ESSAYS ON

EVALUATION OF GLOBAL HEALTH POLICY ON

TUBERCULOSIS CONTROL

A Dissertation

Submitted to the National Graduate Institute for Policy Studies (GRIPS)

in Partial Fulfillment of the Requirements for the Degree of

Ph.D. in Public Policy

by

Yoko Iwaki, MPH

June, 2022

Table of Contents

List of Tables iv

List of Figures v

Acknowledgement vii

Executive Summary viii

Chapter 1 Introduction 1

1.1 Epidemiologic disaster to global pandemic—tuberculosis (TB)........ 1

1.2 Japan’s global health policy toward TB control 3

1.3 TB in Nepal 6

1.4 Objectives 8

1.5 Dissertation structure 11

1.6 Reference........ 13

Chapter 2 Japan's Contribution to Tuberculosis Research: A Text Mining-based Topic Modeling Analysis for 15 Countries (1999-2019)........ 16

2.1 Introduction 16

2.2 Methodology 20

2.2.1 Data and pre-processing 20

2.2.2 Data analysis........ 23

2.2.2.1 Topic modeling for thematic analysis 23

2.2.2.2 Correspondence analysis and cluster analysis 23

2.3 Results........ 24

2.3.1 Identification of high proportion of topics and productivities........ 24

2.3.2 Identified characteristics and priorities of research topics........ 29

2.3.3 Evaluation of scale of research engagement and contribution 32

2.4 Discussion........ 34

2.5 Limitations 40
2.6 Conclusion 41
2.7 Appendix 43
2.8 Supplements 44
2.9 Reference 49
Chapter 3 Assessing Factors Associated with TB Awareness in Nepal: A National and Subnational Study 54
3.1 Introduction 54
3.2 Materials and Methods 57
3.2.1 Data-In-Use 57
3.2.2 Outcome Variables and Covariates 57
3.2.3 Statistical Analysis 58
3.3 Results 59
3.3.1 Summary of Socio-Demographic Characteristics of Respondents 59
3.3.2 Proportion of People with TB Awareness at a Subnational Level in Nepal 60
3.3.3 Variables Associated with TB Awareness 61
3.4 Discussion 63
3.5 Conclusion 70
3.6 Appendix 71
3.7 Reference 72
Chapter 4 Cost-benefit analysis of pre-entry tuberculosis screening policy: Nepalese and Japanese perspectives 77
4.1 Introduction 77
4.2 Methods 79
4.2.1 Policy scenarios for analysis 79
4.2.2 Analytical framework 81

4.2.3 Estimation of active TB population.. 82
4.2.4 Present Condition 84
4.2.5 Expected impact on the cost and benefit 86
4.2.6 Cost of TB screening test 87
4.2.7 Cost of TB treatment 87
4.2.8 The benefit by avoidance of capacity loss 88
4.2.9 Sensitivity analysis.. 89
4.2.10 Conceptualization toward burden sharing 90
4.3 Results.. 90
4.4 Discussion... 95
4.4.1 Policy implications 95
4.4.2 Limitations and future perspective 98
4.5 Conclusion 99
4.6 Ethical and conflict of interest statement 100
4.7 Supplement.. 101
4.7.1 Formula of target population 101
4.7.2 Formula of cost and benefit.. 104
4.7.3 Sensitivity test result in Japan 106
4.7.4 Sensitivity test result in Nepal 106
4.8 Reference.. 107
Chapter 5 Conclusions.. 114
5.1 Concluding remarks 114
5.2 Research limitation and future prospects.. 119
5.3 Reference.. 124

List of Tables

Table 2.1 Classification of 15 topics ... 26

Table A2.1 Proportion of publications on selected research topics in affiliated countries ... 43

Table A2.2 Proportion of research and innovation types based on WHO TB strategy, by country ... 43

Table S2.1 Classification of 15 topics (Scopus only dataset) ... 45

Table S2.2 Proportion of publications on selected research topics in affiliated countries, by country, by using only Scopus dataset ... 48

Table S2.3 Proportion of research and innovation types based on WHO TB strategy, by country by using only Scopus dataset ... 48

Table 3.1 Demographic and socio-economic characteristics of study participants, 2016 ... 60

Table 3.2 People with TB awareness at a subnational level in Nepal ... 61

Table 3.3 Demographic and socioeconomic factors associated with TB awareness in Nepal, 2016 ... 62

Table 4.1 Number of predicted active TB cases and net social benefit for workers/students in Japan and Nepal ... 92

Table 4.2 Sensitivity analysis of net present value in Japan ... 93

Table 4.3 Sensitivity analysis of net present value in Nepal ... 94

List of Figures

Figure 2.1 Data collection flow 22

Figure 2.2 Topic coherence scores..... 25

Figure 2.3 Number of publications, 15 most published countries for 20 years 27

Figure 2.4 Proportion of publications on selected research topics in 15 affiliated countries..... 29

Figure 2.5 Topic community 30

Figure 2.6 Country cluster..... 31

Figure 2.7 Topic community (with Japan All data distinguished Scopus (Japan-1) and J dream III (Japan-2))..... 31

Figure 2.8 Country cluster (with Japan All data distinguished Scopus (Japan-1) and J dream III (Japan-2))..... 32

Figure 2.9 Proportion of research and innovation types based on WHO TB strategy, by country 33

Figure S2.1 Topic coherence scores (Scopus only dataset)..... 44

Figure S2.2 Proportion of publications on selected research topics in 15 affiliated countries (Scopus only dataset)..... 46

Figure S2.3 Topic community (Scopus only dataset) 46

Figure S2.4 Country cluster (Scopus only dataset)..... 47

Figure S2.5 Proportion of research and innovation types based on WHO TB strategy, by country (Scopus only dataset)..... 47

Figure 3.1 TB awareness at a subnational level in Nepal 61

Figure A3.1 Factors associated with TB awareness..... 71

Figure 4.1 Policy scenario: TB screening procedure in Nepal and Japan 81

Figure 4.2 Policy scenario: Policy simulation algorithm..... 86

Figure 4.3 Net present value for Nepalese workers and students in Nepal and Japan 94

Figure S4.1 Sensitivity test of net present value for workers/students in Japan 106
Figure S4.2 Sensitivity test of net present value for workers/students in Nepal 106

Acknowledgement

The process of interdisciplinary knowledge advancement is done at a series of stages. In the completion of this dissertation, I am mostly grateful to my main advisor – Professor Atsushi Sunami, who guided me with great enlightenment, freedom, and cultivation to develop my research. My heartfelt appreciation also goes to Professor Takayuki Hayashi, who provided the timely support and insightful feedback to consolidate the methodology and robustness. Special thanks were given to Professor Michiko Iizuka for her kind instruction at the very beginning of my thesis with the tender advice that sustain me till the goal.

The evaluation study reported in this dissertation also represent a global partnership with both international and domestic researchers, in line with internationalization. In addition, to take on global leadership as female researchers, we are researching in collaboration with other institutions even though direct communication is not sufficiently available due to the global COVID-19 pandemic. Despite the extreme circumstances, we managed to collaborate with respiratory physicians and global health experts at the National Center for Global Health and Medicine (NCGM), the Department of Global Health Policy (GHP) in the University of Tokyo, and Juntendo University Hospital, as well as research collaborators in Nepal, UN organizations and health care providers.

During my Ph.D. journey, I cannot feel too privileged to be accompanied by brilliant fellows – Prof. Shuhei Nomura, Dr. Santosh Kumar Rauniyar, Dr. Arda Akdemir, Ms. Rohita Gauchan, MPH, and Dr. Shoko Sonobe Shimamura to cope with adversity with a faith of believing that nothing is insurmountable. All in all, I must thank Prof. Dr. Yoshikazu Inoue and Prof. Dr. Kenji Shibuya, being a mentor who brought me to the field of medical research and global health.

The past four years were very challenging, but all the hardship of research adventure will make me strong enough to mend. I am overwhelmed with gratitude for the support of my families from Australia, Taiwan, and most important of all – OSAKA!

Executive Summary

Infectious respiratory diseases have threatened our lives and had a global impact on our health and our economy for decades. In particular, Tuberculosis (TB) is a threat to global health; it was one of the top 10 causes of death worldwide in 2019, according to the World Health Organization (WHO). TB eradication has been widely discussed as global health issue to be resolved, from the viewpoint of human security. Based on WHO End TB Strategy 2015, an international strategy framework has been set for holistically combating TB through intensified TB research and innovation in the development of new technologies at the national and global levels. Even though multiple sectors have engaged in innovative approaches toward more appropriate medical and programmatic health care services, due to inadequate research information sharing there are knowledge gaps between policymakers and researchers. The evaluation of research efforts, health research trends, and priorities must reflect previous research contributions to the achievement of national and global TB strategic goals.

In Japan, a health care system for respiratory tract infections, including TB, has been developed in a multifaceted and systematic way so as to provide

people with easy access to medical care and treatment for the prevention and control of TB. Nevertheless, in low and middle-income countries (LMICs), TB control is ineffective due to inadequate health care development and insufficient systems; there has been only limited reduction in TB morbidity and mortality. On the other hand, the situation in high-income countries such as Japan has been improved thanks to medical science progress and ongoing strengthening of the health care system—although comprehensive evaluation of global health policy in terms of TB control by means of Japanese research in LMICs has not been sufficiently evaluated.

Therefore, international health research, development, and assistance related to LMIC issues ranging from global health-related to respiratory tract infections are essential for human security. For that reason, it is essential to achieve a full understanding of the needed level of effectiveness, through evaluation studies that can support global health policy formulation. Under those circumstances, it is indispensable to conduct quantitative analysis evaluation studies to determine the effectiveness of TB control in health for LMICs. For example, in 2021, Nepal was a high TB burden country, with an increasing prevalence of cases. We choose Nepal as the target country of this study because of the increase in the number of Nepalese students and laborers in Japan since 2010. To fill a perceived evaluation analysis methodology gap, the study reported in this dissertation conducted evidence-based evaluations of TB controls to confirm the validity of the results and develop a policy evaluation method to support the formulation of policy recommendations.

We first evaluated the contributions of scientific research to global health achievements aimed at the elimination of TB by identifying major trends in Japan's scientific research development, as evidenced by published articles. Then, we conducted topic modeling to generate a probability distribution of topics influenced by academic text documents on TB research in the pre-proceeded dataset for the period 1999–2019. In-depth analysis for the learning of latent topics was conducted using Latent Dirichlet Allocation (LDA) modeling using the Python library Gensim. In addition, we categorized the results of the analysis into five spectra of TB research for each affiliated country in terms of intensified research and innovation toward the implementation of the END TB Strategy. We found that Japan had the highest proportion of clinical studies and medical trials as case reports in the fields studied. At the same time, the contribution of Japan to reciprocal linkage with social factors affecting wider health systems and dynamics among policy effectiveness was extremely low. We conducted policy effectiveness evaluation, evaluating the reciprocal relationship between social factors, to identify weaknesses in Japan’s TB research engagement. Gaining an understanding the priorities and contributions of pulmonary tuberculosis research in Japan by means of international comparisons will help guide decision-making toward the implementation of future medical and health policies.

Secondly, we applied multilevel logistic regression to examine the association between demographic and socioeconomic factors and TB awareness, using data from the Nepal Demographic and Health Survey (June 2016 to January 2017). The results showed a high level of TB awareness in all seven provinces of Nepal. Importantly, socioeconomic factors such as wealth, education, and owning a mobile phone were found to be significantly associated with TB awareness—and socioeconomic determinants were found to be influential factors associated with TB awareness in Nepal. The wide variation in the level of awareness at the regional level emphasizes the importance of formulating tailored strategies for the raising of TB awareness. For instance, mobile phones promise to be an effective strategy for the promotion of TB awareness at a regional level. This study provides valuable evidence to support further research on the contribution of information and communication technology (ICT) usage to the raising of TB awareness in Nepal.

Thirdly, we conducted cost-benefit analysis of data sourced from the Nepal Demographic and Health Survey and Japan's Legal Affairs Bureau and Tuberculosis Surveillance Center, to examine the effect of Japan's pre-entry TB screening policy, including testing and treatment in Japan and Nepal for the period 2014–2018. The total cost, total benefit, and net benefit for both countries were compared for two policy scenarios, "With" and "Without", using net present value (NPV). In order to address parameter difference for uncertainty, we conducted a sensitivity analysis using Monte Carlo simulation with secondary transmission rate. The results showed that implementing a policy of pre-entry TB screening for foreign migrants with a high TB burden arriving in Japan from Nepal would achieve efficient cost-saving by reducing the number of newly diagnosed TB cases, including those with transmission risk. Moreover, the results indicate that pre-entry TB screening would have prevented an increase in the number of new TB cases in Japan and reduced TB healthcare costs and capacity loss.

The research findings highlight the importance of TB research on trend identification, technology application, and collaboration in TB control towards significant progress in global health, science, and technology diplomacy. We close with a depiction of research limitations, and provide lists of future prospects based on the evaluation analysis.

Chapter 1

Introduction

1.1 Epidemiologic disaster to global pandemic—tuberculosis (TB)

At the 2019 United Nations General Assembly, the World Health Organization (WHO), stressed that "global health security affects us all." When countries have robust, end-to-end primary health systems, they added, outbreaks are prevented, crises are infrequent, and families and communities are empowered in ways that go beyond the specifics of health care [1]. Tuberculosis (TB) is classified as a communicable disease, which could spare rapidly by air within the community and globally. According to the Global Tuberculosis Report by the WHO [2], TB is listed in the top ten causes of death in the world with approximately 25% of the world's population infected with social economic determinants such as poverty, vulnerability, marginalization, stigma, and discrimination, etc.

The modernization of TB began in the mid-1980s, and WHO declared TB a global emergency in 1993. Despite these interventions, it is estimated that the number of deaths from TB will increase from the current three million per year to five million by 2050. There are four main reasons for this: global population growth, co-infection with HIV/AIDS, poverty, and declining programs. Multidrug-resistant tuberculosis (MDR-TB), migration, and apathy are also contributing to the global epidemic. Realistic solutions must focus on the completion of the proper treatment, especially for those who are sputum smear-positive. For this reason, WHO is actively promoting the Directly Observed Therapy Short Course (DOTS) campaign to engage public health system physicians. The TB patients should have access to appropriate bacteriological detection services and good quality drugs and be assured that drugs are administered under supervision [3]. With the improvement of medical science in the late 20th century, TB has been proven to be curable and preventable under the provision of 6-month drug regiment, the curtailing transmission could also be terminated [2]. Given the substantial impact on the economy domestically and globally, rising attention to TB has prompted countermeasures by the public health sector, and stimulated political will. Evidence-based research and evaluation are essential to efforts to enhance the effectiveness of control over TB.

1.2 Japan’s global health policy toward TB control

Since the 2010’s, Japan’s global health policy presents both opportunities for global TB control and related challenges. The Ministry of Foreign Affairs of Japan unveiled its *Basic Design for Peace and Health* in 2015, a design for development cooperation and the creation of global collaboration outlines utilizing Japan’s experience related to the aims of human security [4]. Global health is a priority issues in the current era, given the advance of globalization and threats of cross-border spread of infectious diseases including TB [5]. Moreover, in 2014, the Office of the Prime Minister of Japan issued its “Healthcare Policy” aimed at improving societal life standards, for healthy aging, providing all with quality of healthcare, medical treatment and access to health technologies [6]. Japan’s healthcare policy task force is charged with identifying priority health issues and creating a national strategic plan (NSP) for the enhancement of health facilitations and advancing the promotion of health quality through acceleration of research and development (R&D). One of the key task forces has given priority to TB elimination through the use of advanced medical technologies to promote holistic R&D and practical use of medical technologies with multi-sectoral collaboration [7]. Work towards the achievement of *End TB* through the national TB control program (NTP) under the NSP is widely integrated within government and health sector efforts in collaboration with international organizations and national and international NGOs [8]. Japan's TB control program delivers good quality medical skills and health technologies as well as health care systems for nations with universal health coverage (UHC), leading to a decrease in the number of TB deaths [9]. An effective TB response requires robust health systems with equitable access to adequate TB medical support provided by health care services under UHC [10,11]. Under UHC, Japan has been able to integrate its TB control law into infectious disease laws since World War II, without imposing financing barriers on Japanese patients with TB [12,13]. The latest TB Control Law, the 2016 version, is mainly focused on the improvement of TB crisis management including prevention of contamination from biological pathogens; transmission control; and appropriate treatment with advanced research knowledge and technologies [14]. Despite the decline in the incidence rate of TB in Japan with scaling up the TB healthcare systems [15], Japan's current TB control strategy is insufficient to achieve TB elimination nationwide. Furthermore, the TB control strategy under the global health policy for advancing R&D can be scaled up for better outcomes to ensure the evidence-based policymaking [7].

However, there is no policy evaluation methodology to support appropriate decision-making regarding TB control efforts in collaboration with multiple stakeholders [16].

