



Universiteit  
Leiden  
The Netherlands

## **Preventing Leprosy: Epidemiological and immunological aspects of chemo- and immunoprophylaxis in leprosy patients' contacts**

Richardus, R.A.

### **Citation**

Richardus, R. A. (2020, February 4). *Preventing Leprosy: Epidemiological and immunological aspects of chemo- and immunoprophylaxis in leprosy patients' contacts*. Retrieved from <https://hdl.handle.net/1887/84691>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/84691>

**Note:** To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/84691> holds various files of this Leiden University dissertation.

**Author:** Richardus, R.A.

**Title:** Preventing Leprosy: Epidemiological and immunological aspects of chemo- and immunoprophylaxis in leprosy patients' contacts

**Issue Date:** 2020-02-04

**LIST OF ABBREVIATIONS**

|                  |                                                                |
|------------------|----------------------------------------------------------------|
| Ab               | antibody                                                       |
| BB               | borderline borderline leprosy                                  |
| BCG              | Bacillus Calmette-Guérin                                       |
| BI               | Bacterial Index                                                |
| BL               | borderline lepromatous leprosy                                 |
| BT               | borderline tuberculoid leprosy                                 |
| CCL4             | chemokine (C-C motif) ligand 4                                 |
| CMI              | cell-mediated immunity                                         |
| ELISA            | Enzyme-Linked Immunosorbent Assay                              |
| ENL              | erythema nodosum leprosum                                      |
| HAART            | highly active antiretroviral treatment                         |
| HIV              | human immune deficiency virus                                  |
| I                | indeterminate leprosy                                          |
| IDEAL            | Initiative for Diagnostic & Epidemiological Assays for Leprosy |
| IFN- $\gamma$    | interferon-gamma                                               |
| IGRAs            | Interferon-Gamma Release Assays (IGRAs)                        |
| IL-10            | interleukin-10                                                 |
| IP-10            | IFN- $\gamma$ -inducible protein 10                            |
| IRIS             | immune reconstitution inflammatory syndrome                    |
| LL               | lepromatous leprosy                                            |
| (L)PEP           | (leprosy) post-exposure prophylaxis                            |
| M1               | type 1 macrophages                                             |
| M2               | type 2 macrophages                                             |
| MALTALEP         | the Order of Malta-Grants-for-Leprosy-Research                 |
| MB               | multibacillary                                                 |
| MDT              | multidrug therapy                                              |
| <i>M. leprae</i> | <i>Mycobacterium leprae</i>                                    |
| NSE              | non-specific effects                                           |
| PGL-I            | phenolic glycolipid I                                          |
| PB               | paucibacillary                                                 |

|         |                                                      |
|---------|------------------------------------------------------|
| SDR     | single dose rifampicin                               |
| Th1     | T helper 1                                           |
| Th2     | T helper 2                                           |
| Treg    | regulatory T-cells                                   |
| TT      | tuberculoid leprosy                                  |
| UCP-LFA | up-converting phosphor technology lateral flow assay |
| WBA     | whole-blood assay                                    |
| WHO     | World Health Organisation                            |

## LIST OF PUBLICATIONS

1. Knauff EA, **Richardus R**, Eijkemans MJ, Broekmans FJ, de Jong FJ, Fauser BC, Bosch AM. Heterozygosity for the classical galactosemia mutation does not affect ovarian reserve and menopausal age. *Reprod Sci*. 2007 Dec;14(8):780-5.
2. **Richardus RA**, Jansen JC, Steens SC, Arend SM. Two immigrants with tuberculosis of the ear, nose, and throat region with skull base and cranial nerve involvement. *Case Rep Med*. 2011;2011:675807. doi: 10.1155/2011/675807. Epub 2011 Apr 7.
3. **Richardus RA**, Alam K, Pahan D, Feenstra SG, Geluk A, Richardus JH. The combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG to prevent leprosy in contacts of newly diagnosed leprosy cases: a cluster randomized controlled trial (MALTALP study). *BMC Infect Dis*. 2013 Oct 3;13:456. doi: 10.1186/1471-2334-13-456.
4. **Richardus RA**, Butlin CR, Alam K, Kundu K, Geluk A, Richardus JH. Clinical manifestations of leprosy after BCG vaccination: an observational study in Bangladesh. *Vaccine*. 2015 Mar 24;33(13):1562-7. doi: 10.1016/j.vaccine.2015.02.017. Epub 2015 Feb 18.
5. Van Hooij A, Tjon Kon Fat EM, **Richardus R**, van den Eeden SJF, Wilson L, de Dood CJ, Faber R, Alam K, Richardus JH, Corstjens PLAM, Geluk A. Quantitative lateral flow strip assays as User-Friendly Tools To Detect Biomarker Profiles For Leprosy. *Scientific Reports* | 6:34260 | DOI: 10.1038/srep34260.
6. **Richardus RA**, Hooij van A, Eeden van den SJF, Wilson L, Alam K, Richardus JH, Geluk A. BCG and Adverse Events in the context of Leprosy. *Frontiers in Immunology*. 2018 April 4, doi: 10.3389/fimmu.2018.00629.
7. **Richardus RA**, Zwet van K, Hooij van A, Wilson L, Oskam L, Faber R, Eeden van den SJF, Pahan D, Alam K, Richardus JH, Geluk A. Longitudinal assessment of anti-PGL-I IgM serology in contacts of leprosy patients in Bangladesh. *PLoS Negl Trop Dis*. 2017 Dec 11;11(12):e0006083. doi: 10.1371/journal.pntd.0006083. eCollection 2017 Dec.
8. **Richardus RA**, Alam K, Kundu K, Roy JC, Zafar T, Chowdhury AS, Nieboer D, Faber R, Butlin CR, Geluk A, Richardus JH. Effectiveness of single dose rifampicin after BCG vaccination to prevent leprosy in close contacts of patients with newly diagnosed leprosy: a cluster randomized controlled trial. *International Journal of Infectious Diseases* November 2019, Volume 88, pages 65-72. doi.org/10.1016/j.ijid.2019.08.035. Published Online First: 2019/10/05.
9. Hooij van A, Eeden van den S, **Richardus R**, Tjon Kon Fat E, Wilson L, Franken KLMC, Faber R, Khatun M, Alam K, Chowdhury AS, Richardus JH, Corstjens P and Geluk A. Application of new

