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RESEARCH ARTICLE

HANSEN'S DISEASE: GLOBAL SCENARIO AND CURRENT PERSPECTIVE

[1]Megha Rastogi, [2]Abhijit Das, [1]Swati Sharma, [3]Poonam Gupta, [2]Madhu Sinha and [4]Man Mohan Mehndiratta

[1]Department of Microbiology, Janakpuri Super Speciality Hospital Society, New Delhi, India
[2]Department of Pathology, Janakpuri Super Speciality Hospital Society, New Delhi, India
[3]Department of Microbiology, MGM, New Bombay Vashi, India
[4]Department of Neurology, Janakpuri Super Speciality Hospital Society, New Delhi, India

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****Corresponding author:*** **Megha Rastogi**

ABSTRACT

Hansen's disease caused by the bacillus *Mycobacterium leprae*, is a chronic granulomatous disease. As this bacterium cannot be cultured, it remains the least understood bacterial pathogen. Skin, peripheral nerves & nasal mucosa are mainly affected but this bacterium is capable of affecting any tissue or organ. National leprosy control program was launched in 1955 with an aim to achieve leprosy control but it did not succeed. Later on, global leprosy strategy (2016-2020) have been adopted. Global statistics show that 203600 (96%) of new leprosy cases were reported from 22 priority countries. With 127,369 new cases, India accounted for 60% of the global new cases. Brazil, reported 26395 new cases, representing 13% of the global new cases; & Indonesia reported 17202 new cases, 8% of the global case load. Diagnosis of Hansen's disease can be done by examination of skin smear, animal inoculation, immunological tests, histopathological test, FNAC, PCR, radiological examination. BCG vaccine was being widely implemented for control of both leprosy & tuberculosis. *Mycobacterium indicuspranii* (MIP) vaccine has received approval from central drug standard control organization & the U.S food & drug administration (FDA) as a vaccine against leprosy.

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INTRODUCTION

Leprosy is assumed to be originated in the tropics & from there it has been spread to rest of the world. Dr Gerhard Henrik Armauer Hansen of Norway has discovered lepra bacillus in 1868. Hansen's disease, is a chronic granulomatous disease caused by the bacillus *Mycobacterium leprae* which is an obligate intracellular bacillus. It primarily affects skin, peripheral nerves & nasal mucosa but capable of affecting any tissue or organ. [1,2,3,4.]

History of national leprosy programmein India: In 1955 National Leprosy Control Programme was launched with an aim to achieve leprosy control but it did not succeed. With the advent of multi drug resistant (MDT) in 1982, this programme was redesignated as National Leprosy Eradication Programme (NLEP) in 1983. Prevalence of leprosy showed a decreasing trend from 57/10,000 in 1983 to 24 in 1992, 1.34 in April 2005 & finally to 0.95 per 10,000 population in December 2005 thus achieving elimination at national level.[5] WHO launched the "Global Leprosy Strategy 2016-2020: accelerating towards a leprosy-free world" in 2016 which aims to control leprosy and disabilities caused by it, with special focus on children affected by the disease in endemic countries.[5,6]

EPIDEMIOLOGY

The prevalence rate of leprosy was reduced by 99%: from 21.1 cases per 10 000 people in 1983 to 0.2 cases per 10 000 people in 2015. According to official reports received from 138 countries from all WHO regions, the global registered prevalence of leprosy at the end of 2015 was 176 cases (0.18 cases per 10 000 people). Global statistics show that 203600 (96%) of new leprosy cases were reported from 22 priority countries. Three countries i.e. India, Brazil & Indonesia have reported more than 10000 cases. With 127,369 new cases, India accounted for 60% of the global new cases. Brazil, reported 26395 new cases, representing 13% of the global new cases; & Indonesia reported 17202 new cases, 8% of the global case load.[6]