Japan has attached vital importance to support activities for the acceleration of global TB control since 2020 [17]. Japan has been providing global leadership in various TB control partnerships, especially the Global Fund to Fight AIDS, TB and Malaria, in order to promote innovative solutions to global health challenges related to binding resilient and sustainable systems for health [5,18]. As a contributor, Japan has provided the largest financial support for the fight against those three diseases since 2002, aimed at the improvement of community empowerment works with local leadership in underserved communities, so as to provide essential healthcare systems and delivery [18]. The Global Fund in Nepal, for example, has succeeded in delivering healthcare services including early diagnosis and treatment—although evaluation and monitoring in healthcare management remain insufficient [19]. Clearly Japan has been continuing to lead in those national and global efforts towards TB elimination at various levels of program and assistance, but the influence of issue-based development for global society remains unclear, given the inadequate level of evaluation research towards the scaling up of implementation of development programs and assistance.

1.3 TB in Nepal

The gap between WHO TB estimates and the number of TB cases identified by the Nepali national system widened from 22% in 2015 (44,000 estimated vs. 34,112 notified) to 27% in 2016 (44,000 estimated vs. 32,056 notified); to 29% in 2017 (45,000 estimated vs. 31,764 notified). Clearly it is of critical importance to find the missing TB cases and close that epidemic prevention loophole [20]. TB remains a public health problem in Nepal, affecting thousands of people every year. Nepal has set a goal of ending its TB epidemic by 2050, with interim targets including: reduction of TB incidence, by 20% from 2016 levels, before 2021; and increasing the cumulative number of reported cases by 20,000 between July 2016 and July 2021. The Government of Nepal appointed the National Tuberculosis Control Center developed a comprehensive National strategy plan (2010–2015) [21], which builds on the previous national strategy and outlines enhanced and more focused commitment to tackling the TB epidemic, which is consistent with the new *STOP TB* strategy and the UN

Sustainable Development Goals (SDGs) in line of targets. The National Tuberculosis Programme (NTP) is fully integrated within the general primary health care system of the Government of Nepal under the National Tuberculosis Control Centre, which is responsible for program policy formulation, strategy, and planning. Nepal's first TB prevalence survey was efficiently conducted with multi-partner involvement under the public sector [21].

WHO indicated that another TB threat for global health security is the type of MDR-TB, which are mostly exist in low- and middle- income countries (LMICs), including Ghana, Mongolia, Nepal, Philippines, Tajikistan and South Africa [2]. According to the report provided by Japan Student Services Organization (JASSO), Nepal has become the third biggest contributor of international students to Japan, with a rapid increase since 2010 [22]. In the context of globalization, it will be necessary to extend TB detection measures to foreign countries, especially countries with strong economy and large personnel interchange with Nepal. To achieve the *Stop TB* target, TB control enhancement needs to be accelerated through appropriate strategic interventions and increased investment.

1.4 Objectives

Infectious diseases can easily cross borders and seriously affect the entire international community. To obtain the effective control of this, there are multiple medical engagement that Japan should undertake, either solely or in cooperation with developing countries.

First, based on the conduction of “Basic Design for Peace and Health”, which indicates international collaborative clinical research with statements such as “utilizing Japan's research, development and innovation capabilities while promoting the medicine R&D for developing countries in cooperation via public-private partnership”, through elucidating the medical aspects of the target diseases by developing new medicines and advanced health technologies. The conductions include the development of pharmaceutical of target diseases, as well as health and sanitation technologies. This will enable the sharing of knowledge on infectious diseases and their medical care research across national borders and the implementation of countermeasures against infectious diseases for global health.

Second, it is indispensable to deliver the accumulated knowledge in clinical medicine and health and hygiene to the general public in the form of information that they can understand. In the area of infectious disease control, it is essential to strengthen the health systems of developing countries through prevention at the individual citizen level and by encouraging people to seek diagnosis and treatment.

Third, it is vital to limit the potential for the international spread of infectious diseases so that screening tests could be conducted, especially at the boarder measures of international migration. Screening tests can help contain infectious diseases within a country and prevent their spread abroad. In this study, we believe that these three perspectives are essential, and we will use evidence to analyze the effectiveness of policy efforts being made from these perspectives.

Regarding the global health research on infectious disease, there are only few Japanese studies have evaluated comprehensive policy for global health in TB control in low-income countries. The key elements of global health policy (as presented in Basic Design for Peace and Health) demonstrate emphasis on clarifying the results of policy evaluation. Therefore, it is essential to acquire an understanding of the needed degree of effectiveness, which would support global health policy formulation and link the findings to policy recommendations. To achieve the above objectives, it is essential to analyze, through evaluation-based visualizations: (a) the knowledge accumulation of Japan and global TB research trends; (b) TB awareness associated with social economic determinants of health system in LMICs, and; (c) the effectiveness of TB screening policy toward TB infection control in Japan's high vulnerability counterpart country. That scientific, evidence-based evaluation analysis would be of considerable value for decision making toward successful implementation with trackable outcomes and process on global health policymaking. These policy analyses for evaluation will help implement the research on the specific aspects of the TB strategy for intensified research and innovation nationally and globally, tackling innovative strategies in all countries to ensure more effective interventions. In addition, the key research characteristics and major research priorities scaled research engagement would help understand the challenges and improve policymaking of health systems with more efficient service delivery.

In the investigation of social determinates that affect the awareness of TB, the approach of analyzing survey data is emphasized because most actions on consequences of TB may hinge on determinants outside the health sector. Therefore, assessing the effectiveness of local implementation strategies and innovative tools for acquiring information are key elements of achieving essential prevention, treatment, and care interventions in migrant communities. Moreover, the cost and benefit analysis and health policy frameworks across the countries could reinforce case notification, vital registration, quality and rational use of medicines, and infection control. Such progress can be achieved through the ex-ante financing of health care with comprehensive geographical coverage with quality service under adequate monitoring and evaluation.

We carry out case studies targeted on Nepal because of the increasing presence of emigrant Nepalese students and workers in Japan, which makes TB control collaboration between Japan and Nepal a significant key to the advancement of global health. Taking a detailed approach to the above issues, the dissertation aims to conduct evidence-based analysis of available data to capture global research trends in TB control, and to develop a policy evaluation method for use in the framing of specific policy recommendations towards global health research.

1.5 Dissertation structure

The dissertation proceeds as follows; after the background introduction in Chapter 1, Chapter 2 demonstrates bibliometric evaluation, a method for obtaining an understanding of the structure of TB research including its trends, characteristics, and networks from publication outputs. The research uses natural language processing with text mining at Python platform. Chapter 3 reports a social evaluation using STATA and R programming to find relationships between variables influencing improvements in TB awareness in Nepal. Chapter 4 discusses the validation of economic evaluation using cost-benefit analysis of the economic impact of TB screening and testing policies targeted on Nepal. Finally, Chapter 5 presents overall conclusions and policy recommendations.

1.6 Reference

[1] United Nations (UN)., (2019). General Assembly, 73rd Session, Interactive Multi-Stakeholder Hearing. [Viewed 1 Aug 2021]. Available from: https://www.un.org/press/en/2019/ga12142.doc.htm

[2] World Health Organization., (2020). *Global Tuberculosis Report 2020*. Geneva: WHO. [Viewed 1 Aug 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf.

[3] Davies, P. (2000) Tuberculosis: the global epidemic. *Journal of Indian Medicine Association*, 98(3), 100-2.

[4] Ministry of Foreign Affairs of Japan., Yamatani, Y., (2015). Trends in the international community on health issues and Japan's contribution in Japanese. *Journal of Health and Society*. 25(3), 263-271.

[5] Ministry of Foreign Affairs (MOFA) of Japan., (2015). Approval of Basic Design for Peace and Health (Global Cooperation) 2015. Available from: https://www.mofa.go.jp/files/000110234.pdf. [Accessed December 10 2021].

[6] Prime Minister of Japan and his Cabinet., (2014). Healthcare Policy 2014 in Japanese. Available from: https://www.kantei.go.jp/jp/singi/kenkouiryou/suisin/ketteisiryou/dai2/siryou1.pdf. [Accessed December 10 2021]

[7] Prime Minister of Japan and his Cabinet., (2017). The revision of Healthcare Policy 2017 in Japanese. Available from: https://www.kantei.go.jp/jp/singi/kenkouiryou/suisin/ketteisiryou/kakugi/r020327senryaku.pdf . [Accessed December 12 2021]

[8] WHO., (2020). National strategic plan for ending TB 2020-2024. Available online: https://apps.who.int/iris/bitstream/handle/10665/333646/National-Plan-TB2020-2024-eng.pdf [Accessed on 14 December 2021].

[9] Kodama, T., (2021). Human resources of health for universal health coverage in Japan: in the era of COVID-19. *J. Natl. Inst. Public Health*, 70 (1), 13-21.

[10] WHO., (2021). Universal health coverage (UHC). Available online: https://www.who.int/news-room/fact-sheets/detail/universal-health-coverage-(uhc). [Accessed on 14 December 2021].

[11] WHO., (2017). No UHC without strong TB response, no ending TB without UHC. Available online: https://www.who.int/news/item/13-12-2017-no-uhc-without-strong-tb-response-no-ending-tb-without-uhc. [Accessed on 14 December 2021].

[12] Seita, A., (2008). Think PHC, Do TB" Integration-based scale up of tuberculosis control in Japan. Available online: https://cdn1.sph.harvard.edu/wp-content/uploads/sites/114/2012/10/rp217.pdf.

[13] Tsukahara, T., (2006). Tuberculosis Control Law of Japan: current issues and prospects of tuberculosis control plan. Kekkaku Dec;81(12):737-43.

[14] Ministry of Health, Labour and Welfare (MHLW), Japan. Guidelines for the prevention of specific infectious diseases related to tuberculosis. Available online: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou03/index.html. [Accessed on 14 December 2021].

[15] Kato, S., (2017). "Issues and directions for TB control in Japan and overseas" in Japanese. Fukujyuji (376): 2-3.

[16] Sakamoto, H., Lee, S., Ishizuka, A., et al (2019). "Challenges and opportunities for eliminating tuberculosis – leveraging political momentum of the UN high-level meeting on tuberculosis". *BMC Public Health* 19, 76. Available online: https://doi.org/10.1186/s12889-019-6399-8.

[17] MOFA of Japan., (2015). Japan's ODA White Paper 2015: Official Development Assistance (ODA). Available online: https://www.mofa.go.jp/policy/oda/white/2015/html/honbun/b3/s2_1_3_02.html. [Accessed on 14 December 2021].

[18] The Global Fund., (2021). Results Report 2021. Available online: https://www.theglobalfund.org/media/11304/corporate_2021resultsreport_report_en.pdf. [Accessed on 14 December 2021].

[19] Trägård, A., and Shrestha I. B., (2010). System-wide effects of Global Fund investments in Nepal. *Health Policy Plan* Nov;25 Suppl 1:i58-62. doi: 10.1093/heapol/czq061. PMID: 20966112.

[20] Adhikari, N., Joshi, L., Subedi, B., Acharya, D., Adhikari, M., Thapa, P.,

Sultana,
R., Karki, K. (2019) Tuberculosis in Nepal: Situation, Challenges and Ways Forward. *SAARC J. Tuberc. Lung Dis. HIV/AIDS,* 17, 34–40.

[21] Government of Nepal., (2017). Community System Strengthening, Kathmandu: The Government of Nepal (www.nepalntp.gov.np/community-system-strengthening/).

[22] Japan Student Services Organization (JASSO)., (2021). *Result of an annual survey of International Students Survey in Japan, 2020*. Tokyo: Japan Student Services Organization. [Viewed 1 Aug 2021]. Available from: https://www.studyinjapan.go.jp/en/_mt/2021/04/date2020z_e.pdf

Chapter 2

Japan's Contribution to Tuberculosis Research: A Text Mining-based Topic Modeling Analysis for 15 Countries (1999-2019)

2.1 Introduction

Tuberculosis (TB) is one of the biggest threats to global health: it was ranked in the top ten causes of death worldwide in 2019 in the World Health Organization (WHO) [1,2]. Several studies have reported that mycobacterium tuberculosis (M.tb), the causative bacterial agent of TB, affected the lungs in approximately 80% of all adult cases of TB surveyed [3,4]. According to the 10th edition of *International Statistical Classification of Disease and Related Health Problems (ICD-10)* in 2016, WHO classified respiratory tuberculosis as code-A15 and A16 for systematic analysis of global health disease data [5]. In Japan in 2019, 86.7% of respiratory tuberculosis cases were confirmed bacteriologically and the number of cases in adults over age 15 reached 94.5% [6]. TB infection rate is affected by socio-economic determinants including social, economic and political factors, all of which have a negative impact on equitable access to essential TB health services and systems, both globally and locally [1,7]. In a move toward joint action on those social issues, United Nations SDG 3 and WHO's END TB Strategy set urgent targets for 2030 regarding research and innovation expansion as part of a global effort [8]. In the COVID-19 era, public concern about respiratory infectious diseases has prompted requests for a global integrated pandemic control response involving intensified research and innovation at the global, national (central government) and community (local government and rural area) levels.

The continuing efforts to eliminate TB is a great challenge for researchers, funding bodies and policymakers. Meeting the challenges involved in ending the current TB epidemic will require newer and better tools for prevention and control of TB [8]. WHO TB Factsheet 2019 [9] indicates that newly developed TB technologies such as rapid diagnostic tests, drugs for treatment and vaccines have not demonstrated sufficient efficacy in terms of TB incidence and mortality reduction in field evaluation studies and trials. Clearly, further research is required to accelerate technological progress toward achievement of the global goal of eliminating TB through national level and community-based efforts [10]. Although the multisector takes innovative approaches for more appropriate medical and programmatic health care services, there are significant gaps between information and opinions held by policymakers and by researchers as a result of insufficient research information sharing [11]. To ensure the tracking of research efforts and impacts, it is necessary that health research trends and priorities reflect previous research contributions with regard to achieving both global and national TB strategic goals [8,11]. Bridging gaps among policymakers, funders and researchers and other relevant stakeholders' calls for the systematic evaluation of existing TB research information and long-term accumulation of knowledge, as evidenced by scientific publications, to identify the urgent priorities of TB research.

Japan's healthcare policy, established by Prime Minister of Japan and his Cabinet, places great importance on research and development (R&D) on emerging and re-emerging infectious diseases including tuberculosis, using advanced medical technology, to promote large-scale development and practical use of medical and health technologies through multi-sectoral collaboration. Along with its emphasis on strengthening R&D, the Japanese government has placed a higher priority on global health as a key issue in Japanese health diplomacy [12,13]. However, there is no process for evaluation, by means of publication of methods and results, to ensure that such feedback will be absorbed and reflected in future global health policy in Japan [14,15]. Evaluation of scientific publications using text mining processing has been widely conducted in the last few years; it can help to disseminate academic information, knowledge and findings to enable health experts to understand research trends [16,17]. Moreover, health research text mining in massive interdisciplinary research can evaluate determines research impact, and compares research performance and R&D, both effectively and efficiently [18]. Through syntheses of the literature, this paper first evaluates the contributions of TB research using text mining method for effective development as one of the core pillars to support END TB strategy. In recognition of the necessity of evaluation of contributions to the large-scale implementation of TB research for effective development, and to disseminate information on further TB research priorities, it is essential to promote the development of future global health policy with multi-stakeholders in society.

This study evaluates the contributions of scientific research to global health achievements aimed at the elimination of TB. We investigate the major trend of Japan's scientific research development as evidenced by published articles, towards an understanding of research themes and trends, and of research fronts, by topic modeling analysis of qualitative publication data for the period 1999–2019. The objective of this evaluation is to identify (1) the high share of research topics and productivities; (2) key research characteristics and major research priorities; and (3) the scale of research engagement and contribution towards the elimination of TB, with cross-country comparisons.

2.2 Methodology

2.2.1 Data and pre-processing

We conducted topic modeling using data obtained from Scopus and J-Dream III. Scopus is a well-known database of bibliographic data for academic articles including abstracts and citations across a wide variety of scientific disciplines. J-dream III, a database constructed by Japan Science and Technology Agency (JST), contains many scientific research articles in Japanese as well as English. It includes articles from the fields of science, technology, medicine and social science, reviews and case reports. The Scopus database mainly collects English language publications and also collects some other language publications with English abstract. Thus, Scopus is of limited use for trend analysis in Japanese research. Since most Japanese publications in the health care related academic journals are written in Japanese, we gathered data from the J-dream III database as well as Scopus to achieve a more extensive base for analysis. In order to manage those databases in the analysis of a wide range of studies towards an examination of global trends, it is necessary to identify Japan's scientific research structure holistically.

The main disease-related keyword of our topic search was "respiratory tuberculosis". Respiratory tuberculosis associated with other disease complications was included, but tuberculosis of other organs was not. Search queries were set for "respiratory tuberculosis" OR "lung tuberculosis" OR "pulmonary phthisis" OR "pulmonary tuberculosis" in Scopus searches, while J-dream III search queries were translated into Japanese as "Hai Kekkaku". Using these English and Japanese search terms, we obtained publication titles and summaries. The raw data for all document types published during 1999–2019 was obtained from Scopus and J-dream III in 2020. After translating the Japanese search result in English by machine translation (google translation), a dataset was created by merging these two results. Data for a total of 31,885 publications were downloaded from Scopus. In addition, we added another 14,468 publications from J-dream III, excluding 126 overlapping items with Scopus.