host biomarker profiles in quantitative point-of-care tests facilitates leprosy diagnosis in the field. EBioMedicine 2019 Sep;47:301-308. doi: 10.1016/j.ebiom.2019.08.009. Epub 2019 Aug 14.

**CURRICULUM VITAE**

Renate Alicia Verbiest-Richardus was born in Rotterdam, the Netherlands, on the 13<sup>th</sup> of September 1983. She graduated cum laude from her secondary education (tweetalig-VWO) in 2001, which included an International Baccalaureate in English A1. She started medical school at the University of Leiden, and received her Master (Artsexamen Geneeskunde) in 2007. After an internship in internal medicine, she decided to specialize in Tropical Medicine and focused on mother-child health in the tropics, completing internships in both gynaecology and paediatrics (IJsselland Ziekenhuis, Capelle aan den IJssel; Amphia Ziekenhuis, Breda). This included a three months intensive training course in Tropical Medicine and Hygiene at the Koninklijk Instituut voor de Tropen in Amsterdam, The Netherlands. From 2012 to 2016 she moved to the northwest of Bangladesh with her family, and worked as a medical doctor on the gynaecology and paediatric department of LAMB Hospital. Alongside this, she supervised the MALTALEP/IDEAL trial from 2012 onwards, which had just started in Nilphamari Hospital, as part of the Rural Health Program (RHP) of The Leprosy Mission International Bangladesh (TLMIB). This is a collaboration of TLMIB, the department of Public Health at the Erasmus MC, University Medical Center Rotterdam and the Department of Infectious Diseases at the Leiden University Medical School (LUMC). In 2016 she started as an official PhD candidate at the Department of Infectious Diseases at the LUMC under supervision of Professor dr. Annemieke Geluk. Since 2017, Renate is trained at the LUMC to be a general practitioner.

## ACKNOWLEDGEMENTS

When I moved to Bangladesh together with my family in 2012 to work at LAMB Hospital, I never thought to be involved in leprosy research, let alone complete a doctoral thesis. However, when my predecessor Sabiena Feenstra left Bangladesh, someone was needed to take over from her and supervise the MALTALAP trial, which had just started in Nilphamari Hospital. Since the hospital was only an hour drive from our home, and the combination of research activities with my clinical activities at LAMB was appealing and feasible, I agreed to the project. And what a trip it has been! The four years in Bangladesh became extra special with the monthly visits to Nilphamari, sometimes together with Jelle and our children. After moving to the Netherlands, I visited Nilphamari five times in order to continue supervising the ongoing field work. And now, in my second year of GP training, the end of this 7 year trip is drawing to an end!

It would not have been possible for me to write this thesis without the help and support of many people around me, to some of whom I want to give particular mention. First, my promotor. Thank you so much for your continued support and guidance! I am amazed at how quick and concise you always reacted to my questions and drafts of articles, despite your numerous other activities and travels. You encouraged me to delve into leprosy immunology and the corresponding laboratory work, even though it did not always come naturally to me as a clinician.

Secondly, a big thanks to my father, Jan Hendrik Richardus, who had a very special role in this PhD project. I am at awe at your huge dedication to the leprosy work in Bangladesh, and I have seen how much it means to the staff in Nilphamari. Thank you for coaching me through this PhD project! You were always available for advice about the (epidemiological) aspects of the trial. I especially enjoyed our visits to Bangladesh together, it was special to have quality time with my father as well as work together as colleagues.

Dear Jelle, thank you for supporting me through it, and especially for taking care of the children when I was travelling and being patient with me when I was pondering over the databases on numerous evenings. A special thanks to my mother and in-laws for their love and support as well.

