agusni 2002). It is well known that *M.leprae* are shed into the environment by patients during coughing, sneezing and can survive for varying periods depending on environmental conditions such as sun-light, temperature, moisture, etc. (Lavania et al 2008, Rahfiludin et al 2017). Climate and seasonal changesdo not appear important (Maske et al 2015). While there has been global interest in environmental factors more studies including the interventions are necessary to use the information to eradicate the disease.

A One Health transdisciplinary research approach is required to increase our understanding of the intricate picture the transmission of leprosy. This should include combining human, animal and environmental health elements in order to better explain the mechanisms and patterns of transmission of *M. leprae* and *M. lepromatosis*. In addition, geographically tailored methods integrating epidemiological, laboratory and anthropological data may be required to better understand the ecological differences between leprosy pockets (Ploemacher et al 2020). Environmental factors, such as conducive temperature, soil type and water, environmental acidity, etc. may promote the amplification of the transmission cycle in biotopes with existing acceptable ecological abiotic and biotic

determinants (i.e. tropical and subtropical settings) along with the release of *M.leprae* from human cases (e.g. nasal soil and water contaminants). Chemoprophylaxis (or preventive care) of contacts and successful treatment of leprosy cases would decrease the release of *M.leprae* to environmental reservoirs (Franco-Paredes & Morales 2016).

Conclusions

Several factors have been identified as probable contributors to immune dysregulation related to leprosy; host factors (health services, stigma, vaccination, chemoprophylaxis, nutritional status, antenatal care, mode of delivery, proper breast feeding) and environmental health factors (residential aspects, type of floor, humidity, intensity of sunlight, ventilation, clean water facilities), which ultimately cause failure to terminate the transmission chain of leprosy. However, further research is needed to identify specific roles of these possible contributors towards shedding, persistence and transmission through environment as well as immune dysregulation(s) which enhance the vulnerability of anindividuals and communities towards leprosy. The identification of these factors is paramount in order to evoke a new approach to ultimately eradicate leprosy.

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