Figure 2.1 is a schematic diagram of the data collection flow. In the first scheme, the total number of potentially relevant articles (N=46,353) are identified for eligibility, excluding overlapping articles. We identified the top 15 countries in terms of number of author affiliations from the relevant articles. Authors were classified by affiliated country, based on author address. The number of articles by country was measured by integer counting. For example, in the case of an article co-authored by multiple institutions in the United States and multiple institutions in Japan, the number of papers is designated as one in the United States and one in Japan. A total of 40,609 of the 46,353 articles were identified as articles from the top 15 countries for analysis after exclusion of overlapping country affiliation.

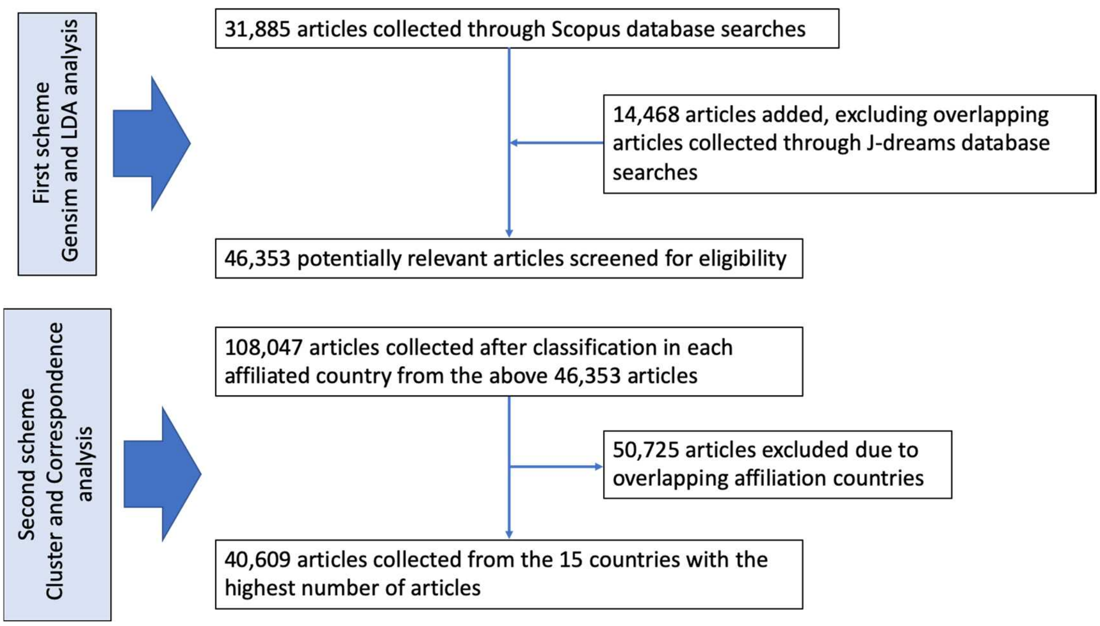

Figure 2.1 Data collection flow

2.2.2 Data analysis

2.2.2.1 Topic modeling for thematic analysis

We conducted topic modeling to generate the probability distribution of topics in the pre-proceeded dataset for the period 1999–2019. In-depth analysis for learning latent topics, using Latent Dirichlet Allocation (LDA) modeling, was conducted using the Python 3.8. LDA, a common methods of topic modeling, was configured to identify the latent topic from a large number of text corpora [19,20]. In support of these analysis, we conducted text normalization using stemming and lemmatization techniques from the field of natural language processing and removed numbers and stop words, e.g., “abstract”, “introduction”, and “result”. After the data cleaning, the LDA was applied using Gensim to identify the optimization of topic coherence scores over all topics with random sampling. In order to determine the probability of topic coherence, it is vital to allocate the high-frequency words in each clustered topic by applying LDA model across all topics [21]. We set the top 40 words from each clustered topic as criteria.

2.2.2.2 Correspondence analysis and cluster analysis

We used correspondence analysis and cluster analysis to elucidate an understanding of the relationship between the allocated topics and affiliation countries, to support science mapping. Correspondence analysis was performed to analyze national level strategies for ensuring research prioritized in each country. Cluster analysis was used by cosine similarity measures to identify characteristics and topic-related attributes of affiliation countries that identify homogenous groups among affiliation countries. Finally, we classified the analysis results into the five spectrums of TB research for each affiliated country in terms of intensified research and innovation toward implementation of *END TB* Strategy: The essentials 2015 [8]. The classification was evaluated based on the author's independent perspective on the topics.

2.3 Results

2.3.1 Identification of high proportion of topics and productivities

Regarding the first scheme of the Gensim model approach, the result of topic coherence assumption is presented in Figure 2.2. The optimal topic coherence was estimated to be 15 topics from randomly assigned after pre-processed dataset, because high probability points were represented within the size of 20,000 samples and 25,000 samples. In support of the result, there was no significant the performance of topic coherence improvement over the topic 15 in the analysis. Table 2.1 lists the 15 topics classified by LDA with the top 40 representative words for each clustered topic, shown in order of the most frequency words. To determine the optimal topic number and topic classification in the analysis, it is necessary to understand the influential topics, as evidenced by the publication productivities and the strength of research topics in each affiliated county in the subsequent scheme.

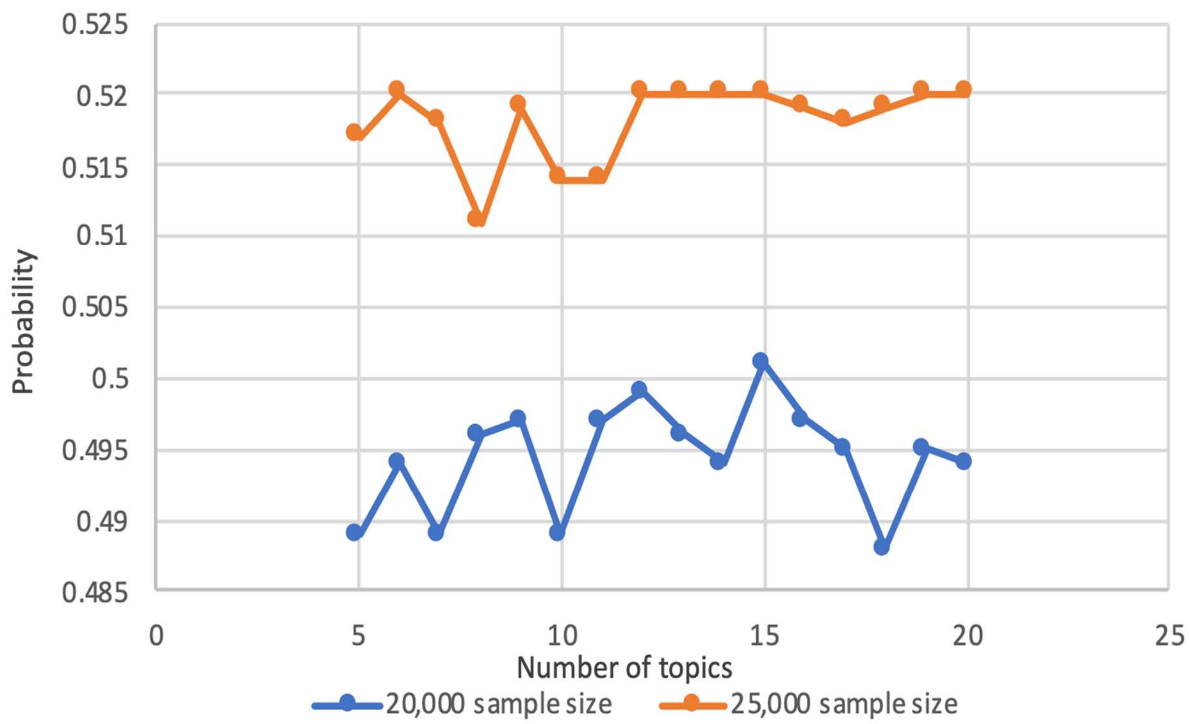

Figure 2.2 Topic coherence scores

Table 2.1 Classification of 15 topics

	Top 40 words	Potential term of disease	Potential term of target population	Summary	Research field
Topic 1	tuberculosis health care treatment patient human infection control pulmonary case medical risk public incidence lung humans hospital rate population transmission data prevalence child new practice management cost world program high adult therapy year review prevention ha research country national service	Tuberculosis, Pulmonary, Lung	Patient, Human, Population, Country, National	Examination of TB infection and disease	4:Clinical studies / Trials
Topic 2	protein tuberculosis gene level factor human receptor cell expression lung interleukin blood macrophage tumor necrosis pulmonary tnf patient response alpha infection cytokine serum control host activity marker inflammatory immune controlled role genetic healthy like inflammation metabolism biological plasma enzyme mycobacterium	Tuberculosis, Lung, Tumor, Necrosis, Pulmonary	Human	Response to therapy including molecular and immunology	1: Fundamental science
Topic 3	tuberculosis diagnosis pulmonary lung case chest ray ct di pneumonia examination infection lesion differential respiratory image old human year cough test radiography sputum imaging patient elderly shadow mycobacterium showed tomography pathology diagnosed clinical medical miliary cavity nodule cases tumor fever	Tuberculosis, Pulmonary, Chest, Pneumonia, Nodle, Tumor	Human, Patient, Elderly	Examination of the safety and efficacy of diagnosis	3: Preclinical studies
Topic 4	tuberculosis patient treatment drug clinical liver case male human agent therapy infection adult isoniazid skin lung anti kidney rifampicin female aged blood hepatitis pyrazinamide ethambutol agents humans renal transplantation mycobacterium outcome arthritis fever biopsy level pulmonary tuberculostatic chronic year bone	Tuberculosis, Liver, Skin, Lung, Kidney, Hepatitis, Renal, Arthritis, Pulmonary, Born	Patient, Male, Human, Adult, Female,	Disease outcome research for progression of active disease	4: Clinical studies / Trials
Topic 5	tuberculosis patient aged risk adult pulmonary male female treatment group middle age factor clinical case associated outcome lung adolescent patients ci studies retrospective control human major mortality association factors polymorphism rate population incidence diabetes humans cohort child ratio higher young	Tuberculosis, Pulmonary, Diabetes	Patuent, Aged, Adult, male ,Female, Adolescent, Population, Human, Young	Investigation of social and personal factors	5:Development and scale-up implementation
Topic 6	test tuberculosis sensitivity diagnostic specificity assay tuberculin value accuracy diagnosis bcg interferon screening detection tst gamma latent positive using qft active predictive release cost skin clinical vaccination li negative infection tests vaccine based used human contact high mycobacterium gold performance	Tuberculosis, Latent	Human	Drug or diagnostics intervention for efficacy	2: Translational research
Topic 7	drug therapy tuberculosis treatment case effect compound dt combination pulmonary acid antituberculosis anti administration use year adverse pregnancy alcohol patient therapeutic aromatic complications month human day dc old amino fatty nitrogen tu aliphatic isoniazid amine test oxygen compounds secondary heterocyclic	Tuberculosis, Pulmonary	Patient, Human	Drug or diagnostics intervention for efficacy	2: Translational research
Topic 8	delay patient exposure tuberculosis lung health occupational pulmonary cross male sectional questionnaire life spinal adult chronic female smoking silicosis factor aged symptom quality status diagnosis associated prevalence extract respiratory human air death risk dust pneumoconiosis score clinical patients pollution plant	Tuberculosis, Pulmonary, Spinal, Silicosis, Respiratory, Pneumoconiosis	Patient, Male, Adult, Female, Aged, Human	Investigation of social and personal factors	5:Development and scale-up implementation
Topic 9	infection hiv human respiratory virus patient therapy immunodeficiency pneumonia lung syndrome infections chronic agent pulmonary treatment clinical infected aids count failure tuberculosis antiretroviral opportunistic acquired acute immune tract art male adult lymphocyte blood obstructive case related drug pressure oxygen complication	HIV, Respiratory, Pneumonia, Lung, AIDS, Tuberculosis	Human, Patient, Male, Adult	Disease outcome research across clinical trials	4: Clinical studies / Trials
Topic 10	lung pulmonary aspergillosis history asthma respiratory chronic human aspergillus century bronchial fibrosis airy delivery tuberculosis fungal cancer using air medicine allergic inhalation mass humans ha used function 20th laser obstructive breath spectrometry review use aspergilloma fumigatus medical antifungal gas fungus	Pulmonary, Aspergilosis, Asthma, Respiratory, Bronchial, Fibrosis, Aspergillus, Tuberculosis, Cancer	Human	Implementation research	3: Preclinical studies
Topic 11	pleural effusion vitamin level serum pleura infection fluid jst deficiency pleurisy ml influenza human virus iron adenosine patient blood deaminase malaria tuberculosis concentration ada hiv kyoto pulmonary mac pneumonia cause english japanese supplementation spatial infectious translated ng lung higher group	Pleural, Influenza, Malaria, Tuberculosis, Mac, Pneumonia, Lung	Human, Patient	Examination of TB infection and disease	4: Clinical studies / Trials
Topic 12	tuberculosis cell mycobacterium antigen lung animal vaccine bacterial infection human response bcg lymphocyte protein mouse pulmonary immune interferon immunity antibody mice ifn model interleukin cytokine gamma cells specific bovis production infected female animals antigens vaccination immunology blood controlled tissue priority	Tuberculosis, Lung	Animal, Human, Mouse, Mice	Response to therapy including molecular and immunology	1:Fundamental science
Topic 13	lung tuberculosis case tomography pulmonary cancer patient human male surgery biopsy aged adult surgical female treatment assisted tumor thorax lymph computer imaging clinical radiography computed diagnosis node humans resection year hemoptysis complication fistula tissue carcinoma cell bronchoscopy right postoperative diagnostic	Lung, Tuberculosis, Tumor, Thorax, Lymph node, Hemoptysis, Carcinoma	Patient, Human, Male, Aged, Adult, Female	Drug or diagnostics intervention for efficacy	2: Translational research
Topic 14	tuberculosis drug resistant mycobacterium resistance treatment multidrug isoniazid rifampicin bacterial human agent mdr strain ethambutol antibiotic pyrazinamide clinical isolates antitubercular agents lung dna pulmonary tuberculostatic gene sensitivity regimen patient streptomycin sputum therapy culture humans bacterium mutation rifampin anti molecular trial	Tuberculosis, MDR, Lung, Pulmonary, Tuberculosis	Human	Examination of TB infection and disease	4: Clinical studies / Trials
Topic 15	tuberculosis sputum patient smear pulmonary positive culture child clinical hiv mycobacterium human adult male female diagnosis case negative aged test diagnostic lung bacterium patients infection prevalence sample sensitivity acid adolescent humans fast major contact immunodeficiency middle microscopy specimen virus pcr	Tuberculosis, Pulmonary, HIV, Lung	Patient, Child, Adult, Male, Female, Aged, Adolescent	Implementation research	3: Preclinical studies

Figure 2.3 shows a total of 40,609 articles from 15 countries for the 20-year period 1999-2019. “Japan All”, which includes both Scopus and J-dream III, yielded the highest number of publications (N=15,772), accounting for 39% of total publications, whereas “Japan-1” with only Scopus data was ranked in the top five (N=1,829) following China (N=2,410). The J dream III (Japan-2) had the 8 times higher publication number written in Japanese compared to Scopus (Japan-1) written in English. The United States had the second largest number of publications (N=5,436), followed by India (N=3,921).

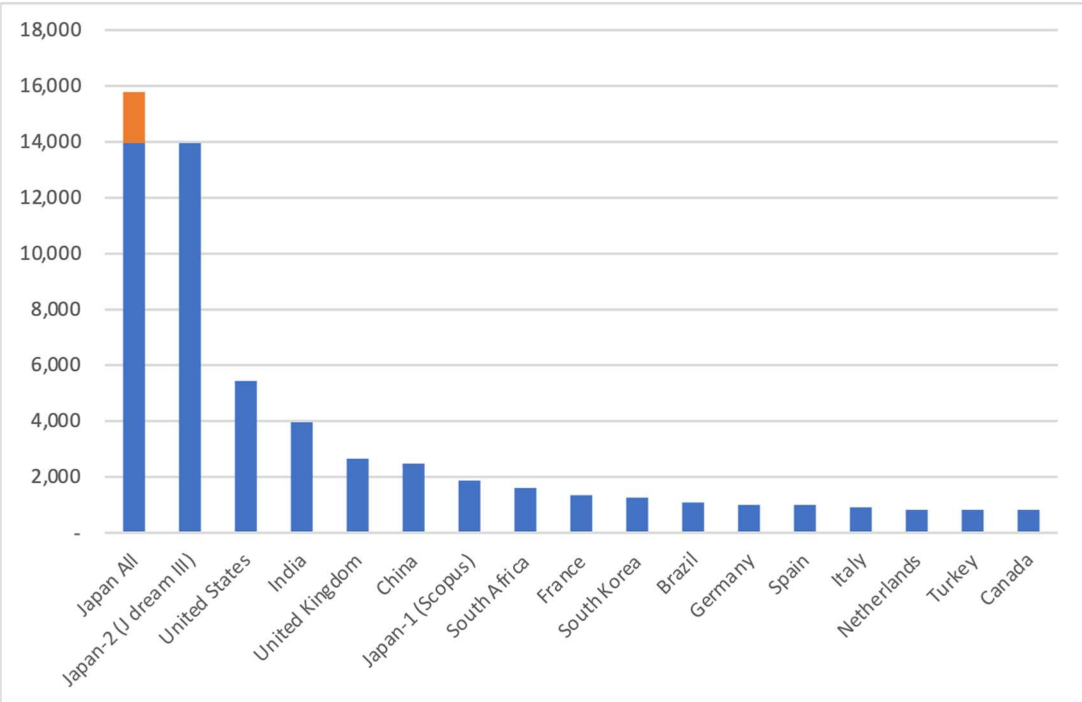

Figure 2.3 Number of publications, 15 most published countries for 20 years
Note: Japan All = Scopus + J dream III.