To the staff in Nilphamari: you are such a great group of people! I admire your commitment to the leprosy patients of Bangladesh and your dedication to the research projects. I especially enjoyed our staff meetings: you were always eager to ask questions, to think with us about the direction of the research projects, to continue visiting households of leprosy patients notwithstanding the weather and political unrest, and thank you too for allowing me to run staff meetings in my 'motamoeti' Bangla!

Dear Khorshed, a special thanks to you for you for running the project so dedicatedly. You were the key contact person between the Netherlands and the staff of Bangladesh; with your amicable character I believe you have done a great job binding people together to get the job done! I also very much appreciate the warm friendship that has developed between our families!

Also a big thank you to Kallyan and Johan for their endless work in the database. What a tremendous job: entering all the field data into the databases with as little possible mistakes as humanly possible! Thank you for being patient with my endless questions and corrections. Marufa apu, a special thanks to you too, for your dedication in the laboratory work. Ruth Butlin, a special thanks for you as well. It was wonderful to learn the basics of leprosy (diagnosis) from you, both theoretically and in clinic, and to work on my second article together.

A special thanks goes to the help of the staff at the LUMC and Erasmus MC as well. Susan, you taught me the ABC of laboratory work. Thank you Anouk and Louis, too, for your laboratory support in my third and fourth article! Roel, thank you for all your technical support on the MALTALEP database and for endlessly puzzling on the SPSS syntaxes with me! Daan, thank you for your statistical support!

Finally, this thesis would never have been completed without all the leprosy patients and their families who participated in our studies. I hope this thesis has somehow played a small contribution in ameliorating their situation and that it will help towards preventing the further spread of leprosy.

## REFERENCES OF THE GENERAL INTRODUCTION AND DISCUSSION

1. van Brakel WH, Sihombing B, Djarir H, et al. Disability in people affected by leprosy: the role of impairment, activity, social participation, stigma and discrimination. *Global health action* 2012;5 doi: 10.3402/gha.v5i0.18394 [published Online First: 2012/07/25]
2. Global leprosy update, 2016: accelerating reduction of disease burden. *Releve epidemiologique hebdomadaire* 2017;92(35):501-19. [published Online First: 2017/09/02]
3. Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. *Health technology assessment (Winchester, England)* 2013;17(37):1-372, v-vi. doi: 10.3310/hta17370 [published Online First: 2013/09/12]
4. Garnier T, Eiglmeier K, Camus JC, et al. The complete genome sequence of *Mycobacterium bovis*. *Proceedings of the National Academy of Sciences of the United States of America* 2003;100(13):7877-82. doi: 10.1073/pnas.1130426100 [published Online First: 2003/06/06]
5. Coppola M, van den Eeden SJF, Robbins N, et al. Vaccines for Leprosy and Tuberculosis: Opportunities for Shared Research, Development, and Application. *Front Immunol* 2018;9:308. doi: 10.3389/fimmu.2018.00308 [published Online First: 2018/03/15]
6. Report of the Third Meeting of the Scientific Working Group on Chemotherapy of Leprosy (THELEP) of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, Geneva, 20-22 October 1980. *Leprosy review* 1981;52(4):349-54. [published Online First: 1981/12/01]
7. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *International journal of leprosy and other mycobacterial diseases : official organ of the International Leprosy Association* 1966;34(3):255-73. [published Online First: 1966/07/01]
8. Yawalkar SJ. Leprosy for medical practitioners and paramedical workers 2009.
9. Rada E, Aranzazu N, Convit J. [Immune response of Hansen's disease. Review]. *Investigacion clinica* 2009;50(4):513-27. [published Online First: 2010/03/24]
10. Ab BK, Kiessling R, Van Embden JD, et al. Induction of antigen-specific CD4+ HLA-DR-restricted cytotoxic T lymphocytes as well as nonspecific nonrestricted killer cells by the recombinant mycobacterial 65-kDa heat-shock protein. *European journal of immunology* 1990;20(2):369-77. doi: 10.1002/eji.1830200221 [published Online First: 1990/02/01]
11. Verreck FA, de Boer T, Langenberg DM, et al. Human IL-23-producing type 1 macrophages promote but IL-10-producing type 2 macrophages subvert immunity to (myco)bacteria. *Proceedings of the National Academy of Sciences of the United States of America* 2004;101(13):4560-5. doi: 10.1073/pnas.0400983101 [published Online First: 2004/04/09]
12. Joosten SA, van Meijgaarden KE, Savage ND, et al. Identification of a human CD8+ regulatory T cell subset that mediates suppression through the chemokine CC chemokine ligand 4. *Proceedings of the National Academy of Sciences of the United States of America* 2007;104(19):8029-34. doi: 10.1073/pnas.0702257104 [published Online First: 2007/05/08]