Situation in India: Out of total 36 states/ union territories (UTs), 34 states/UTs have achieved elimination of leprosy. Chhattisgarh and Dadra & Nagar Haveli are still lacking behind to achieve elimination of leprosy. In India, 551 districts (82.36%) out of the total 669 districts had a prevalence of <1/10,000 population by the end of March 2016 which is the target of elimination as a public health problem. The number of districts with prevalence between 1 and 2/10,000 were 76,

number of districts with prevalence between >2 and 5/10,000 were 39, and those between 5 and 10 were 2. Despite of the decreasing trend of leprosy, India continues to account for 60% of new cases reported globally each year. According to last 4 years of NELP annual report four UTs (Orrisa, Chandigarh, Delhi and Lakshadweep) which have achieved elimination earlier in 2011-2012, have shown a prevalence of >1 per 10,000 population, making this a matter of concern for the programme.[5,6,7,8,9,10]

- Mycobacterium leprae: The taxonomic order is Actinomycetales, the family Mycobacteriaceae. M. leprae is an obligate intracellular bacillus which is an acid-alcohol-fast as well as gram-positive. It has predilection for the cells of reticuloendothelial system and peripheral nervous system.2,9. M. leprae organisms are slightly curved, measure from 1 to 8 µm in length & 0.3 µm in diameter. Lepra bacilli can neither be cultured on bacteriological media nor it can be grown in tissue culture Lepra bacilli can be transmitted to experimental animals like footpads of mice, nine-banded armadillos. Replication takes from 11 to 13 days, considerably longer than the 20 hours required by Mycobacterium tuberculosis.[1,2,3,4]

- Incubation Period: As lepra bacillus multiplies very slowly it is difficult to define an incubation period for leprosybut on an average, it is considered to be 5 years. In some cases, symptoms may occur within 1 year but can also take as long as 20 years to occur.[1,2,3,4]

- Risk Factors: Poor sanitary condition is the main risk factor for those living in endemic areas such as inadequate bedding, contaminated water & insufficient diet, or other conditions that weakenthe immune system are at maximum risk of acquiring leprosy.[1,2,3,4,11]

- Transmission: Leprosy can be transmitted via droplets, from the nose & mouth, during close & frequent contacts with untreated cases.[1,2,3,4,11]

DISEASE CLASSIFICATION

Ridley & Jopling introduced a classification system in 1996 which was mainly for research purposes & is still used in many parts of the world. The disease has two poles with tuberculoid leprosy (TT) at one pole and lepromatous leprosy (LL) at another pole. These two poles are considered to be clinically stable. Dimorphic cases or intermediate cases which are clinically unstable are classified according to which pole they tend to shift. These cases can be further classified as borderline tuberculoid (BT), mid-borderline(BB) & borderline lepromatous (BL), of which BB is least stable. This classification however does not include indeterminate & pure neuritic forms of leprosy.[1,2,3,4,12,13.] In 1981 the WHO classification system (1981) simplified the administration of chemotherapy. This classification classified leprosy can as multibacillary (MB) or paucibacillary (PB). The sensitivity & specificity of the WHO classification has been reported to be around 90%. Nerve involvement is not part of the WHO's clinical classification.[1,4,12,13.] Indian classification was introduced in 1995. This classification includes six groups: tuberculoid, borderline, lepromatous, indeterminate, pure neuritic and maculoanesthetic. Maculoanesthetic leprosy was later removed from this classification.[1,4,12,13.] NLEP classification, India (2009) was developed by the National Leprosy Eradication Program (NLEP) of the government of India, the Global Alliance for Leprosy Elimination & the WHO.[1,3,4,12,13,14]

Clinical features

Cardinal signs of leprosy are:

i. Hypo-pigmented or reddish skin lesions with definite sensory deficit.
ii. Involvement of peripheral nerves: demonstrated by definite thickening of nerves with or without loss of sensation and/or weakness of muscles of hands, feet or eyes supplied.
iii. Demonstration of Mycobacterium leprae in lesions.[1,4,13]