Figure 2.4 shows the results of the influential research topics in each affiliated country. In “Japan All”, the percentage of topic 1 is the highest (53%) that is the research fields of clinical studies and medical trials as case report. The Topic 1 focuses on the specific science themes, e.g., *Health Care, Treatment, Control, Case, Risk, and Incidence*. in the country category. It is followed by Topic 12 (12%) of the fundamental science fields including *Cell, Mycobacterium, Antigen, Vaccine, Bacterial, Infection, and Response* among all cases of animal experimentation (Table 2.1). Moreover, the highest rates for Topic 14 were seen in Turkey and India (*Drug, Resistant, Treatment, Multidrug, Isoniazid*) for 19% and 14%, respectively. In addition, South Africa had the highest rates for Topic 9 for HIV/AIDS related research (12%). In contrast, China had the highest share for topic 2, the major research themes (*Gene, Factor, Human, Receptor, Cell, Expressio*n) at 9%, compared with other affiliated countries (Table 2.1, Figure 2.4). Exact values for Figure 2.4 can be followed in Table A2.1.

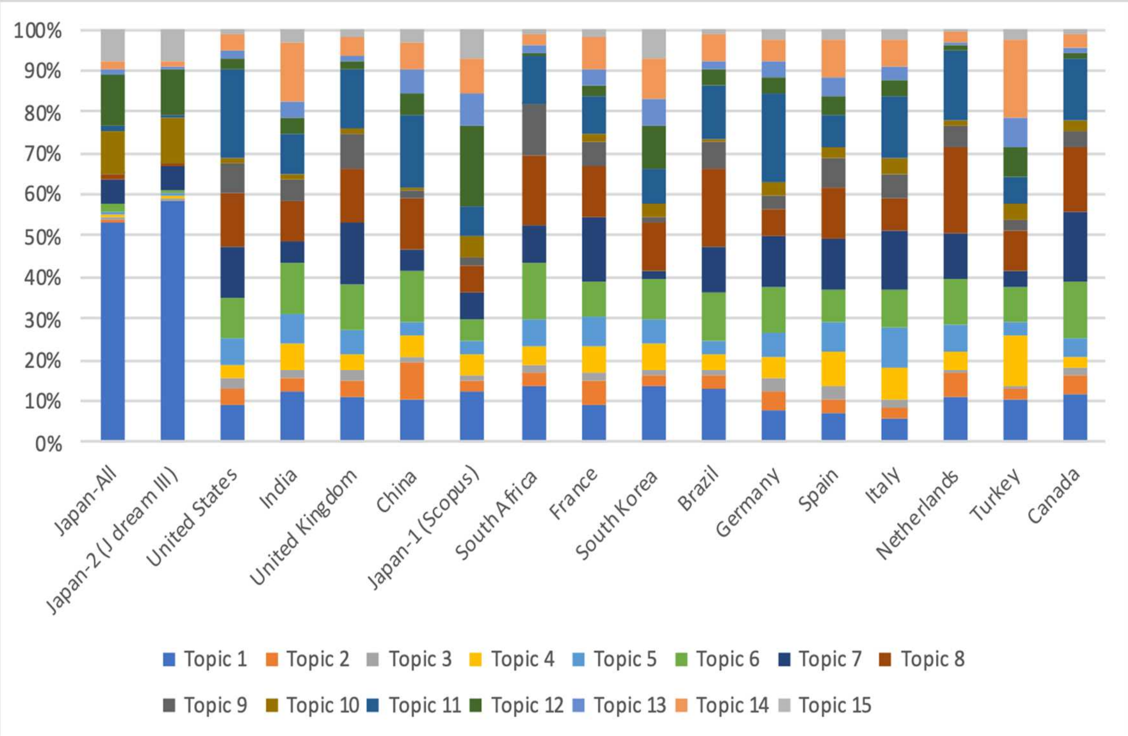

Figure 2.4 Proportion of publications on selected research topics in 15 affiliated countries

Note: Japan All = Scopus + J dream III.

2.3.2 Identified characteristics and priorities of research topics

Data for the top 15 affiliated countries were subjected to correspondence analysis in order to identify the qualitative relationship between variables (Figure 2.5), and to hierarchical clustering analysis (Figure 2.6). Moreover, "Japan All" data was divided into Scopus (Japan-1) and J dream III (Japan-2), as shown in Figure 2.7 and 2.8. The two-dimensions visualization of topic community and country cluster shows that "Japan All" data was located into different groups, compared with other countries, while its predominant topic-related attribute was

1, 10, 12 and 15. On the other hand, China, France and Germany showed a stronger degree of correlation between topics 2, 5 and 6 (Figure 2.5 and 2.7). The resulting dendrogram shows that “Japan All” was strongly independent whereas there was a close similarity between United States and United Kingdom, as can be seen in Figure 2.6 and 2.8. Furthermore, as a result of the visualization in Figure 2.7 and 2.8, Scopus (Japan-1) was moderate isolated.

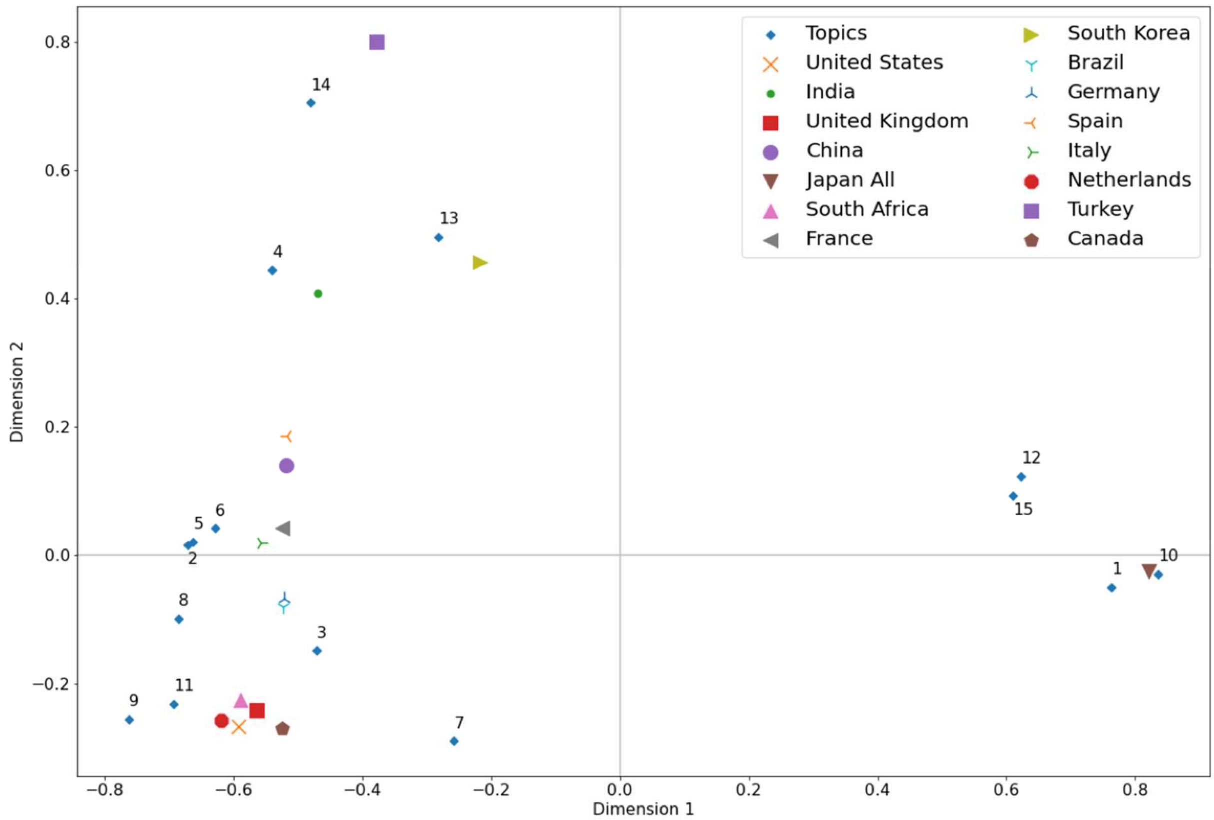

Figure 2.5 Topic community
Note: Japan All = Scopus + J dream III.

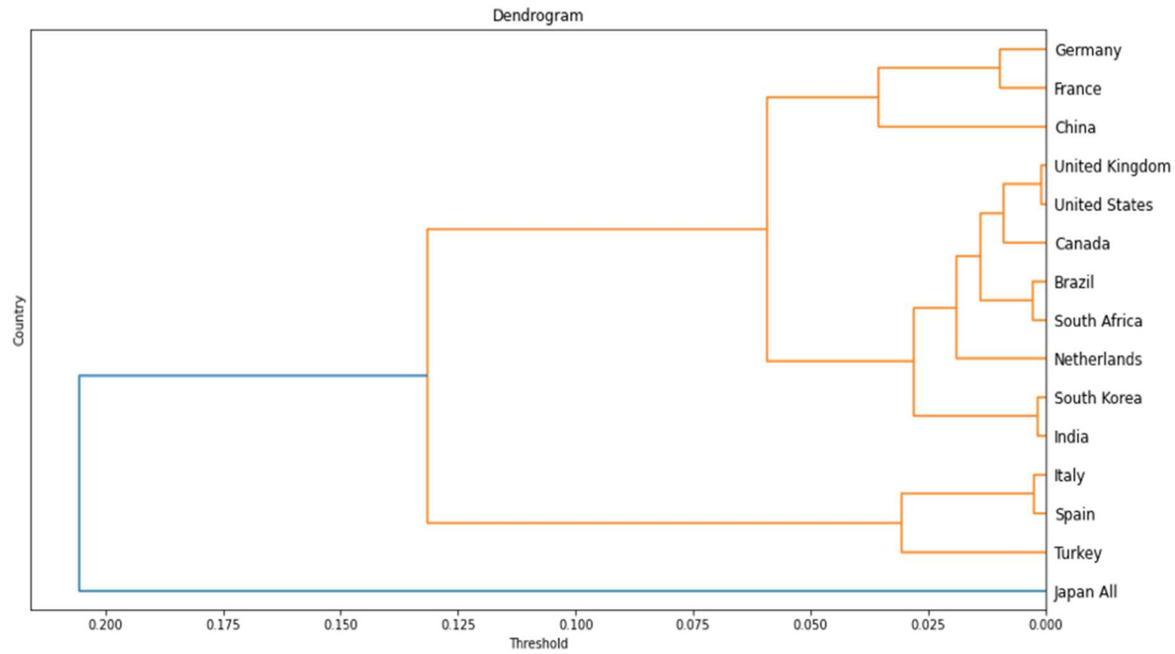

Figure 2.6 Country cluster

Note: Japan All = Scopus + J dream III.

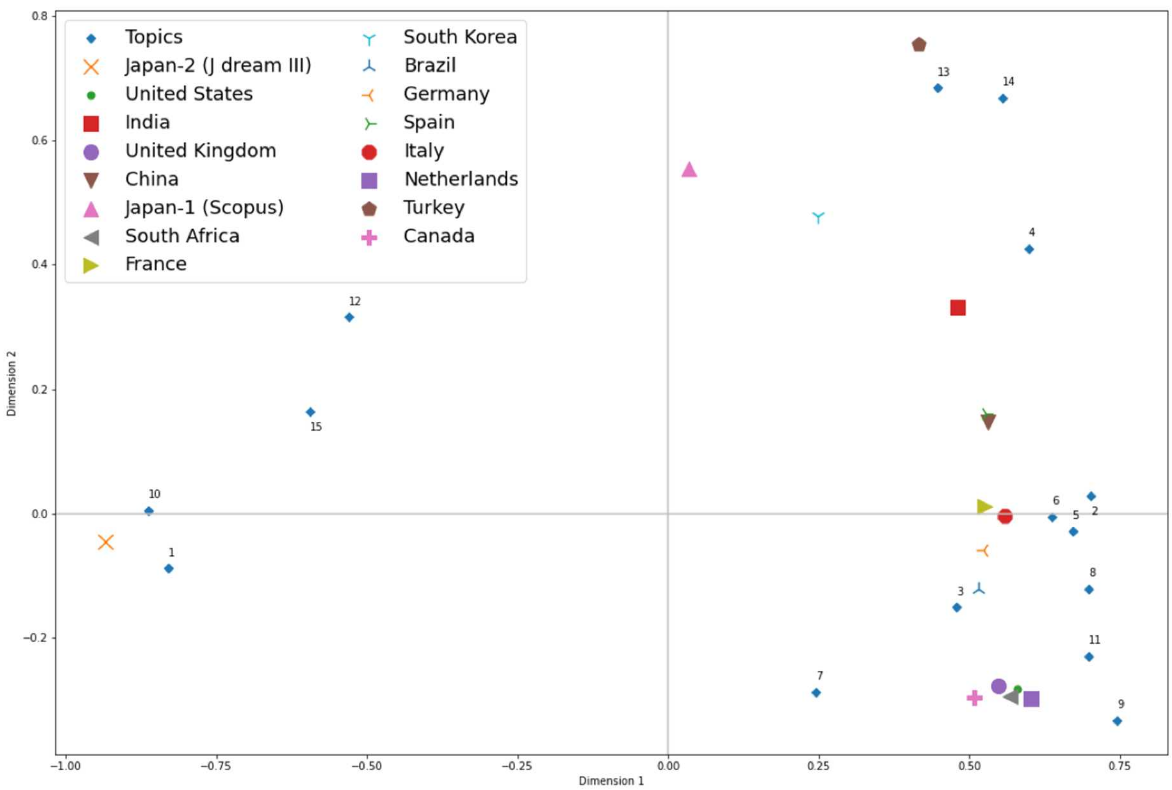

Figure 2.7 Topic community (with Japan All data distinguished Scopus (Japan-1) and J dream III (Japan-2))

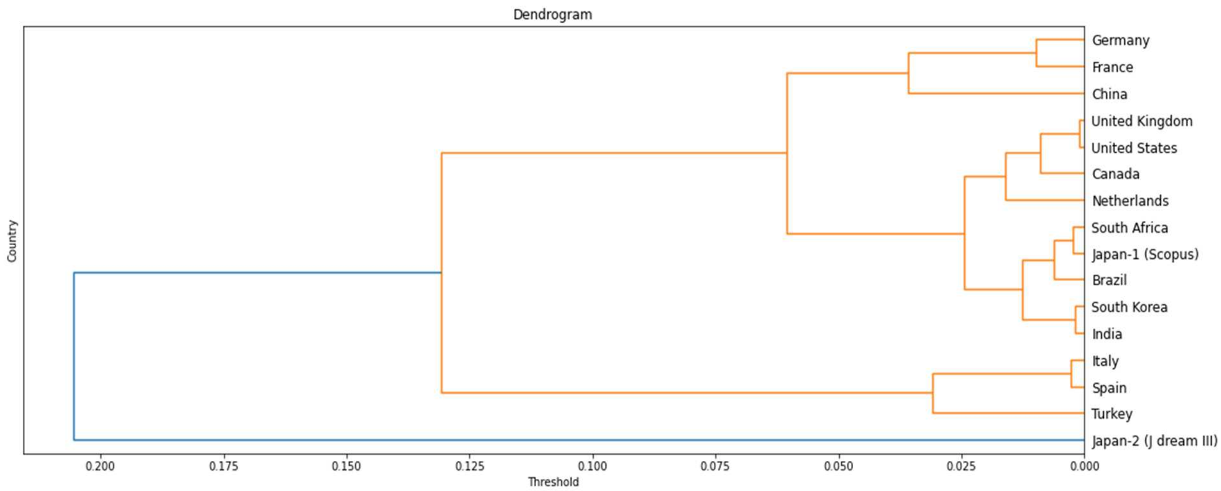

Figure 2.8 Country cluster (with Japan All data distinguished Scopus (Japan-1) and J dream III (Japan-2))

2.3.3 Evaluation of scale of research engagement and contribution

To identify the scale of research engagement and/or contribution to END TB strategy, five-spectrums for in-depth research and innovation were classified into the following categories: 1) fundamental science; 2) translational studies; 3) pre-clinical studies; 4) clinical studies / trials and development; and 5) scale-up implementation / operational research. The classification method was determined according to keywords from the spectrum of research in the END TB strategy and the 15 topics of LDA; for instance, the immunology and molecular biology research is categorized as 1) fundamental science. The categorization details could refer to Table 2.1. As can be seen in Figure 2.9, compared to that of other countries, the contribution of “Japan All” to category 5 was extremely low, at 2%; and the largest portion of research engagement was 19% for category 3 comparing to other countries. Besides, Scopus (Japan-1)’s research contribution to category 5 was small proportion (10%) compared with other countries. In contrast, all countries showed high research engagement in category 4, ranging from 37% (Canada) to 58% (Japan All). Exact values for Figure 2.9 can be followed in Appendix Table A2.1 and A2.2.