13. Boer MC, Joosten SA, Ottenhoff TH. Regulatory T-Cells at the Interface between Human Host and Pathogens in Infectious Diseases and Vaccination. *Frontiers in immunology* 2015;6:217. doi: 10.3389/fimmu.2015.00217 [published Online First: 2015/06/02]
14. Ottenhoff TH, Elferink DG, Klatser PR, et al. Cloned suppressor T cells from a lepromatous leprosy patient suppress Mycobacterium leprae reactive helper T cells. *Nature* 1986;322(6078):462-4. doi: 10.1038/322462a0 [published Online First: 1986/07/06]
15. Mutis T, Cornelisse YE, Datema G, et al. Definition of a human suppressor T-cell epitope. *Proceedings of the National Academy of Sciences of the United States of America* 1994;91(20):9456-60. doi: 10.1073/pnas.91.20.9456 [published Online First: 1994/09/27]
16. Sieling PA, Abrams JS, Yamamura M, et al. Immunosuppressive roles for IL-10 and IL-4 in human infection. In vitro modulation of T cell responses in leprosy. *Journal of immunology (Baltimore, Md : 1950)* 1993;150(12):5501-10. [published Online First: 1993/06/15]
17. Libraty DH, Airan LE, Uyemura K, et al. Interferon-gamma differentially regulates interleukin-12 and interleukin-10 production in leprosy. *The Journal of clinical investigation* 1997;99(2):336-41. doi: 10.1172/jci119162 [published Online First: 1997/01/15]
18. Bobosha K, Wilson L, van Meijgaarden KE, et al. T-cell regulation in lepromatous leprosy. *PLoS neglected tropical diseases* 2014;8(4):e2773. doi: 10.1371/journal.pntd.0002773 [published Online First: 2014/04/12]
19. Palermo ML, Pagliari C, Trindade MA, et al. Increased expression of regulatory T cells and down-regulatory molecules in lepromatous leprosy. *The American journal of tropical medicine and hygiene* 2012;86(5):878-83. doi: 10.4269/ajtmh.2012.12-0088 [published Online First: 2012/05/05]
20. Saini C, Ramesh V, Nath I. Increase in TGF-beta secreting CD4(+)CD25(+) FOXP3(+) T regulatory cells in anergic lepromatous leprosy patients. *PLoS neglected tropical diseases* 2014;8(1):e2639. doi: 10.1371/journal.pntd.0002639 [published Online First: 2014/01/24]
21. Gomes GI, Nahn EP, Jr., Santos RK, et al. The functional state of the complement system in leprosy. *The American journal of tropical medicine and hygiene* 2008;78(4):605-10. [published Online First: 2008/04/04]
22. Kamath S, Vaccaro SA, Rea TH, et al. Recognizing and managing the immunologic reactions in leprosy. *Journal of the American Academy of Dermatology* 2014;71(4):795-803. doi: 10.1016/j.jaad.2014.03.034 [published Online First: 2014/04/29]
23. Geluk A. Correlates of immune exacerbations in leprosy. *Seminars in immunology* 2018;39:111-18. doi: 10.1016/j.smim.2018.06.003 [published Online First: 2018/06/29]
24. Motta AC, Pereira KJ, Tarquinio DC, et al. Leprosy reactions: coinfections as a possible risk factor. *Clinics (Sao Paulo, Brazil)* 2012;67(10):1145-8. [published Online First: 2012/10/17]
25. Deps P, Lucas S, Porro AM, et al. Clinical and histological features of leprosy and human immunodeficiency virus co-infection in Brazil. *Clinical and experimental dermatology* 2013;38(5):470-7. doi: 10.1111/ced.12028 [published Online First: 2013/05/18]