- *INDETERMINATE LEPROSY* (I): It is characterized by ill-defined hypopigmented patch or macule which is commonly located on the lateral/outer aspect of the thigh, face & extensor aspect of the limbs. Sensory loss is unusual in this form & SSS is usually negative.[1,2,4,13,14,15,16]

- *TUBERCULOID LEPROSY* (TT): This form manifests as a few well-defined hypopigmented anesthetic macules which occur on any part of the body but there is a predilectionforexposed/uncovered areas of the body. Neural involvement in TT is uncommon,neural involvement is usually patchy, unilateral & asymmetrical.[1,2,3,4,13,14,15,16]

- *BODERLINE LEPROSY*: Borderline leprosy cases contribute to major disease load of leprosy globally. Skin lesions vary according to the shift of these cases to either poles of disease spectrum i.e. TT or LL. Nerve involvement is common in borderline leprosy.[1,4,13,14,15,16]
- *BODERLINE TUBERCULOID* (BT): This form resembles TT. Lesions in BT have finger like projections known as pseudopodia. Skin lesions are scaly, dry, hypoesthetic plaques with loss of appendages & sweating seen mostly on the face, lateral aspect of extremities, buttocks & scapulae. Nerve involvement is common.[1,4,13,14]

- *BODERLINE BODERLINE* (BB): These are immunologically most unstable part of disease spectrum. The hallmark lesion of these patients is an annular plaque with a well-demarcated 'punched-out' inner margin & a sloping outer margin, giving it a 'swiss cheese' appearance. Nerve involvement is variable.[1,4,13,14]

- *BODERLINE LEPROMATOUS*: Lesions begin as multiple, hypopigmented to coppery-red macules that have indistinct borders thatmerges into the adjacent skin. With time, the macules undergo induration/infiltration beginning from the center & forming plaques & nodules. In BL, the peripheral nerve trunks are thickened & tend to be symmetrical.[1,4,13,14]

- *LEPROMATOUS LEPROSY*(LL*)*: LL with a de novo appearance is called polarlepromatous leprosy (LLp) & when a result of downgrading it is called subpolar lepromatous leprosy (LLs). Cutaneous lesions of LL are multiple with bilateral symmetrical distribution over the arms, legs, buttocks, face & trunk. Clinically, the LL

disease may present with any of the stages described below or with a mix of these lesions.

i. *Early macular stage:* In early stage, lesions frequently present as macules.
ii. *Infiltrated stage:* Infiltration is often marked on the face & ear lobules.
iii. *Late nodulo-plaque stage:* If the above stage is left untreated, there is increase in infiltration & macules progress to form papules, nodules & plaques. In ear cartilage repeated episodes of ulceration & healing gives it a 'rat bitten' appearance. Ulcers present mostly in nose, mouth & throat. LL patient who are untreated has leonine faces, thickening & nodulations of ear lobes & a broad & swollen nose, which may be collapsed, thinning of eyebrows (supraciliary madarosis) & eyelashes (ciliary madarosis) & may have characteristic facies leprosa. Muscle weakness, wasting & paralysis can occur as a result of damage to motor neurons & can result in claw hand deformity, ape thumb deformity, wrist drop, foot drop & facial palsy. [1,3,4,13,14,15,16]

➢RARE VARIANTS OF LEPROSY

- *Histoid leprosy*: The term was coined after the histopathological appearance of histoid lesions. Lesions appear as firm, erythematous, shiny, smooth, hemisphere, round to oval non-tender nodules present on the face, back, buttocks & extremities as well as over bony prominences.[14,15]

- *Pure neuritic leprosy (PNL)*: In this type of leprosy peripheral nerve trunk is involved in the absence of skin lesions. This form of leprosy is commonly found in Nepal, Brazil & India. Clinical features include nerve thickening, pain, tenderness & sensory-motor impairment. Mononeuritis is the most common presentation & is asymmetric in nature. The nerve trunks commonly involved are the ulnar nerve, superficial radial nerve, sural nerve, common peroneal nerve & posterior tibial nerve.[2,14]