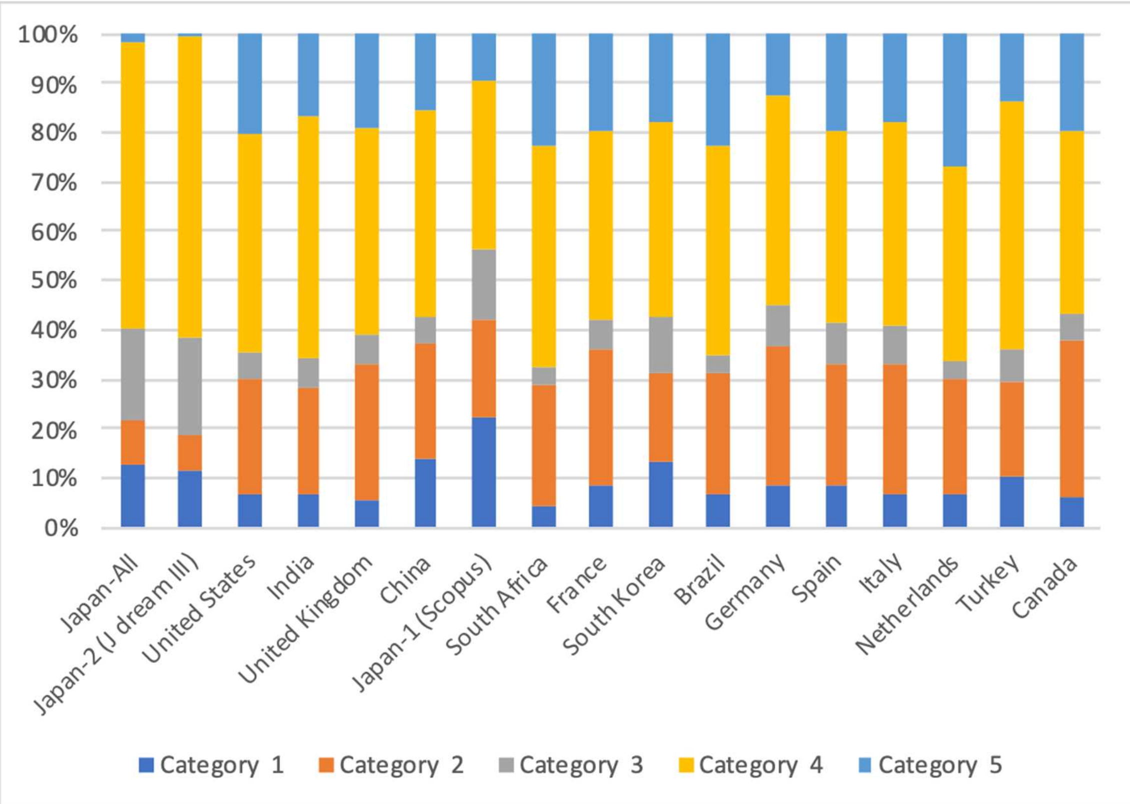

Figure 2.9 Proportion of research and innovation types based on WHO TB strategy, by country

Note: Japan All = Scopus + J dream III.

2.4 Discussion

In order to conduct evaluation analysis holistically compared with top 15 ranked countries using topic modelling, overall contribution of Japan's scientific development is clearly visible to obtain schematic information of each topic from long-term dataset.

In the first findings, realistic scientific research interest, trend and characteristic were identified, the health value orientation of research outputs was significant difference between comparison courtiers. For instance, TB research field in "Japan All" had attracted interest from healthcare and treatment for patients in domestic level through clinical studies and trials as case report (Topic 1), following by topic 12 including mycobacterium, immunology, antibody and mice via fundamental science (Table 2.1 and Figure 2.5). Specifically, the Scopus (Japan-1) of Topic 1 had the third largest share of the research output, while the J dream III (Japan-2) of the Topic 1 was the highest level of research output at 53% compared with other countries. It is evident that Japanese medical scientists have efforts being familiar with the art of medicine, treatment and care in patient related with clinical experience. Case report typically provide detailed information toward science communication that it is enhance to share rare medical or disease information of the symptoms, diagnosis, treatment care, and follow-up of an individual patient even though the research quality is inadequate without value-added scientific research methodology based on statistical aspects [22]. Furthermore, separated Scopus (Japan-1) data was most heavily attributed to topic 12, at 19% (Figure 2.7). That finding points to the need for fundamental research on the biology of mycobacterium, antigens, antibodies in immune systems, which was also identified as a priority in Japan. It is necessary to support R&D towards new drugs and vaccines, although this basic TB research area is relatively smaller than other research areas [23]. Japanese government healthcare policy emphasizes the development of new antibiotics, rapid diagnostic examination tools, and vaccine towards TB elimination [13]. The government policy priority could respond to the enhancing needs and motivations of Japanese R&D, is one of the key factors of TB research outputs.

On the other hand, the highest level of publication output in Topic 2 was China, which is more focused on genetic and molecular-related research development across fundamental science. It can be recognized that Chinese research and development interests have been moving into the spotlight of genetic-based science. According to Wang D. et al. 2020, genetic-based science in China has been developed for effective gene-target therapy and treatment involving infectious diseases since the introduction of gene-therapy regulation in 1993 [24]. As a result, the establishment of regulatory policy by the Chinese government could give rise to an evolving interest in gene-related medical development for two decades. To summarize, the performance of scientific research was appeared obvious at the country category, the national health care policy can influence publication output and impact.

From the result of topic community and country cluster, it is found that Japan was placed significantly in the opposite position to other country cluster group in global comparison. From the topic community analysis (Figure 2.5), the topic community visualization shows that the biggest impact on topic 1 and 10 was Japan in field of general TB health care research whereas Topic 14 strongly attributed to Turkey and India with large distance from other countries, had strong relativities to Multi-drug resistant TB (MDR)-TB treatment research. Japan’s core academic publications in topic 1 and topic 10 could be influential clinical research and medical trails that could directly address healthcare services for enhancing societal life standard by utilizing medical technologies through healthcare policy.

Additionally, according to WHO European Region Report 2013 [25], Turkey is one of the highest MDR-TB burden countries in the WHO European region. Besides, India had the largest number of drug-resistant TB globally, imposed an increased risk of TB incidence in younger population [26,27]. These evidences have been suggested that both countries are focusing on MDR-TB research as prioritized global health threats, National TB program (NTP) has been facilitated for scaling-up further MDR-TB research development and prevention by various initiatives since 2004 [24,28]. The National Strategic Plan for Tuberculosis Control (NSP-RNTCP) in India is expanding for scaling up MDR-TB treatment services with more than 10 million TB patients under the RNTCP [29]. The predominance of MDR-TB research in high burden countries can relate to concentration of prioritized specific disease target by the presence of National strategic plan of policy frameworks.

As shown in Figure 2.6 and 2.8, the country cluster mapping of scientific network in major Japan's research fields had disparate impact while America and United Kingdom had a close relationship reflected with closest distance matrix. The huge difference the country cluster is between Japan versus westernization countries. Despite the extremely difference in Japan's research field and limited network, scientific communication with network in American and European regions were existed their close geographical or historical proximity. In fact, American and European countries had strong relationship with scientific research network due to sharing close communication with regional research activities [30] such as conference, symposium and workshop with working on TB partnership [31,32]. It was also found that funding agency in America and other European union shared the set of value and policy of TB research priority within consensus statement on MDR-TB and other TB-related R&D into developing countries at a local as well as global levels [23]. The understanding of scientific consensus and priorities through the TB research collaboration with the working group could be useful for improving awareness of political attention and financial needs for guiding scientists and policy makers in order to scaling up R&D [33]. The collaboration with multinational regions could be one of the factors associated with improvement of scientific international network and activities into healthcare policy. For connecting wider international research network, the relationship with multi-stakeholders could evolve research knowledge and motivation for the researchers to set increasing the value of the research outputs.

From the result of the classified performance based on the WHO's key components of TB research, the finding emphasized the necessity of the national level TB research engagement in the research process to facilitate effective research uptake. In fact, Japan had the smallest proportion of category 5 (2%) involving evaluation of reciprocal relationship between social factors such as affecting health seeking behaviors, wider health systems and dynamics through policy effectiveness and regulatory science on TB prevention and care (Figure 2.7). On the other hand, category 3 (pre-clinical studies) and 4 (clinical studies and trials) was high proportion of research engagement in “Japan All” for 19% and 58%, respectively.

It can be seen that the degree of research engagement was identified, could lead to the national research priorities where the knowledge-generated of category 5 is less incorporated into Japan’s healthcare policy for achievement national as well as global goals. These results reflected the recognitions of research needs and trends made by the requirements from policymakers and funders’ decision [34,35]. The policymakers and funders are obligated to understand how much level of research scope are implementing as a result of research performance with the quantitative measurement from published article outputs, are essential measure of the impact and quality of research [16]. Therefore, the classification matrix can highlight the efficient TB research, which detect to engage in the degree of quality and performing TB research compared with other countries. The recognition of the TB research gaps and contribution will help stakeholders such as researchers, policymakers and funders to enhance the effectiveness of decision making.

2.5 Limitations

Our dataset was collected from Scopus and J dream III publication databases, with overlapping publications excluded. In the analysis using the combined dataset, the inclusion of data from the J dream III publication database may have modified the results, in that a systematic estimation error may have occurred due to an unbalanced database combination and to translation into English. Nevertheless, the purpose of this study is to assess Japan's contribution to TB research, and including the J-dream III dataset could sufficiently identify Japanese TB research trends. Head et al. (2015) suggested that it is difficult to accurately assess the effect of data collection, data size or paper on the results [16]. In addition, the classification here of the TB research field into five categories, based on the author's independent perspective alone, without confirmation by another researchers, could give rise to an underestimation of classification, as a sort of measurement bias.

On the other hand, it is difficult to classify into five categories the data from Scopus alone based on the dataset in the Supplement section, since the data scale is insufficient for the analysis due to the low-quality of medical scientific terms used. The small resource dataset is not useful for identifying of the significant impact of topic performance in the text mining [17,36]. From the above, it is evident that the Scopus database has a wider range of scientific keywords [37], while the J dream III database provides more medical scientific terms, the combination of the two datasets may lead to better topic modeling performance. Therefore, the results from those different viewpoints could enhance the credibility of our main analysis for evaluation of the schematic characteristics of Japan's progress in TB research.

2.6 Conclusion

This study assessed the contribution of scientific TB research over the last two decades to global health achievements aimed at the elimination of TB. We holistically identified the characteristics of scientific TB research based on national health care policy by topic modeling analysis of qualitative publication data with global comparison. The result of the study highlighted that Japanese research was most influential in research fields ranging from healthcare and treatment of patients in domestic-level clinical research and medical trials. Most importantly, in a science mapping of topic community and country cluster and the visualized characteristics and priorities of TB research worldwide, Japanese TB research in particular was independent. Moreover, we identified the weakness of Japan’s TB research engagement of which evaluation of reciprocal relationship between social factors such as affecting health seeking behaviors, wider health systems and dynamics through policy effectiveness and regulatory science fields. Regarding directions for future work, there is a need for a high performing analytical system for detecting medical trends, so as to enable higher validation outputs in text mining methodology. Furthermore, such a system could enable implementation of plausible policy, allowing for acceleration of element in research, which could serve as a reference for ensuring that future health care system innovations would continue to be needs-driven in line with the urgent priorities in TB research and innovation. Finally, appropriate funding allocation could enable operation with a substantial degree of social ownership, in the interests of sustainable health and social care.

2.7 Appendix

Table A2.1 Proportion of publications on selected research topics in affiliated countries

	Topic 1	Topic 2	Topic 3	Topic 4	Topic 5	Topic 6	Topic 7	Topic 8	Topic 9	Topic 10	Topic 11	Topic 12	Topic 13	Topic 14	Topic 15
Japan-All	53%	0%	1%	1%	1%	2%	6%	1%	0%	10%	2%	12%	1%	2%	8%
Japan-2 (J dream III)	59%	0%	1%	0%	0%	1%	6%	0%	0%	11%	1%	11%	1%	1%	8%
United States	9%	4%	2%	3%	7%	9%	12%	13%	7%	2%	21%	3%	2%	4%	2%
India	12%	3%	2%	7%	7%	12%	5%	10%	6%	1%	10%	4%	4%	14%	3%
United Kingdom	11%	4%	3%	4%	6%	11%	15%	13%	9%	1%	14%	2%	1%	4%	2%
China	10%	9%	1%	5%	3%	12%	5%	12%	2%	1%	18%	5%	6%	6%	3%
Japan-1 (Scopus)	12%	3%	1%	5%	3%	5%	6%	7%	1%	5%	7%	19%	8%	8%	7%
South Africa	14%	3%	2%	5%	6%	14%	9%	17%	12%	0%	11%	1%	1%	3%	2%
France	9%	6%	2%	6%	7%	8%	15%	12%	6%	2%	9%	3%	4%	8%	2%
South Korea	13%	3%	1%	7%	6%	10%	2%	12%	1%	3%	8%	11%	6%	10%	7%
Brazil	13%	3%	1%	4%	3%	12%	10%	19%	6%	1%	13%	4%	2%	7%	1%
Germany	8%	5%	3%	5%	6%	11%	12%	7%	3%	3%	21%	4%	4%	5%	3%
Spain	7%	4%	3%	8%	7%	8%	12%	13%	7%	2%	8%	5%	5%	9%	3%
Italy	5%	3%	2%	8%	10%	9%	14%	8%	6%	4%	15%	4%	3%	7%	2%
Netherlands	11%	6%	1%	5%	6%	11%	11%	21%	5%	1%	16%	1%	1%	2%	1%
Turkey	10%	3%	1%	12%	4%	8%	4%	10%	3%	3%	7%	8%	7%	19%	2%
Canada	12%	5%	2%	3%	4%	14%	17%	16%	4%	3%	15%	1%	1%	3%	1%

Note: Japan All = Scopus + J dream III.

Table A2.2 Proportion of research and innovation types based on WHO TB strategy, by country

	Category 1	Category 2	Category 3	Category 4	Category 5
Japan-All	13%	9%	19%	58%	2%
Japan-2 (J dream III)	11%	8%	19%	61%	1%
United States	7%	23%	6%	44%	20%
India	7%	21%	6%	49%	17%
United Kingdom	6%	27%	6%	42%	19%
China	14%	23%	6%	42%	16%
Japan-1 (Scopus)	22%	20%	14%	34%	10%
South Africa	4%	24%	4%	45%	23%
France	8%	27%	6%	38%	20%
South Korea	14%	18%	11%	40%	18%
Brazil	7%	24%	3%	43%	23%
Germany	9%	28%	9%	43%	12%
Spain	8%	25%	8%	39%	20%
Italy	7%	26%	8%	41%	18%
Netherlands	7%	23%	3%	40%	27%
Turkey	10%	19%	6%	51%	14%
Canada	6%	32%	5%	37%	20%

Note: Japan All = Scopus + J dream III.

2.8 Supplement

To ensure reasonable data selection and classification, we conducted the same analysis using Scopus dataset alone as a supplement. We present here the most significant results from the supplement. First, optimal topic coherence was measured for 16 topics; probability fluctuated and thus it made no difference to detection of the optimal topic number, given the small sample size (Figure S2.1, Table S2.1). Second, the analysis outcome for topic community using Scopus dataset only was diversified among the 15 target countries (Figure S2.2, 2.3 and 2.4). Finally, the results of classification are consistent with those for the combined dataset (Figure S2.5) followed in supplementary Table S2.2 and S2.3.