26. Hagge DA, Parajuli P, Kunwar CB, et al. Opening a Can of Worms: Leprosy Reactions and Complicit Soil-Transmitted Helminths. *EBioMedicine* 2017;23:119-24. doi: 10.1016/j.ebiom.2017.08.026 [published Online First: 2017/09/09]
27. Geluk A. Challenges in immunodiagnostic tests for leprosy. *Expert opinion on medical diagnostics* 2013;7(3):265-74. doi: 10.1517/17530059.2013.786039 [published Online First: 2013/03/30]
28. Fava V, Orlova M, Cobat A, et al. Genetics of leprosy reactions: an overview. *Memorias do Instituto Oswaldo Cruz* 2012;107 Suppl 1:132-42. [published Online First: 2013/01/11]
29. Geluk A, van Meijgaarden KE, Wilson L, et al. Longitudinal immune responses and gene expression profiles in type 1 leprosy reactions. *Journal of clinical immunology* 2014;34(2):245-55. doi: 10.1007/s10875-013-9979-x [published Online First: 2013/12/29]
30. Andreoli A, Brett SJ, Draper P, et al. Changes in circulating antibody levels to the major phenolic glycolipid during erythema nodosum leprosum in leprosy patients. *International journal of leprosy and other mycobacterial diseases : official organ of the International Leprosy Association* 1985;53(2):211-7. [published Online First: 1985/06/01]
31. Smith SG, Kleinnijenhuis J, Netea MG, et al. Whole Blood Profiling of Bacillus Calmette-Guerin-Induced Trained Innate Immunity in Infants Identifies Epidermal Growth Factor, IL-6, Platelet-Derived Growth Factor-AB/BB, and Natural Killer Cell Activation. *Front Immunol* 2017;8:644. doi: 10.3389/fimmu.2017.00644 [published Online First: 2017/06/22]
32. von Gierke U, Stagelschmidt P, Prantl F, et al. [A rare cause of carpal tunnel syndrome: leprosy. Latency period of decades is possible]. *MMW Fortschritte der Medizin* 2000;142(10):39-40. [published Online First: 2000/04/05]
33. Shepard CC. The nasal excretion of Mycobacterium leprae in leprosy. *International journal of Leprosy* 1962;30:10-8. [published Online First: 1962/01/01]
34. Smith WC, van Brakel W, Gillis T, et al. The missing millions: a threat to the elimination of leprosy. *PLoS neglected tropical diseases* 2015;9(4):e0003658. doi: 10.1371/journal.pntd.0003658 [published Online First: 2015/04/24]
35. Moet FJ, Pahan D, Schuring RP, et al. Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy. *J Infect Dis* 2006;193(3):346-53. doi: 10.1086/499278 [published Online First: 2006/01/03]
36. Truman RW, Singh P, Sharma R, et al. Probable zoonotic leprosy in the southern United States. *The New England journal of medicine* 2011;364(17):1626-33. doi: 10.1056/NEJMoa1010536 [published Online First: 2011/04/29]
37. Deps PD, Alves BL, Gripp CG, et al. Contact with armadillos increases the risk of leprosy in Brazil: a case control study. *Indian journal of dermatology, venereology and leprology* 2008;74(4):338-42. [published Online First: 2008/09/18]
38. Stefani MMA, Rosa PS, Costa MB, et al. Leprosy survey among rural communities and wild armadillos from Amazonas state, Northern Brazil. *PloS one* 2019;14(1):e0209491. doi: 10.1371/journal.pone.0209491 [published Online First: 2019/01/11]
39. Lavania M, Katoch K, Katoch VM, et al. Detection of viable Mycobacterium leprae in soil samples: insights into possible sources of transmission of leprosy. *Infection, genetics and evolution* :

- journal of molecular epidemiology and evolutionary genetics in infectious diseases* 2008;8(5):627-31. doi: 10.1016/j.meegid.2008.05.007 [published Online First: 2008/07/05]
40. Turankar RP, Lavania M, Singh M, et al. Dynamics of Mycobacterium leprae transmission in environmental context: deciphering the role of environment as a potential reservoir. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases* 2012;12(1):121-6. doi: 10.1016/j.meegid.2011.10.023 [published Online First: 2011/11/22]
  41. Tio-Coma M, Wijnands T, Pierneef L, et al. Detection of Mycobacterium leprae DNA in soil: multiple needles in the haystack. *Scientific reports* 2019;9(1):3165. doi: 10.1038/s41598-019-39746-6 [published Online First: 2019/03/01]
  42. Kerr-Pontes LR, Barreto ML, Evangelista CM, et al. Socioeconomic, environmental, and behavioural risk factors for leprosy in North-east Brazil: results of a case-control study. *International journal of epidemiology* 2006;35(4):994-1000. doi: 10.1093/ije/dyl072 [published Online First: 2006/04/29]
  43. Feenstra SG, Nahar Q, Pahan D, et al. Recent food shortage is associated with leprosy disease in Bangladesh: a case-control study. *PLoS neglected tropical diseases* 2011;5(5):e1029. doi: 10.1371/journal.pntd.0001029 [published Online First: 2011/05/17]
  44. Schaible UE, Kaufmann SH. Malnutrition and infection: complex mechanisms and global impacts. *PLoS medicine* 2007;4(5):e115. doi: 10.1371/journal.pmed.0040115 [published Online First: 2007/05/03]
  45. Bakker MI, May L, Hatta M, et al. Genetic, household and spatial clustering of leprosy on an island in Indonesia: a population-based study. *BMC medical genetics* 2005;6:40. doi: 10.1186/1471-2350-6-40 [published Online First: 2005/11/26]
  46. Oktaria S, Effendi EH, Indriatmi W, et al. Soil-transmitted helminth infections and leprosy: a cross-sectional study of the association between two major neglected tropical diseases in Indonesia. *BMC infectious diseases* 2016;16:258. doi: 10.1186/s12879-016-1593-0 [published Online First: 2016/06/10]
  47. Carvalho L, Sun J, Kane C, et al. Review series on helminths, immune modulation and the hygiene hypothesis: mechanisms underlying helminth modulation of dendritic cell function. *Immunology* 2009;126(1):28-34. doi: 10.1111/j.1365-2567.2008.03008.x [published Online First: 2009/01/06]
  48. Resende Co T, Hirsch CS, Toossi Z, et al. Intestinal helminth co-infection has a negative impact on both anti-Mycobacterium tuberculosis immunity and clinical response to tuberculosis therapy. *Clinical and experimental immunology* 2007;147(1):45-52. doi: 10.1111/j.1365-2249.2006.03247.x [published Online First: 2006/12/21]
  49. Moet FJ, Schuring RP, Pahan D, et al. The prevalence of previously undiagnosed leprosy in the general population of northwest bangladesh. *PLoS neglected tropical diseases* 2008;2(2):e198. doi: 10.1371/journal.pntd.0000198 [published Online First: 2008/02/28]
  50. van Hooij A, Tjon Kon Fat EM, Richardus R, et al. Quantitative lateral flow strip assays as User-Friendly Tools To Detect Biomarker Profiles For Leprosy. *Sci Rep* 2016;6:34260. doi: 10.1038/srep34260 [published Online First: 2016/09/30]