- *Lucio's leprosy*: A diffuse form of polar LL, now known as diffuse leprosy of Lucio &Latapi (LuLp). This form of leprosy has been associated with both M. leprae & Mycobacterium lepromatosis. In LuLp there is diffuse infiltration of the skin. Diffuse infiltration of the face & hands mimics "myxedema"-like appearance, often giving the impression of a "moon face" or "healthy look" & imaginatively called Lepra bonita (beautiful leprosy). Lucio phenomenon seen in LuLp which is akin to Type 2 lepra reaction & is characterized by well-defined, angular, jagged, purpuric lesions evolving into ulcerations & spreading in ascending fashion & healing with atrophic white scarring.[14,15]

LEPRA REACTION

These reactions are immunologically mediated that occur during the chronic course of disease. They are of two types: type I & type II reactions. Type I reaction (reversal reaction; RR) is characterized by swelling & erythema of existing skin lesions. They occur in borderline patients (BT, midboderline & BL). This is due to type I T-helper cell response which results in upgrading of cell-mediated immunity. Type II reaction (erythema nodosum leprosum; ENL) is characterized by the appearance of tender, erythematous, subcutaneous nodules located on normal skin & is frequently accompanied by systemic symptoms. This is due to type II T-helper cell response (Th 2 response) which leads to induction of humoral immunity. Both types of reactions have been found to cause neuritis, representing the primary cause of irreversible deformities.[1,2,3,4,17]

LABORATORY DIAGNOSIS

- *Examination of skin smear*: Sites from where skin smear can be taken are earlobes, elbow, knee, skin lesion, forehead, chin, buttocks. It is highly specific but sensitivity is low approximately 70%.
- *Culture*: Agar & cell culture for Mycobacterium leprae is not yet achieved.
- *Animal inoculation*: Mycobacterium leprae can be cultivated in SCID mice (athymic/nude) & nine banded armadillo.
- *Immunological testing:*
  - ➢ It is analogous to tuberculin test. Two antigens have been used, original Ag was mitsuda Ag & modern Ag (4×10^7bacilli/ml-lepromin A replacing lepromin H).
  - ➢ ELISA or lateral flow immunochromatography to detect Abs against carbohydrate portion of PGL-1.
  - ➢ Lymphocyte transformation test (LTT) to detect CMI
  - ➢ *Histopathological testing*: Punch biopsy or incision biopsy for histopathological examination may help in reaching the conclusion if analyzed along with clinical criteria.
- *Fine needle aspiration cytology*: FNAC from lymph glands is usually helpful if patient is in suspected lepra reaction type 2.
- *Polymerase chain reaction*: Facilities for PCR are available at specialized institutions like National institute of communicable disease (NICD) at New Delhi, National Jalma institute of leprosy and other mycological disease (JALMA) Agra, Central leprosy teaching & research institute) CLTRI Chengalpattu.
- *Radiological examination*: X-rays are helpful in diagnosing osteoporosis, fractures of small bones, absorption of bones, sequestra.[1,3,4,13,14,16]

TREATMENT

Multidrug Therapy (MDT) [1,2,4,116,18]

Type of leprosy	Drug used	Dosage (adult) 15 years & above	Dosage (children 10-14 years)	Dosage children below 10 years	Frequency of administration adults (children in bracket)	Criteria for released from medicine (RFT)
MB leprosy	Rifampicin Dapsone Clofazimine Clofazimine	600 mg 100 mg 150 mg 50 mg	450 mg 50 mg 150 mg 50 mg	300 mg 25 mg 100 mg 50 mg (alternate day, not daily)	Once monthly Daily once monthly, Daily (every other day) for adults	Completion of 12 monthly pulses
PB leprosy	Rifampicin Dapsone	600 mg 100 mg	450 mg 50 mg	300 mg 25 mg	Once monthly Daily	Completion of 6 monthly pulses