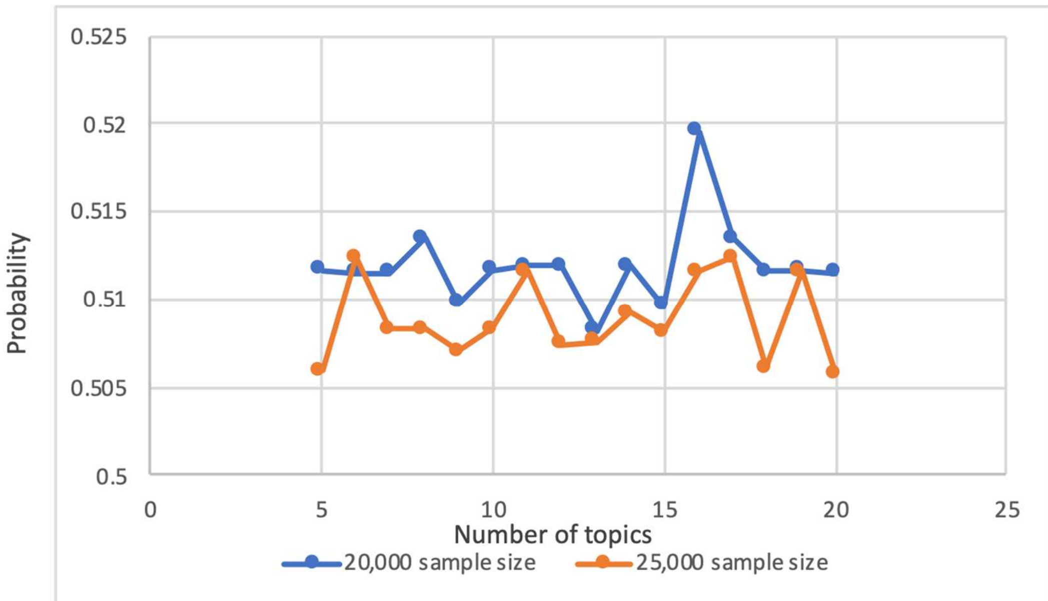

Figure S2.1 Topic coherence scores (Scopus only dataset)

Table S2.1 Classification of 15 topics (Scopus only dataset)

	Top 40 words	Potential term of disease	Potential term of target population	Summary	Research field
Topic 1	tuberculosis drug resistant resistance mycobacterium multidrug mdr bacterial strain rifampicin isoniazid isolates antibiotic human patient sensitivity treatment bacterium agent ethambutol streptomycin pulmonary molecular dna lung clinical culture antitubercular susceptibility mutation agents case tuberculostatic humans sputum microbial adult line genotype microbiology	tuberculosis, pulmonary, lung	human, patient, Humans, adults	Drug or diagnostics intervention for efficacy	2: Translational research
Topic 2	tuberculosis child case incidence contact adolescent male infant female adult pulmonary infection aged prevalence age preschool year human tuberculin test population risk positive screening rate transmission humans children clinical cases lung high middle retrospective data childhood distribution newborn active major	tuberculosis, pulmonary, lung	child, adolescent, male, infant,preschool, female, adult, human	Popuration-leveled research	4: Clinical studies / Trials
Topic 3	infection pneumonia patient drug agent therapy arthritis clinical transplantation lung human treatment respiratory rheumatoid tract kidney factor infections bacterial immunosuppressive chronic syndrome antibody antibiotic necrosis risk corticosteroid skin fever acute infliximab tumor aspergillosis tuberculosis anti systemic blood lupus review response	pneumonia, respiratory, rheumatoid, kidney, necrosis, askin, spergillosis	patient, human	Progression to active disease	4: Clinical studies / Trials
Topic 4	hiv virus infection human immunodeficiency tuberculosis patient infected infections aids therapy count adult clinical syndrome antiretroviral male treatment immune lymphocyte female opportunistic agent related lung art pulmonary patients acquired active mortality case humans highly meningitis anti hospital africa deficiency associated	hiv, tuberculosis, aids, lung, pulmonary	human, patient, adult, male, female,	Examination of TB infection and disease	4: Clinical studies / Trials
Topic 5	health patient tuberculosis care treatment hospital adult pulmonary female male cross delay control aged sectional india human patients medical diagnosis public middle questionnaire lung rural case social program humans education clinical service facility quality community observed adherence dots compliance therapy	tuberculosis, pulmonary, lung	patient, adult, female, human, patient,	Investigation of social and personal factors	5: Development and scale-up implementation
Topic 6	drug tuberculosis treatment isoniazid therapy rifampicin agent pyrazinamide ethambutol human patient agents liver level blood anti antitubercular clinical dose pulmonary tuberculostatic regimen combination effect lung trial concentration male activity mg humans female outcome induced adult efficacy rifampin administration acid month	tuberculosis, liver, pulmonary, lung,	human, patient, male, female, human	Disease outcome research	4: Clinical studies / Trials
Topic 7	tuberculosis antigen cell patient level interferon protein blood pulmonary gamma response assay adult mycobacterium human serum test lymphocyte antibody active interleukin aged male female ifn enzyme control cytokine clinical healthy linked tuberculin bcg lung group release positive marker infection latent	tuberculosis	patient, adult, female, human, patient,	Response to therapy including molecular and immunology	1: Fundamental studies
Topic 8	patient tuberculosis treatment pulmonary aged sputum clinical patients male group adult female lung outcome diabetes middle mycobacterium smear retrospective month positive culture case hospital mellitus rate age human therapy mean failure conversion major studies follow chest time humans results year	tuberculosis, pulmonary, lung, diabetes, chest	patient, male, female, human	Treatment or clinical study	4: Clinical studies / Trials
Topic 9	lung cancer respiratory chronic pulmonary obstructive smoking heart asthma aged pleural tuberculosis human function exposure effusion copd pneumonia patient humans tract fibrosis male bronchiectasis air ventilation volume carcinoma risk silicosis forced history cause occupational failure death oxygen acute female disease	Lung, cancer, respiratoty, pulmonary, heart, asthma, pleural, copd, bronchiectasis, carcinoma, silicosis,	aged, human, patient,	Investigation of social and personal factors	5: Development and scale-up implementation
Topic 10	tuberculosis cell mycobacterium lung animal protein human infection bacterial mouse vaccine expression bcg response macrophage immune model immunity mice interleukin pulmonary factor lymphocyte gene host drug antigen receptor animals tissue cytokine cells infected growth priority bovis granuloma controlled activation experiment	tuberculosis, lung, pulmonary	animal, human, mouse, mice	Response to therapy including molecular and immunology	1: Fundamental studies
Topic 11	gene tuberculosis genetic polymorphism genotype pulmonary vitamin association control human susceptibility associated nucleotide patient adult single protein case dna receptor frequency risk male sequence population allele female predisposition aged group chain polymerase reaction lung clinical genetics mutation humans hla major	tuberculosis, pulmonary, lung	human, patient, adult, male ,female	Response to therapy including molecular and immunology	1: Fundamental studies
Topic 12	tuberculosis sputum culture sensitivity diagnostic smear diagnosis positive mycobacterium pulmonary specificity test negative clinical value detection patient microscopy sample human accuracy bacterium acid assay lung specimen xpert pcr reaction chain polymerase predictive using adult fast rif time respectively laboratory female	tuberculosis, pulmonary, lung	patient, human, female	Implementation research	3: Preclinical studies
Topic 13	risk tuberculosis treatment factor ci adult outcome mortality aged cohort associated patient age female male factors rate ratio clinical studies death pulmonary data model controlled major regression incidence middle sex retrospective survival logistic population prevalence multivariate assessment year association interval	tuberculosis, pulmonary	adult, aged, patient, female, male, population	Investigation of social and personal factors	5: Development and scale-up implementation
Topic 14	eye visual ocular placebo treatment uveitis clinical acuity patient trial group optic glaucoma outcome week retina blind controlled intraocular retinal drug vision double therapy follow nerve laser female complication dose randomized agent hemorrhage postoperative safety surgery cataract human blindness injection	eye	patient, female	Intervention to imparove the use of drug resimens	3: Preclinical studies
Topic 15	tuberculosis lung case pulmonary tomography diagnosis human patient male biopsy adult radiography aged clinical female assisted thorax computer imaging computed differential lesion ct humans year chest lymph diagnostic ray tissue examination node old bronchoscopy middle feature hemoptysis treatment surgery cell	tuberculosis, lung, pulmonary, thorax, chest, lymph,	human, patient, male, adult, aged, female	Drug or diagnostics intervention for efficacy	2: Translational research
Topic 16	tuberculosis health human lung review control care humans infection cost medical risk world pulmonary screening research public ha new practice united history organization priority vaccine transmission country test pregnancy bcg states based management century guideline clinical prevention medicine incidence developing	tuberculosis, lung, pulmonary	human	Examination of TB infection and disease	4: Clinical studies / Trials

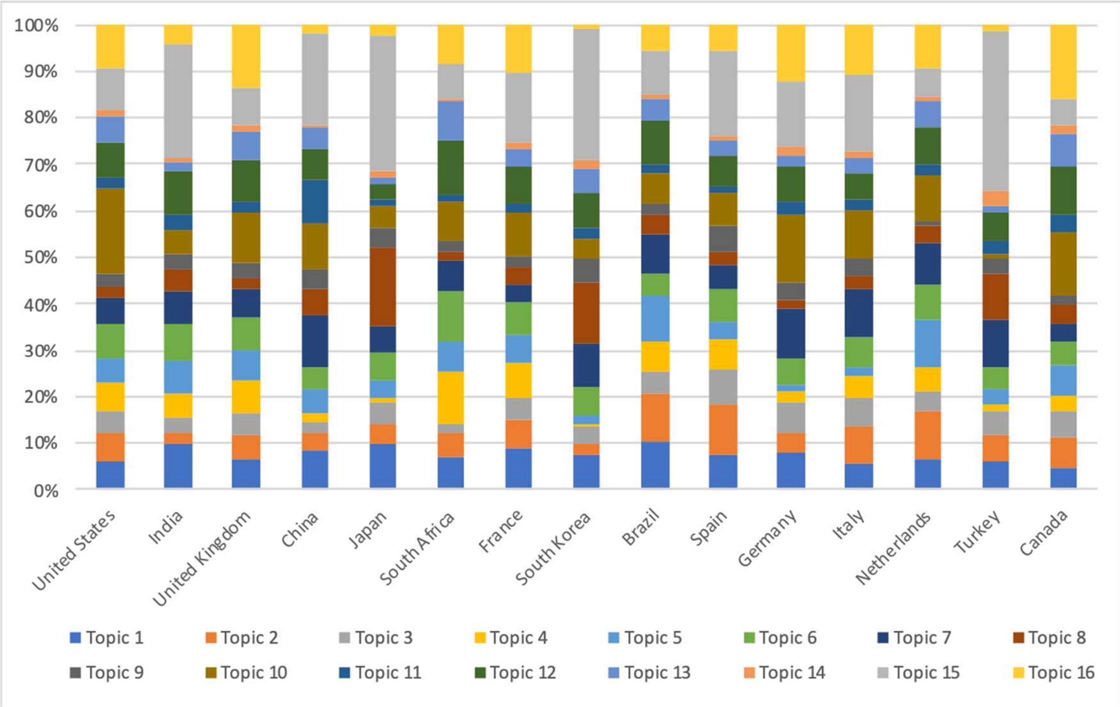

Figure S2.2 Proportion of publications on selected research topics in 15 affiliated countries (Scopus only dataset)

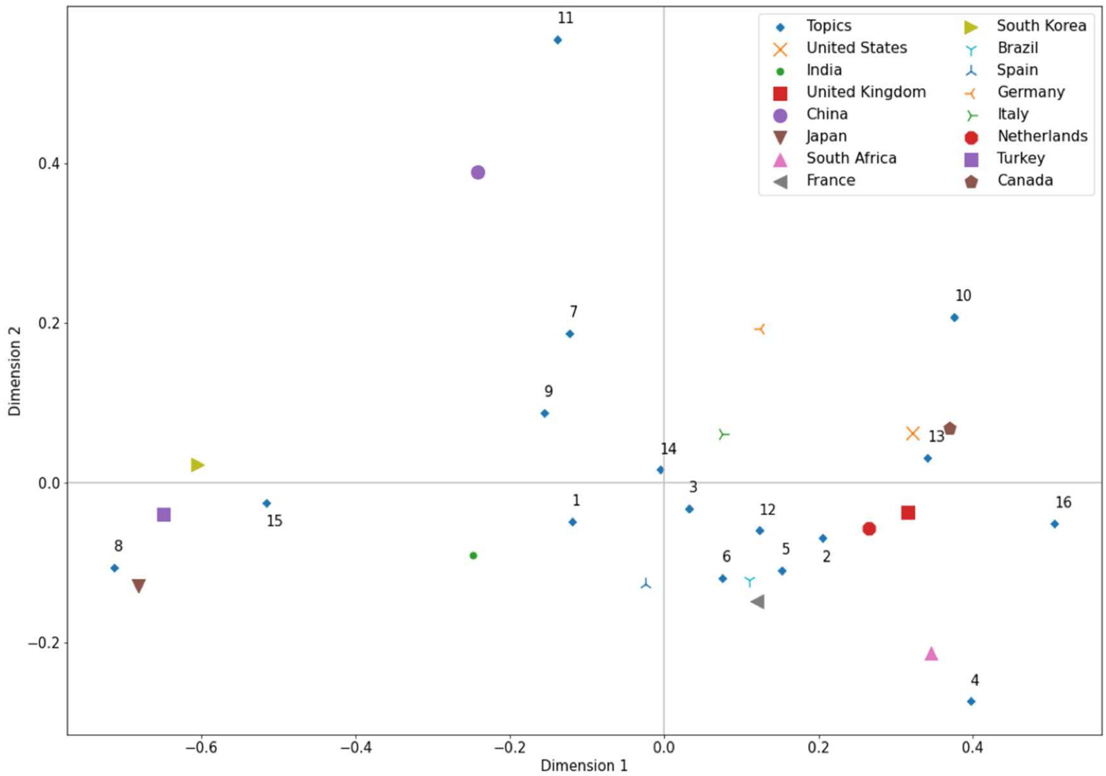

Figure S2.3 Topic community (Scopus only dataset)

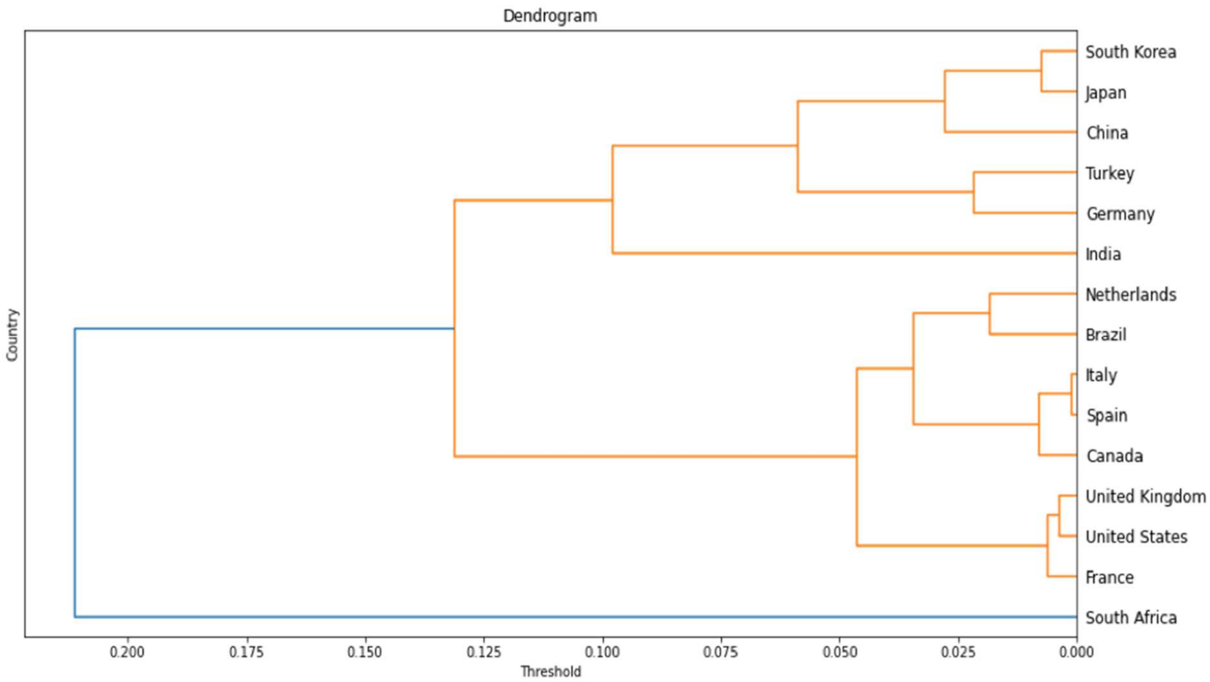

Figure S2.4 Country cluster (Scopus only dataset)

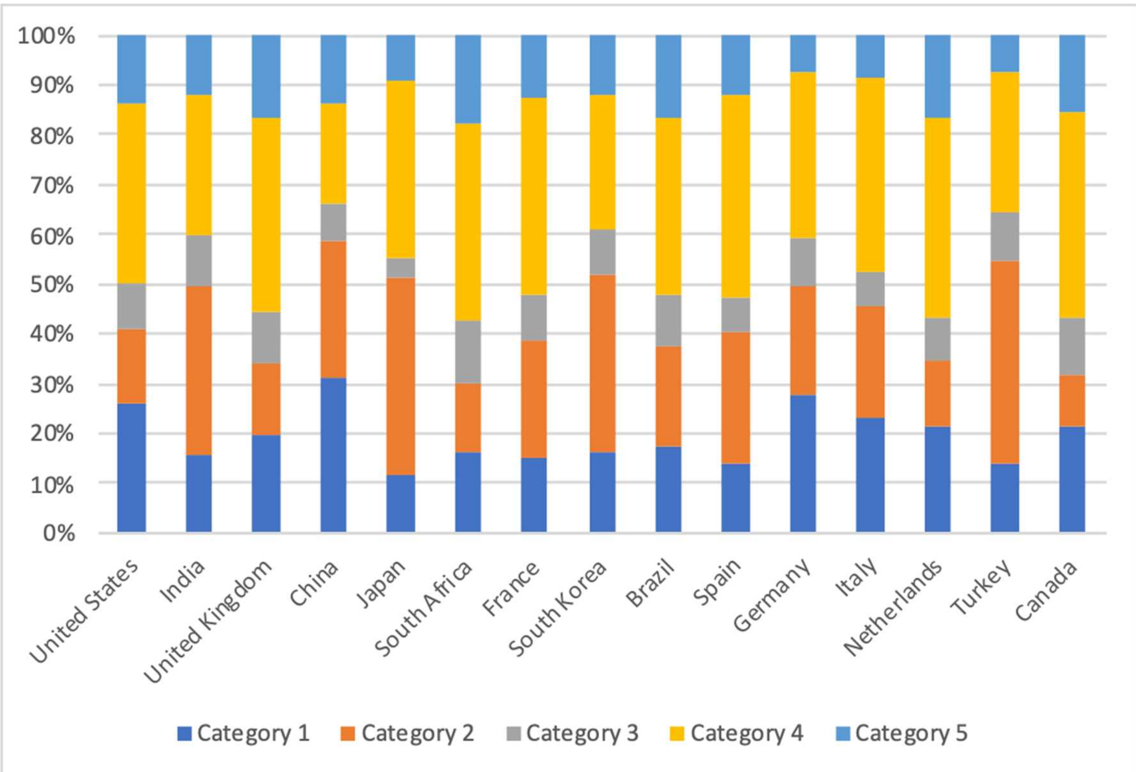

Figure S2.5 Proportion of research and innovation types based on WHO TB strategy, by country (Scopus only dataset)