51. Bobosha K, Tjon Kon Fat EM, van den Eeden SJ, et al. Field-evaluation of a new lateral flow assay for detection of cellular and humoral immunity against *Mycobacterium leprae*. *PLoS neglected tropical diseases* 2014;8(5):e2845. doi: 10.1371/journal.pntd.0002845 [published Online First: 2014/05/09]
52. Geluk A, Duthie MS, Spencer JS. Postgenomic *Mycobacterium leprae* antigens for cellular and serological diagnosis of *M. leprae* exposure, infection and leprosy disease. *Leprosy review* 2011;82(4):402-21. [published Online First: 2012/03/24]
53. Corstjens P, van Hooij A, Tjon Kon Fat EM, et al. Fingerstick test quantifying humoral and cellular biomarkers indicative for *M. leprae* infection. *Clinical biochemistry* 2019;66:76-82. doi: 10.1016/j.clinbiochem.2019.01.007 [published Online First: 2019/01/30]
54. van Hooij A, Tjon Kon Fat EM, Batista da Silva M, et al. Evaluation of Immunodiagnostic Tests for Leprosy in Brazil, China and Ethiopia. *Scientific reports* 2018;8(1):17920. doi: 10.1038/s41598-018-36323-1 [published Online First: 2018/12/19]
55. Spencer JS, Brennan PJ. The role of *Mycobacterium leprae* phenolic glycolipid I (PGL-I) in serodiagnosis and in the pathogenesis of leprosy. *Leprosy review* 2011;82(4):344-57. [published Online First: 2012/03/24]
56. Spencer JS, Kim HJ, Wheat WH, et al. Analysis of antibody responses to *Mycobacterium leprae* phenolic glycolipid I, lipoarabinomannan, and recombinant proteins to define disease subtype-specific antigenic profiles in leprosy. *Clinical and vaccine immunology : CVI* 2011;18(2):260-7. doi: 10.1128/cvi.00472-10 [published Online First: 2010/12/24]
57. Schuring RP, Moet FJ, Pahan D, et al. Association between anti-pGL-I IgM and clinical and demographic parameters in leprosy. *Leprosy review* 2006;77(4):343-55. [published Online First: 2007/03/09]
58. Setia MS, Steinmaus C, Ho CS, et al. The role of BCG in prevention of leprosy: a meta-analysis. *The Lancet Infectious diseases* 2006;6(3):162-70. doi: 10.1016/s1473-3099(06)70412-1 [published Online First: 2006/02/28]
59. Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert review of vaccines* 2010;9(2):209-22. doi: 10.1586/erv.09.161 [published Online First: 2010/01/30]
60. Duppre NC, Camacho LA, da Cunha SS, et al. Effectiveness of BCG vaccination among leprosy contacts: a cohort study. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2008;102(7):631-8. doi: 10.1016/j.trstmh.2008.04.015 [published Online First: 2008/06/03]
61. de Bree LCJ, Koeken V, Joosten LAB, et al. Non-specific effects of vaccines: Current evidence and potential implications. *Seminars in immunology* 2018;39:35-43. doi: 10.1016/j.smim.2018.06.002 [published Online First: 2018/07/17]
62. Welsh RM, Selin LK. No one is naive: the significance of heterologous T-cell immunity. *Nature reviews Immunology* 2002;2(6):417-26. doi: 10.1038/nri820 [published Online First: 2002/07/03]
63. Netea MG, Quintin J, van der Meer JW. Trained immunity: a memory for innate host defense. *Cell host & microbe* 2011;9(5):355-61. doi: 10.1016/j.chom.2011.04.006 [published Online First: 2011/05/18]