LEPROSY VACCINE

BCG vaccine is widely used for the prevention of tuberculosis but was originally invented with the notion to prevent both leprosy and tuberculosis. Systemic meta-analysis reveals an overall protective efficacy of 26-41% in experimental vs. 61% in observational studies. BCG vaccination against leprosy affords highest protection among younger individuals which tends to wane over time. In a retrospective study based on the number of BCG scars found in an individual, it was concluded that BCG alone conferred 56% protection against leprosy in the study group & it was suggested that several doses of BCG may offer additional protection.[19,21,22,23,24,25.] In a double-blind study, randomized prophylactic trail of four potential leprosy vaccines (BCG alone, BCG/killed M. leprae, alternative mycobacterium w & international committee of red cross ICRC) was conducted & studied. It was concluded that BCG provided 34% protection, BCG/M. leprae provided 64% protection, ICRC provided 65.5% protection & M.w provided 25.7% protection. This indicated that BCG/M.leprae vaccine & ICRC vaccine, met the requirements of public health utility & might be further evaluated for control of leprosy.[19,22,23,26,27,28,29] In 2005, Sharma & colleagues reported the results of a large scale, double blind immunoprophylactic trail of a M.w vaccine in Kanpur Dehat, U.P which was conducted between 1992 & 2001. The vaccine comprises of 1×10^9 heat killed M.w bacilli for the first dose & a second, half dose given 6 month later. The efficacy of vaccine was found greatest in children when compared with adolescents & adults. When the index cases, & not the contacts received M.w vaccine surveys at the end of first, second & third follow up periods showed protective efficacies of 43%, 31% & 3% respectively. When only contacts received the vaccine, protective efficacy of 69%, 59% & 39% were observed. When both contacts & patients received the M.w vaccine, the protective efficacy was 68%, 60% & 28% at each follow up time. Thus, it was concluded that the protective effect of M.w vaccine was retained for a period of about 7-8 years, after which booster vaccination may be needed, however it is unclear if the M.w vaccine can be boosted.[19]

In a trial conducted in Vietnam, which involved the vaccination with killed M. vaccae alone (10^8 bacteria), BCG alone or BCG plus 10^7 killed M. vaccae. It showed that there was no major difference in protection afforded by each of the three vaccines, which implicates that both live BCG & killed M. vaccae provided protection in this trial, but the addition of killed preparation of M. vaccae to BCG did not enhance protection afforded by either alone.[19,21,22,23,24,25.] Vaccination with M. habana has also been in pipeline on the basis of protection afforded by it in mice & induction of lepromin reaction in monkeys. M. habana vaccination induced stable lepromin conversion in 100% of LL cases and lepromin negative household contacts and augmentation of lepromin reactivity in 100% of lepromin positive household contacts. Overall, following M. habana vaccination, individuals without prior BCG vaccination scars showed higher augmentation of lepromin responses. BCG is best available vaccine for the prevention of leprosy till date, although it is variable in its protective efficacy.[19,21,22,23,24,25]

Advances towards defined vaccines: Proteins present in the cell wall, cell membrane and cytosol of M. leprae provide protection when administered along with adjuvant before infection. Major limitation regarding the use of crude M. leprae Ags in a vaccine is to cultivate large numbers of M. leprae and lack of consistency in production. 35KD, Ag85B & hsp65 Ags have all been shown to confer protection when expressed in a DNA vaccine. Both purified and/or recombinant 10 KD, 25KD & 65 KD proteins also provided protection when administered with Freund's incomplete adjuvant (FIA).[19]

Recombinant BCG vaccine (rBCG): Ohara & colleagues produced rBCG strains that over express Ag 85 complex component. Mice immunized with rBCG over-produce either A or A/B components which reduces the multiplication of M. leprae more as compared to the vaccination with parental BCG alone. Maeda & colleagues have created a rBCG that secretes M. leprae major membrane protein (MMP- II) also known as bacterioferritin, ML 2038). Compared with parental BCG, the rBCG strain (BCG-SM) induces more potent Th1 immune response.[19]