Table S2.2 Proportion of publications on selected research topics in affiliated countries, by country, by using only Scopus dataset

	Topic 1	Topic 2	Topic 3	Topic 4	Topic 5	Topic 6	Topic 7	Topic 8	Topic 9	Topic 10	Topic 11	Topic 12	Topic 13	Topic 14	Topic 15	Topic 16
United States	6%	6%	5%	6%	5%	7%	5%	3%	3%	18%	2%	7%	6%	2%	9%	10%
India	10%	2%	4%	5%	7%	8%	7%	5%	3%	6%	3%	9%	2%	1%	25%	4%
United Kingdom	7%	5%	5%	7%	7%	7%	6%	2%	3%	11%	3%	8%	6%	1%	8%	14%
China	8%	4%	2%	2%	5%	5%	12%	5%	4%	10%	9%	7%	4%	1%	20%	2%
Japan	10%	4%	5%	1%	3%	6%	6%	17%	4%	5%	2%	3%	2%	1%	30%	2%
South Africa	7%	5%	2%	12%	7%	11%	7%	2%	3%	8%	1%	12%	8%	1%	7%	9%
France	9%	6%	5%	7%	6%	7%	3%	4%	2%	9%	2%	8%	4%	1%	15%	10%
South Korea	8%	2%	4%	0%	2%	6%	9%	13%	5%	4%	3%	7%	5%	2%	28%	1%
Brazil	10%	10%	5%	7%	10%	5%	9%	4%	2%	6%	2%	9%	5%	1%	10%	5%
Spain	8%	11%	7%	7%	4%	7%	5%	3%	5%	7%	2%	6%	3%	1%	19%	6%
Germany	8%	4%	7%	3%	1%	6%	11%	2%	4%	15%	3%	8%	3%	2%	14%	12%
Italy	6%	8%	6%	5%	2%	7%	10%	3%	4%	11%	2%	6%	3%	2%	16%	11%
Netherlands	7%	10%	4%	5%	10%	7%	9%	4%	1%	10%	2%	8%	5%	1%	7%	9%
Turkey	6%	6%	5%	2%	3%	5%	10%	10%	3%	1%	3%	6%	1%	3%	35%	1%
Canada	5%	7%	6%	3%	6%	5%	4%	4%	2%	13%	4%	10%	7%	2%	6%	16%

Table S2.3 Proportion of research and innovation types based on WHO TB strategy, by country by using only Scopus dataset

	Category 1	Category 2	Category 3	Category 4	Category 5
United States	26%	15%	9%	36%	14%
India	16%	34%	10%	28%	12%
United Kingdom	19%	15%	10%	40%	16%
China	31%	28%	7%	20%	14%
Japan	12%	39%	4%	36%	9%
South Africa	16%	14%	12%	40%	18%
France	15%	24%	9%	40%	12%
South Korea	16%	36%	9%	27%	12%
Brazil	17%	20%	10%	36%	17%
Spain	14%	26%	7%	41%	12%
Germany	28%	22%	9%	33%	8%
Italy	23%	22%	7%	39%	8%
Netherlands	21%	13%	9%	40%	17%
Turkey	14%	41%	9%	28%	8%
Canada	21%	10%	12%	41%	16%

2.9 Reference

[1] World Health Organization., (2020). *Global Tuberculosis Report 2020*. Geneva: WHO. [Viewed 4 May 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf.

[2] World Health Organization., (2020). WHO Tuberculosis Fact Sheets 2020, October. [Viewed 4 May 2021]. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis.

[3] Smith, I., (2003). Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. *Clin Microbiol Rev*. 16(3), 463-96.

[4] Loddenkemper, R., Lipman, M., Zumla, A., (2015). Clinical Aspects of Adult Tuberculosis. *Cold Spring Harb Perspect Med*. 6;6(1): a017848. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4691808/.

[5] World Health Organization., (2016). International statistical classification of diseases and related health problems. - 10th revision, Fifth edition, 2016. [Viewed 4 May 2021]. Available from: https://icd.who.int/browse10/Content/statichtml/ICD10Volume2_en_2016.pdf.

[6] Tuberculosis Surveillance Center., (2020). Tuberculosis in Japan: Annual Report 2020. [Viewed 8 May 2021]. Available from: https://jata.or.jp/english/dl/pdf/TB_in_Japan_2020.pdf

[7] Duarte, R., Lönnroth, K., Carvalho, C., Lima, F., Carvalho, A.C.C., Muñoz-Torrico, M., Centis, R., (2017). Tuberculosis, social determinants and co-morbidities (including HIV). *Pulmonology*. 24(2), 115-119.

[8] World Health Organization., (2015). Implementing the end TB strategy: the essentials. WHO/HTM/TB/2015.31. [Viewed 8 May 2021]. Available from: https://www.who.int/tb/publications/2015/end_tb_essential.pdf

[9] World Health Organization., (2019). Global Tuberculosis Report 2019. [Viewed

10 May 2021]. Available from: < https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf>.

[10] World Health Organization., (2013). Priorities for tuberculosis research: A report of the Disease reference group report on TB, leprosy and Buruli ulcer. [Viewed 10 May 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/85888/9789241505970_eng.pdf?sequence=1.

[11] World Health Organization., (2020). A Global Strategy for tuberculosis research and innovation 2020. [Viewed 10 May 2021]. Available from: https://www.who.int/publications/i/item/9789240010024.

[12] Cabinet Office, Government of Japan, Cabinet Secretariat, Office of Healthcare Policy., (2014). Japan's healthcare policy 2014. [Viewed 10 May 2021]. Available from: https://www.kantei.go.jp/jp/singi/kenkouiryou/en/pdf/policy.pdf.

[13] Cabinet Office, Government of Japan, Cabinet Secretariat, Office of Healthcare Policy., (2017). Japan's healthcare policy 2017 revised ver. [Viewed 10 May 2021]. Available from: < https://www.kantei.go.jp/jp/singi/kenkouiryou/en/pdf/2017_policy.pdf>.

[14] Health and Global Policy Institute., (2013). Japan's Global Health Policy: Challenges and Opportunities 2013. [Viewed 10 May 2021]. Available from: https://hgpi.org/en/wp-content/uploads/sites/2/Gates%20long-version%20E%20report_final_v3.pdf.

[15] Onaya, T., Taketomi, M., Fujii, H., Negishi, T., (2015). ICT trends in Japan's healthcare policy. *FUJITU Sci. Tech. J.* 51(3), 10-17. https://www.fujitsu.com/global/documents/about/resources/publications/fstj/archives/vol51-3/paper02.pdf

[16] Head, M.G., Fitchett, J.R., Derrick, G., Wurie, F.B., Meldrum, J., Kumari, N., Beattie, B., Counts, C.J., Atun, R., (2015). Comparing research investment to

United Kingdom institutions and published outputs for tuberculosis, HIV and malaria: a systematic analysis across 1997-2013. *Health Res Policy Syst*. 13:63.

[17] Chen, X., Lun, Y., Yan, J., Hao, T., Weng H., (2019). Discovering thematic change and evolution of utilizing social media for healthcare research. *BMC Med Inform Decis Mak.* 19(50).

[18] Li X, Lei L. 2019A bibliometric analysis of topic modelling studies (2000–2017). *Journal of Information Science*. 1-15.

[19] David M Blei, Andrew Y Ng, and Michael I Jordan. 2003. Latent Dirichlet allocation. *Journal of Machine Learning Research*, 3:993–1022. https://www.jmlr.org/papers/volume3/blei03a/blei03a.pdf

[20] Yoshida, T., Hisano, R., Ohnishi, T., (2020). Gaussian Hierarchical Latent Dirichlet Allocation: Bringing Polysemy Back. *arXiv: 2002.10855*. https://www.centralbank.e.u-tokyo.ac.jp/wp-content/uploads/2020/03/cb-wp017.pdf

[21] Bhatia, S., Lau, J.H., Baldwin, T., (2017). An Automatic Approach for Document-level Topic Model Evaluation. *ACL Anthology*.

[22] Rison, R.A., Shepphird, J.K. & Kidd, M.R. How to choose the best journal for your case report. *J Med Case Reports* 11, 198 (2017). https://doi.org/10.1186/s13256-017-1351-y

[23] Rylance, J., Pai, M., Lienhardt, C., Garner, P., (2010). Priorities for tuberculosis research: a systematic review. *Lancet Infect Dis*. 10, 889-892. https://www.thelancet.com/action/showPdf?pii=S1473-3099%2810%2970201-2 .

[24] Wang, D., Wang, K., Cai Y., (2020). 2020. An overview of development in gene therapeutics in China. *Gene Ther*. 27, 338–348.

[25] WHO, (2013). WHO Regional office for Europe 2013. [Viewed 10 May 2021]. Available from: https://www.euro.who.int/__data/assets/pdf_file/0020/270920/ProcurementMgm

tRep_highMDRTB_PriorityCountries2013.pdf

[26] Shivelar, S.S., Kaliaperumal, V., Brammacharry, U., Sakkaravarthy, A., Vidya Raj, C.K., Alagappan, C., Muthaiah, M., (2020). Prevalence and factors associated with multidrug-resistant tuberculosis in South India. *Sci Rep*. 10, 17552.

[27] WHO., (2019). WHO TB report 2019. [Viewed 10 May 2021]. Available from: <https://www.who.int/tb/publications/global_report/tb19_Exec_Sum_12Nov2019.pdf>

[28] WHO., (2005). Stop TB partnership: Annual Report 2004. [Viewed 10 May 2021]. Available from: <http://apps.who.int/iris/bitstream/handle/10665/69155/WHO_HTM_STB_2005.33_eng.pdf?sequence=1>.

[29] Central TB Division, Directorate General of Health Services, Ministry of Health with Family Welfare, Nirman Bhavan, New Delhi., (2017). NSP-TB 2017: NATIONAL STRATEGIC PLAN FOR TUBERCULOSIS ELIMINATION 2017–2025 India. [Viewed 10 May 2021]. Available from: https://tbcindia.gov.in/WriteReadData/NSP%20Draft%2020.02.2017%201.pdf.

[30] Abraham, J., (2020). National culture as a correlated of research output and impact. *F1000Research*. 8:237, 1-22. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029754/pdf/f1000research-8-24613.pdf

[31] Mostafavi, E., Bazrafshan, A., (2014). Research and Collaboration Overview of Institut Pasteur International Network: A Bibliometric Approach Toward Research Funding Decisions. *International Journal of Health Policy and Management*. 2(1), 21-28.

[32] Pouris, A., Ho, Yuh-shan., (2016), A bibliometric analysis of research on Ebola in Science Citation Index Expanded. *S. Afr. j. sci*. 112, 3-4.

[33] Sakamoto, H., Lee, S., Ishizuka, A., Hinoshita, E., Hori, H., Komada, K.,

Norizumi, M., Katuma, Y., Akashi, H., Shibuya, K., (2019). Challenges and opportunities for eliminating tuberculosis – leveraging political momentum of the UN high-level meeting on tuberculosis. *BMC public health*. 29:76.

[34] Conalogue, D.M., Kinn, S., Mulligan J.A., McNeil, M., (2017). International consultation on long0term global health research priorities, research capacity and research uptake in developing countries. *BioMed Health research policy and systems*. 15:24, 1-6.

[35] Ralaidovy, A.H., Adam, T., Boucher, P., (2020). Resource allocation for biomedical research: analysis of investments by major funders. *BMC Health Research Policy and systems*. 18:20, 1-9.

[36] Akdemir, A., Shibuya, T., (2020). Transfer Learning for Biomedical Question. *Working Notes of CLEF 2020 - Conference and Labs of the Evaluation Forum*. 2696.

[37] Cho, M.C., Park, C., Song, M., (2020). The evolution of social health research topics: A data-driven analysis. *Social Science & Medicine*. 265, 113-299.

Chapter 3

Assessing Factors Associated with TB Awareness in Nepal: A National and Subnational Study

3.1 Introduction

Tuberculosis (TB) has long been considered a critical infectious disease [1]. In 2019, 10 million people developed TB, leading to 1.4 million TB deaths worldwide [2]. The WHO Global TB Report 2020 found that 98% of the world's registered TB cases were in low- and middle-income countries (LMICs) [2]. In LMICs, low awareness of TB is one of the leading risk factors for high prevalence [3]. Lack of TB awareness has become a severe social concern affecting population health, given the risk of spread of TB [4]. Inadequate knowledge about TB leads to further transmission and delay in diagnoses and treatment [5]. There are 3.6 million people with TB who are undiagnosed and hence do not receive treatment from healthcare facilities in LMICs [6]. As can be seen in the case of India, due to low TB awareness, diagnosis and treatment of TB have been delayed, leading to an increased probability of further spread of TB in the community [7].

In 1965, the national TB program (NTP) of Nepal was implemented by the Nepalese government in collaboration with the WHO and the United Nations Children's Fund (UNICEF). The main aim of the program is to effectively monitor and control TB incidence and prevalence and ensure better access to quality TB treatment services in Nepal [8]. Since 2006, almost 85% of TB cases in Nepal have been successfully treated through the NTP, and the incidence of TB has decreased gradually, by 3% per year until 2019 [9]. Despite efforts made by government and international organizations to end TB, around 40% of Nepalese participants in the End TB program did not seek TB care and treatment, according to Nepal’s 2018 national TB prevalence survey [9]. The results of the national survey indicate that there is inadequate knowledge of access to TB health services; thus, there is a need to increase awareness of the availability of quality TB diagnostics, care and treatment [6,8]. National health policy priorities include: achievement of the main goal, TB elimination; reducing the numbers of new TB cases and TB deaths (by enhancing TB awareness among the entire Nepalese population); removal of barriers to equitable access to TB treatment and care, to improve community wellbeing in regional Nepal [10]. All of those targets were set by the NTP at the central level and at local levels as well, in accordance with the goal of the national strategic plan, to End TB by 2030 in Nepal [8,10].

The level of TB awareness is associated with various demographic and socioeconomic factors such as education level, socioeconomic status and area of residence [8,11]. Low public awareness of and knowledge about TB have been identified as correlated with several socioeconomic factors including family income, education level and gender [12]. In addition, enhanced awareness of TB could improve access to appropriate treatment and better outcomes, especially in socioeconomically vulnerable groups—who have limited access to information about TB due to weak community engagement—and certain areas of residence. [13,14]. In LMICs, including Nepal, specific locations and places at greater distances from TB treatment facilities are susceptible to poor community TB awareness and weak adherence to TB treatment as a health-seeking behavior [15,16]. Examining the demographic and socioeconomic factors associated with TB awareness is important for understanding the socioeconomic gaps that can help to drive infectious TB control in the work to eliminate TB [12,17]. However, few studies have analyzed the magnitude of the associated factors at national and subnational levels in Nepal. Hence, the aim of our study is to evaluate the relationship between TB awareness and demographic and socioeconomic factors at national and subnational levels in Nepal.

3.2 Materials and Methods

3.2.1 Data-In-Use

In our study, we used data from the Nepal Demographic & Health Survey (NDHS) 2016. The NDHS is a nationally representative population-based cross-sectional household survey that obtains socioeconomic and disease-specific questionnaire information, including knowledge, attitudes and behaviors related to TB. The data was collected from June 2016 to January 2017. The overall response rate of the survey was 98.5%. We studied the data of individual household questionnaire responses for respondents aged 15–49 years. Privacy of household members was thoroughly ensured [18]

3.2.2 Outcome Variables and Covariates

Awareness of TB contributes to enhancing understanding of screening necessity, knowledge of good access to health facilities, completion of treatment as per programmatic management, and monitoring and supervision via community engagement; these factors have effective impacts on reducing TB cases [19,20]. The outcome variable included in our study of TB awareness was defined as "people knowing about TB symptoms" and "having knowledge of TB treatment facilities." Data with both positive answers in the previous survey are regarded as dummy variable 1, or else. We considered access to healthcare services as a control variable in the analysis. The covariates included in our study were wealth quantiles, education, place of residence (urban and rural), province and owning a mobile phone. We selected the covariates based on previous empirical studies conducted in similar settings [12,21].