64. Cunha SS, Alexander N, Barreto ML, et al. BCG revaccination does not protect against leprosy in the Brazilian Amazon: a cluster randomised trial. *PLoS neglected tropical diseases* 2008;2(2):e167. doi: 10.1371/journal.pntd.0000167 [published Online First: 2008/02/14]
65. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. Karonga Prevention Trial Group. *Lancet (London, England)* 1996;348(9019):17-24. [published Online First: 1996/07/06]
66. Noordeen SK, Neelan PN. Chemoprophylaxis among contacts of non-lepromatous leprosy. *Leprosy in India* 1976;48(4 Suppl):635-42. [published Online First: 1976/10/01]
67. Wardekar RV. DDS prophylaxis against leprosy. *Leprosy in India* 1967;39:155-59.
68. Noordeen SK. Chemoprophylaxis in leprosy. *Leprosy in India* 1969;41:247-54.
69. Bakker MI, Hatta M, Kwenang A, et al. Prevention of leprosy using rifampicin as chemoprophylaxis. *The American journal of tropical medicine and hygiene* 2005;72(4):443-8. [published Online First: 2005/04/14]
70. Moet FJ, Pahan D, Oskam L, et al. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ (Clinical research ed)* 2008;336(7647):761-4. doi: 10.1136/bmj.39500.885752.BE [published Online First: 2008/03/12]
71. Schuring RP, Richardus JH, Pahan D, et al. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. *Vaccine* 2009;27(50):7125-8. doi: 10.1016/j.vaccine.2009.09.054 [published Online First: 2009/09/30]
72. Guidelines for the diagnosis, treatment and prevention of leprosy. [Available from: [http://www.searo.who.int/entity/global\\_leprosy\\_programme/approved-guidelines-leprosy-executives-summary.pdf?ua=1](http://www.searo.who.int/entity/global_leprosy_programme/approved-guidelines-leprosy-executives-summary.pdf?ua=1) accessed 1 July 2019.
73. Barth-Jaeggi T, Steinmann P, Mieras L, et al. Leprosy Post-Exposure Prophylaxis (LPEP) programme: study protocol for evaluating the feasibility and impact on case detection rates of contact tracing and single dose rifampicin. *BMJ Open* 2016;6(11):e013633. doi: 10.1136/bmjopen-2016-013633 [published Online First: 2016/11/20]
74. Bagshawe A, Scott GC, Russell DA, et al. BCG vaccination in leprosy: final results of the trial in Karimui, Papua New Guinea, 1963-79. *Bulletin of the World Health Organization* 1989;67(4):389-99. [published Online First: 1989/01/01]
75. Richardus R, van Hooij A, van den Eeden SJF, et al. BCG and Adverse Events in the Context of Leprosy. *Frontiers in immunology* 2018;9:629. doi: 10.3389/fimmu.2018.00629 [published Online First: 2018/04/20]
76. Fallows D, Peixoto B, Kaplan G, et al. *Mycobacterium leprae* alters classical activation of human monocytes in vitro. *Journal of inflammation (London, England)* 2016;13:8. doi: 10.1186/s12950-016-0117-4 [published Online First: 2016/03/15]
77. Alcais A, Sanchez FO, Thuc NV, et al. Granulomatous reaction to intradermal injection of lepromin (Mitsuda reaction) is linked to the human NRAMP1 gene in Vietnamese leprosy sibships. *The*

- Journal of infectious diseases* 2000;181(1):302-8. doi: 10.1086/315174 [published Online First: 1999/12/23]
78. Araujo S, Rezende MM, Sousa DC, et al. Risk-benefit assessment of Bacillus Calmette-Guerin vaccination, anti-phenolic glycolipid I serology, and Mitsuda test response: 10-year follow-up of household contacts of leprosy patients. *Revista da Sociedade Brasileira de Medicina Tropical* 2015;48(6):739-45. doi: 10.1590/0037-8682-0245-2015 [published Online First: 2015/12/18]
  79. Boer MC, Prins C, van Meijgaarden KE, et al. Mycobacterium bovis BCG Vaccination Induces Divergent Proinflammatory or Regulatory T Cell Responses in Adults. *Clinical and vaccine immunology : CVI* 2015;22(7):778-88. doi: 10.1128/cvi.00162-15 [published Online First: 2015/05/08]
  80. Rhodes SJ, Knight GM, Fielding K, et al. Individual-level factors associated with variation in mycobacterial-specific immune response: Gender and previous BCG vaccination status. *Tuberculosis (Edinburgh, Scotland)* 2016;96:37-43. doi: 10.1016/j.tube.2015.10.002 [published Online First: 2016/01/21]
  81. Dets P, Lockwood DN. Leprosy presenting as immune reconstitution inflammatory syndrome: proposed definitions and classification. *Leprosy review* 2010;81(1):59-68. [published Online First: 2010/05/26]
  82. Richardus RA, Alam K, Pahan D, et al. The combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG to prevent leprosy in contacts of newly diagnosed leprosy cases: a cluster randomized controlled trial (MALTALEP study). *BMC infectious diseases* 2013;13:456. doi: 10.1186/1471-2334-13-456 [published Online First: 2013/10/04]
  83. Richardus RA AK, Kundu K, Roy JC, Zafar T, Chowdhury AS, Nieboer D, Faber R, Butlin CR, Geluk A, Richardus JH. . Effectiveness of single dose rifampicin after BCG vaccination to prevent leprosy in close contacts of patients with newly diagnosed leprosy: a cluster randomized controlled trial. *International Journal of Infectious Diseases November 2019, Volume 88, pages 65-72*. doi.org/10.1016/j.ijid.2019.08.035[published Online First: 2019/10/05]
  84. Richardus JH. Chemoprophylaxis: sufficient evidence for starting implementation pilots. *Leprosy review* 2015;86(1):128-9. [published Online First: 2015/06/13]
  85. Feenstra SG, Pahan D, Moet FJ, et al. Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. *Lepr Rev* 2012;83(3):292-304. [published Online First: 2013/01/30]
  86. Smith CM, Smith WC. Chemoprophylaxis is effective in the prevention of leprosy in endemic countries: a systematic review and meta-analysis. MILEP2 Study Group. *Mucosal Immunology of Leprosy. The Journal of infection* 2000;41(2):137-42. doi: 10.1053/jinf.2000.0698 [published Online First: 2000/10/12]
  87. Brosch R, Gordon SV, Garnier T, et al. Genome plasticity of BCG and impact on vaccine efficacy. *Proceedings of the National Academy of Sciences of the United States of America* 2007;104(13):5596-601. doi: 10.1073/pnas.0700869104 [published Online First: 2007/03/21]