Subunit vaccine for leprosy: An ideal subunit vaccine against leprosy would induce strong, long-lasting T cell responses directed against M. leprae that would both prevent disease & reduce bacterial transmission, but is still lacking.[19]

Complications: Approximately 50% of leprosy patients naturally develop acute inflammatory reaction known as either type 1 (reversal reaction) or type 2 (erythema nodosum leprosum reaction.[19]

Mycobacterium indicus pranii (MIP): MIP is a rapidly growing nonpathogenic mycobacterium. When administered id, it increases CMI in the host. Vaccine originally called M.w was later renamed MIP. In this name, mycobacterium stands for a genus of gram positive, aerobic, acid-fast bacteria occurring as slightly curved or straight rods, indicus stands for India, pranii stands for the person who discovered the species (Professor Pran Talwar) & national institute of immunology (nii) where trials were conducted (Pran + nii).[19,20.] MIP has received approval from central drug standard control organization & the U.S food & drug administration (FDA) as a vaccine against leprosy. Professor G.P Talwar proposed to the government that MIP may be used to vaccinate contacts of leprosy patients to immunize them, MIP along with MDT may be used for the treatment of leprosy patient. Indian council of medical research & ministry of health, government of India along with representatives of ILEP (international federation of anti-leprosy associations) accepted this proposal only for its use for vaccination of contacts. MIP vaccine is administered through id injection 0.1 ml. It is divided into two equal doses & given on both arms. Booster doses will be given to maintain the immunity level (one after 2 years & another after 5 years). Booster doses are injected only on one arm. MIP has proved its potential in increasing immunity. But the government has not accepted MIP as part of leprosy treatment regimen.[19,20.] Candilla pharma Indida manufactures MIP under the brand name IMMUVAC, & markets it as an immunomodulator injection. Dermatologist doing private practice use this for treating leprosy patients.[19,20]

PREVENTION

a. People who live in intimate contact with the leprosy patient should be tested for leprosy.
b. These people should be examined annually for five years following their last contact with an infectious patient.

c. For preventing & correcting deformities, reconstructive surgery should be done.
d. Comprehensive care involves teaching patients to maintain a range of movement in finger joints & prevent the deformities from worsening.
e. BCG offers a variable amount of protection against leprosy as well as against tuberculosis.
f. Efforts to overcome persistent obstacles to the elimination of the disease include improving detection, educating patients & the population about its cause & fighting social taboos about leprosy.[1,4,7,30]

Conclusion

Leprosy, an enigmatic disease, is one of the oldest diseases to man, yet dramatic gaps remain in our basic understanding of this disease. The long & asymptomatic disease incubation period as well as its insidious symptoms can lead to difficulties in the diagnosis of early & advanced cases, therefore all physicians must have a basic understanding of this disease in order to diagnose it & prevent disability and/or contagion. Educating the people regarding this disease, its symptom & complications can reduce the risk of this disease to spread in future. Our current level of knowledge makes it possible to eliminate leprosy, a goal that calls for the concerned efforts of medical, social, political & scientific resources to prevent the spread of an infection that should no longer exist.

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REFERENCES

1. Arti kapil, Ananthanarayan and Paniker's: Textbook of microbiology. 9th ed. universities press: p. 364-369.
2. Bhat RM, Prakash C. Leprosy: An overview of pathophysiology. Interdisciplinary perspectives on infectious diseases. 2012;1-6
3. Eichelmann, E. *et al.* 2013. Leprosy. An update: Definition, pathogenesis, classification, diagnosis, & treatment. ACTAS, 104(7):554-563.
4. Apurba Sankar Sastry, Sandhya Bhat K. Mycobacteria. In: Essential of Medical Microbiology. 1st ed. Jaypee: p. 285-91.
5. DK Taneja's Health policies and programmes in India. 15th ed. p: 249-256.
6. WHO global leprosy strategy 2016-2020: accelerating towards a leprosy-free world [Internet]. Available from: http://www.who.int/lep/resourses.
7. National Leprosy Eradication Programme, Annual Report (2010-11), GOI. p. 99-101.
8. National Leprosy Eradication Programme, Annual Report (2015-16), GOI. p. 65-67.
9. WHO updates fact sheet on leprosy 2017.
10. Rao P. Narasimha and Suneetha Sujal. Current situation of leprosy in India and its future implications. *Indian Dermatology online Journal,* 2018
11. Bakker M, Hatta M, Kwenang A. Population survey to determine risk factors for Mycobacterium leprae transmission & infection. *Int J Epidemiol.,* 2004; 33:1329-36.
12. Classification & management of leprosy.pdf [Internet] Available from: http://nlep.nic.in.
13. Bhushan K, Uprety S, Dogra S. 2009. Clinical diagnosis of leprosy. *Indian J Dermatol venereal leprol.,* 75(2):111-115.
14. Surinder Kumar: Textbook of Microbiology. 1st ed.Jaypee: p. 325-334
15. Walker SL, Lockwood DN. 2008. Leprosy type 1 (reversal reactions and their management. *Lepr Rev.,* 79:372-86
16. Ho C.K. Leprosy-A review. Hong Kong dermatology & venereology bulletien.1999;7(2):65-70.
17. Saonere JA. 2011. Leprosy: an overview. Journal of infectious diseases and immunity, 3(14),p.233-243.
18. Moschella SL. 2004. An update on the diagnosis and treatment of leprosy. *J Am Acad Dermatol.,* 51:417-26.
19. Duthie M.S, Gills T.P, Reed S.G. Advances & hurdles on the way toward a leprosy vaccine. Human vaccine, 7(11):1172-1183.
20. Faujdar J, Gupta P, Natrajan M *et al.* 2011. Mycobacterium indicus pranii as stand -alone or adjunct immunotherapeutic in treatment of experimental animal tuberculosis. *Indian J Med.,* 134(5):696-703.
21. Ponnighaus JM, Fine PE, Sterene JA *et al.* 1992. Efficacy of BCG vaccine against leprosy & tuberculosis in norther Malawi. *Lancet*, 339:636-9.
22. Setia MS, Steinmaus C, Ho CS, Rutherford GJ. 2006. The role of BCG in prevention of leprosy: a meta-analysis. Lancet infect did., 6:162-70
23. Merle CS, Cunha SS, Rodrigues LC. 2010. BCV vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert Rev Vaccines,* 9:209-22
24. Zodpey SP, Bansod BS, Shrikhande SN, Maldhure BR, Kulkarini SW. 1999. Protective effect of BCG against leprosy: a population based case-control study in Nagpur, India. *Lepr Rev.,* 70:287-94
25. Zodpey SP, Ambadekar NN, Thakur A. 2005. Effectiveness of BCG vaccination in prevention of leprosy: a population based case-control study in Yavatmal district, India. *Public health,* 119:209-16
26. Shepard CC, Van Landingham RM, Walker LL, Ye SZ. 1983. Comparison of the immunogenicity of vaccines prepared from viable Mycobacterium bovis BCG, heat-killed Mycobacterium leprae, and a mixture of the two for normal and M. leprae-tolerant mice. *Infect Immun.,* 40:1096-103
27. Convit J, Sampson C, Zungia M, Smith PG, Plata J, Silva J, *et al.* 1992. Immunoprophylactic trail with combined Mycobacterium leprae/BCG vaccine against leprosy: preliminary results. *Lancet*, 339:446-50
28. Karongsa Prevention trial group. Randomised controlled trail of single BCG, repeated BCG or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet*, 19965;348:17-24
29. Brreto ML, Pereira SM, Ferreira AA. 2006. BCG vaccine: efficacy and indications for vaccination and revaccination. *J Pediatr.,* 82:45-54
30. Chaptini C, Marshman G. 2015. Leprosy: a review on elimination, reducing the disease burden, & future research. *Lepr Rev.,* 86:307-315.

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