88. Zhang W, Zhang Y, Zheng H, et al. Genome sequencing and analysis of BCG vaccine strains. *PLoS one* 2013;8(8):e71243. doi: 10.1371/journal.pone.0071243 [published Online First: 2013/08/27]
89. Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet (London, England)* 1995;346(8986):1339-45. doi: 10.1016/s0140-6736(95)92348-9 [published Online First: 1995/11/18]
90. Richardus RA, van der Zwet K, van Hooij A, et al. Longitudinal assessment of anti-PGL-I serology in contacts of leprosy patients in Bangladesh. *PLoS neglected tropical diseases* 2017;11(12):e0006083. doi: 10.1371/journal.pntd.0006083 [published Online First: 2017/12/12]
91. Penna ML, Penna GO, Iglesias PC, et al. Anti-PGL-1 Positivity as a Risk Marker for the Development of Leprosy among Contacts of Leprosy Cases: Systematic Review and Meta-analysis. *PLoS neglected tropical diseases* 2016;10(5):e0004703. doi: 10.1371/journal.pntd.0004703 [published Online First: 2016/05/19]
92. Douglas JT, Cellona RV, Fajardo TT, Jr., et al. Prospective study of serological conversion as a risk factor for development of leprosy among household contacts. *Clinical and diagnostic laboratory immunology* 2004;11(5):897-900. doi: 10.1128/cdli.11.5.897-900.2004 [published Online First: 2004/09/11]
93. Barreto JG, Bisanzio D, Frade MA, et al. Spatial epidemiology and serologic cohorts increase the early detection of leprosy. *BMC infectious diseases* 2015;15:527. doi: 10.1186/s12879-015-1254-8 [published Online First: 2015/11/18]
94. Groenen G, Pattyn SR, Ghys P, et al. A longitudinal study of the incidence of leprosy in a hyperendemic area in Zaire, with special reference to PGL-antibody results. The Yalisombo Study Group. *International journal of leprosy and other mycobacterial diseases : official organ of the International Leprosy Association* 1990;58(4):641-50. [published Online First: 1990/12/01]
95. Carvalho AP, da Conceicao Oliveira Coelho Fabri A, Correa Oliveira R, et al. Factors associated with anti-phenolic glycolipid-I seropositivity among the household contacts of leprosy cases. *BMC infectious diseases* 2015;15:219. doi: 10.1186/s12879-015-0955-3 [published Online First: 2015/05/31]
96. Duppre NC, Camacho LA, Sales AM, et al. Impact of PGL-I seropositivity on the protective effect of BCG vaccination among leprosy contacts: a cohort study. *PLoS neglected tropical diseases* 2012;6(6):e1711. doi: 10.1371/journal.pntd.0001711 [published Online First: 2012/06/23]
97. Corstjens P, van Hooij A, Tjon Kon Fat EM, et al. Field-Friendly Test for Monitoring Multiple Immune Response Markers during Onset and Treatment of Exacerbated Immunity in Leprosy. *Clinical and vaccine immunology : CVI* 2016;23(6):515-19. doi: 10.1128/cvi.00033-16 [published Online First: 2016/04/01]
98. Geluk A, Bobosha K, van der Ploeg-van Schip JJ, et al. New biomarkers with relevance to leprosy diagnosis applicable in areas hyperendemic for leprosy. *Journal of immunology (Baltimore, Md : 1950)* 2012;188(10):4782-91. doi: 10.4049/jimmunol.1103452 [published Online First: 2012/04/17]

99. Hooij van A E, Richardus R, Tjon Kon Fat E, Wilson L, Franken KLMC, Faber R, Khatun M, Alam K, Chowdhury AS, Richardus JH, Corstjens P and Geluk A. Application of new host biomarker profiles in quantitative point-of-care tests facilitates leprosy diagnosis in the field. *EBioMedicine* 2019 Sep;47:301-308. doi: 10.1016/j.ebiom.2019.08.009. Epub 2019 Aug 14.