3.2.3 Statistical Analysis

We used descriptive statistics to analyze respondents' demographic and socioeconomic characteristics. A multilevel regression model was used to explain the relationship between outcome variables and covariates. The data from the NDHS are nested in multiple levels, i.e., hierarchical in nature. Therefore, we used a multilevel regression model with a random intercept at a cluster level to account for the cluster-level effect in our analysis. The selection of covariates for the multilevel model was based on the significant results obtained from the univariate regression analysis. Both descriptive and multilevel regression analyses were adjusted to the complex survey design using sample weighting. Data were analyzed using STATA 16 (StataCrop LLC, College Station, TX, USA) and R 4.0.3 (The R Foundation for Statistical Computing, Indianapolis, IN, USA).

3.3 Results

3.3.1 Summary of Socio-Demographic Characteristics of Respondents

The summary statistics of the respondent’s characteristics are described in Table 3.1. We included 16,672 respondents (76.1% female and 23.9% male) aged between 15 and 49 years in our analyses. Among them, 96% reported awareness of TB. The proportion of participants aged 15–24 was 38.5%, while for 35–49 years of age, it was 31.6%. Looking at the education level of the respondents, around 50% of respondents had an education lower than secondary level, while 16.7% of respondents had a higher level of education. 76.8% of the total respondents owned a mobile phone. Finally, more than half (63.2%) of the respondents lived in an urban area.

Table 3.1 Demographic and socio-economic characteristics of study participants, 2016

Characteristics	Number	Proportion (%)
Total	16,672	100
Gender		
Male	3978	23.9
Female	12,694	76.1
Age group		
15–24	6424	38.5
25–34	4991	29.9
35–49	5257	31.6
Educational attainment		
No formal education	4534	27.2
Primary education	2889	17.3
Secondary education	6459	38.8
Higher education	2790	16.7
Province		
Province 1 (Not determined)	2826	17.0
Province 2 (Not determined)	3323	19.9
Province 3 (Bagmati)	3670	22.0
Province 4 (Gandagi)	1604	9.6
Province 5 (Lumbini)	2886	17.3
Province 6 (Karmali)	915	5.5
Province 7 (Sudurpashchim)	1448	8.7
Owns a mobile phone		
No	3861	23.2
Yes	12,811	76.8
Residence		
Urban	10,543	63.2
Rural	6129	36.8

3.3.2 Proportion of People with TB Awareness at a Subnational Level in Nepal

The overall TB awareness at subnational levels in Nepal was above 90% across all provinces. Province 5 has the highest proportion of TB awareness (98.3%), followed by provinces 3 and 4 (97.4%); province 6 has the lowest awareness of all (93%) (Table 3.2; Figure 3.1).

Table 3.2 People with TB awareness at a subnational level in Nepal

	Proportion (95% Confidence Interval)
	TB Awareness
Province 1 (Not determined)	96.1 (95.3–96.7)
Province 2 (Not determined)	94.1 (93.3–94.9)
Province 3 (Bagmati)	97.4 (96.9–97.9)
Province 4 (Gandagi)	97.4 (96.5–98.1)
Province 5 (Lumbini)	98.1 (97.6–98.6)
Province 6 (Karmali)	93.2 (91.3–94.6)
Province 7 (Sudurpashchim)	94.5 (93.2–95.6)

TB: Tuberculosis.

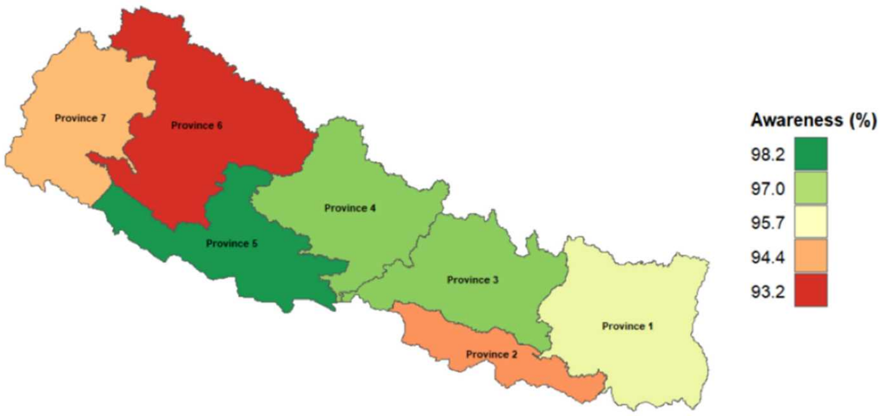

Figure 3.1 TB awareness at a subnational level in Nepal

Note: Provinces 1–7 represent the total number of provinces in Nepal. Province 1 = Not determined, Province 2 = Not determined, Province 3 = Bagmati, Province 4 = Gandagi, Province 5 = Lumbini, Province 6 = Karmali, Province 7 = Sudurpashchim.

3.3.3 Variables Associated with TB Awareness

The results of multilevel logistic regressions with a 95% confidence interval (CI), the odds ratio (OR) and respective p-values are presented in Table 3.3.

Table 3.3 Demographic and socioeconomic factors associated with TB awareness in Nepal, 2016

Variables	TB Awareness Odds Ratio (95% CI)
Age group	
15–24	1.00 (ref)
25–35	1.57 (1.19–2.08) **
35–49	1.61 (1.15–2.26) **
Gender	
Male	1.00 (ref)
Female	1.46 (1.05–2.04) *
Wealth quintile	
Poorest	1.00 (ref)
Poorer	1.74 (1.25–2.42) **
Middle	2.06 (1.44–2.94) ***
Richer	1.64 (1.14–2.36) **
Richest	3.46 (2.05–5.84) ***
Education	
No formal education	1.00 (ref)
Primary education	1.48 (1.10–1.99) *
Secondary education	5.36 (3.76–7.65) ***
Higher education	16.19 (8.04–32.58) ***
Owns a mobile phone	
No	1.00 (ref)
Yes	1.66 (1.30–2.10) ***
Province	
Province 6 (Karmali)	1.00 (ref)
Province 1 (Not determined)	0.87 (0.49–1.57)
Province 2 (Not determined)	0.79 (0.45–1.41)
Province 3 (Bagmati)	1.42 (0.74–2.71)
Province 4 (Gandagi)	1.21 (0.63–2.31)
Province 5 (Lumbini)	2.24 (1.26–3.97) *
Province 7 (Sudurpashchim)	0.84 (0.48–1.50)

TB: Tuberculosis. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

The odds of TB awareness among people in the richest quantile was 3.46 (95% CI 2.05–5.84) times higher compared to those in the poorest wealth quantile. In addition, the middle wealth quantile was also significantly related to TB awareness (OR 2.06, 95% CI 1.44–2.94). Respondents with higher education had significantly higher TB awareness (OR 16.19, 95% CI 8.04–32.58). Similarly, people with secondary level education had 5.36 (95% CI 3.76–7.65) times higher odds of being aware of TB compared to those with no formal education. Owning a mobile phone was significantly associated with TB awareness. Individuals owning a mobile phone had 1.66 (95% CI 1.30–2.10) times higher odds of being aware than those who did not own a mobile phone. Participants residing in province 5 were 2.24 (95% CI 1.26–3.97) times more likely to be aware of TB than those residing in province 6, which has the lowest proportion of TB awareness (Figure A3.1).

3.4 Discussion

The prevalence of bacteriologically confirmed TB cases in Nepal increased from 374.5/100,000 population between 2003 and 2018 to 416.3 in 2019 [22,23]. It is likely that poor TB awareness delays treatment-seeking, resulting in TB prevalence increase, rather than other factors such as accessibility or economic constraints [24]. Hence, why to reduce the prevalence of TB, it is essential to increase TB awareness at national and subnational levels in Nepal. We examined the relationship between socioeconomic factors and awareness of TB at the national and subnational levels in Nepal. The results of our analysis indicated that wealth quintiles, education level, owning a mobile phone, and region of residence were significantly associated with higher TB awareness in Nepal. People in the richest quintile have two times higher odds of being aware of TB compared to those in the poorest wealth quintile. This could be because the people in the richer and richest wealth quintiles tend to have better access to information and knowledge about TB symptoms than those in lower quintiles (the poorest and poorer).

Similar results were obtained from the studies conducted in neighboring countries such as Pakistan and India [13,25]. In the case of Pakistan, it was found that more than half of households living in rural areas were of low socioeconomic status and had limited access to TB healthcare services [13]. Likewise, people of poor socioeconomic status in India—in particular, those living in poverty—were found to have a higher risk of an increased number of TB cases than those of higher socioeconomic status, partly because of lower access to quality healthcare services [25]. Nepal is a low-income country and 25% of its population lives below the poverty line [26,27]. People living in rural areas face a greater risk of delayed TB healthcare and treatment due to poor TB knowledge and limited access to basic health facilities [15,16].

Based on our findings, people who have completed secondary or higher education have more than five times higher odds of being well informed about TB compared to those without any formal education. This could be because people with secondary or higher education are more proactive about acquiring health information and are more concerned about their health than those without formal education [12,17]. According to some recent studies, people with a high education level know the symptoms of TB and recognize TB as a curable disease [11]. In addition, it has been found that there is a significant correlation between high school completion and TB knowledge in Africa [12]. Those findings support our result and suggest that a high socioeconomic status together with a high education level is strongly correlated with TB awareness and knowledge in LMICs. People who own a mobile phone have 1.6 times higher odds of having awareness of TB compared to those who do not own a mobile phone. Due to increased affordability, mobile phone ownership has grown in LMICs [28]. It is estimated that around 81% of the total population of Nepal own mobile phones, which are now the most common information and communication devices [18].

Moreover, Nepalese mobile-cellular subscriptions per 100 inhabitants were estimated as 111.7 in 2017, the same level as in high-income countries [28].

Due to this access, there is considerable potential for the use of mobile phones in TB healthcare systems. Examining digital health and information and communication technology (ICT), Lester et al. [29] found that improvement of TB care adherence by using smartphones to communicate with patients may be an effective support for healthcare systems in LMICs. A case in point: in Cambodia, 97% of mobile phone users with TB can access TB health facilities in targeted intervention areas [30]. The growth of mobile phone use in relation to the health system offers a life-enhancing opportunity in LMICs, particularly for people of low socioeconomic status [31]. Planning better community engagement with digital communication tools for infection control is an important challenge [32], but it is necessary to understand the ICT for community-based adaption to health systems in LMICs because of resource limitations [33]. The utilization of smartphones in this context offers potential benefits such as supporting frequent communication and facilitating remote advice for patients, to provide faster, more accessible and more affordable TB healthcare information [2,8]. The diffusion of mobile phone usage in healthcare systems increases the need to understand that it is essential to enhance communication between healthcare providers and people with TB. Our findings indicate that using mobile phones to increase TB awareness could be an effective strategy to support a community-based healthcare approach to eliminating TB at the national and subnational levels in Nepal.

The region of residence variable was also significantly associated with the level of TB awareness. For instance, Table 3.2 indicated that province 3, 4, and 5 have the highest level of TB awareness; Table 3.3 showed that people living in province 5 are twice as likely to be aware of TB than those living in province 2, which has the lowest level of TB awareness among all provinces. One of the reasons for that difference could be the fact that several TB programs have been implemented by international non-governmental organizations, such as the TB health support provided by the Japan International Cooperation Agency (JICA), starting from 1987. The final development phase by JICA was conducted from 2000 to 2005, focusing development assistance on provinces 3 (Kathmandu) and 5 (Rupandehi). Through a JICA assistance project, Japanese health experts provided technical training to medical workers to improve their healthcare skills at a Directly Observed Treatment Short-Courses (DOTs) center and sub-healthcare centers in provinces 3 and 5 [34]. JICA's TB health assistance report found that a multi-dimensional approach to decrease the burden of TB has the potential to support quality TB healthcare services in the local communities in Nepal [35]. Several orientations and workshops were conducted, for medical staff and mother's groups, in provinces 3 and 5 through JICA's TB project [34]. Resulting changes in those people's behavior toward TB are supportive of a holistic and community-centered approach in healthcare systems led by workshops. It is proposed that people aware of TB who are living in provinces 3 and 5 could facilitate others' TB awareness for several years.

Further development assistance projects may also be conducted to maintain TB health at a community level; this needs to be factored into the complex situation. Another reason for greater awareness in province 3 could be the fact that it is urbanized. The capital city of Nepal is located in province 3, along with many other cities with a high number of healthcare facilities. Indeed, patients with TB in province 3 have the highest TB treatment success rate (94%) thanks to the high number of healthcare facilities, including TB treatment centers, DOTs centers and TB laboratories, compared to other provinces [23]. From the above, it is evident that living in an urban area is one of the factors associated with TB awareness in Nepal.

This research faced the inevitable problem related to household survey analysis: participants whose information was not complete were excluded from the study. Moreover, the analysis on TB awareness behavior of the participants without a mobile phone (23.2%) may not be covered appropriately. This gap should be filled with further investigation. Most importantly, people aged 49 and over were excluded from our study because of data limitations. This exclusion could have led to an overestimation of the TB-aware population, if older citizens were less likely to be aware of TB. Secondly, TB awareness could be influenced by several factors including those related to distance from healthcare facilities, attitude of service providers, and disease complications. However, due to limited data availability, we could not include and analyze those factors. Finally, several TB awareness programs were conducted in different regions of Nepal, which could have affected regional awareness. A thorough analysis of TB programs based on residents' affordability could enhance the findings of this study in the future.

3.5 Conclusion

Our study examined the demographic and socioeconomic factors associated with TB awareness at the national and subnational levels in Nepal. The results of the study highlighted that socioeconomic determinants such as wealth quintile, level of education, and owning a mobile phone were significantly associated with TB awareness at the national and regional levels. The high level of awareness at a regional level emphasizes the importance of formulating tailored strategies to increase TB awareness. The use of mobile phones could be an effective strategy to promote TB awareness at a regional level. The policy implementation of a mobile-focused approach for medical infrastructure could improve TB awareness and access to treatment, effectively and affordably. This study provides valuable evidence to support further research on the contribution of ICT usage to improving TB awareness in Nepal. Further research is required to understand the possible mechanisms that affect the underlying factors determining TB awareness in the context of Nepal, to help to promote and support TB elimination in Nepal.

Institutional Review Board Statement: Ethics approval and consent to participate, Ethical Approval Nepal, obtained from Institutional Review Board, ICF International. Nepal ICF Project Number: 132989.0.000.NP.DHS.01.

Conflict of interest and Informed Consent Statement: The authors declare no conflict of interest and Informed Consent Statement is not applicable.

Data Availability Statement: The datasets analyzed during the study are available in the Demo- graphic and Health Surveys of the DHS repository, https://dhsprogram.com/data/dataset/Nepal_ Standard-DHS_2016.cfm?flag=0 (accessed on 3 February 2021).

3.6 Appendix

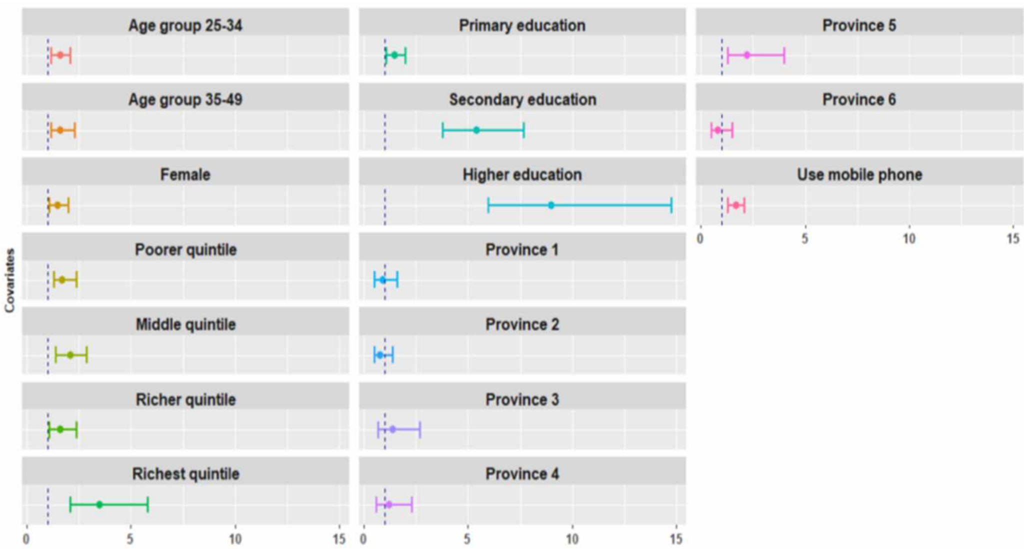

Figure A3.1 Factors associated with TB awareness

3.7 References

[1] World Health Organization (WHO), Global Tuberculosis Programme., (1994). TB: a global emergency, WHO report on the TB epidemic, Available online: https://apps.who.int/iris/handle/10665/58749 (accessed on January 28 2021).

[2] WHO, *Global Tuberculosis Report.*, (2020). Available online: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf (accessed on 14 October 2020).

[3] Yadav, S., (2015) A new concept in tuberculosis awareness in the low-income countries. *Edorium J Tuberc*. 2015; 1, 1-4.

[4] Narayan, B., (2015). Tuberculosis in India: A need of Public Awareness & Education. *University of Mauritius Research Journal*. 1-27.

[5] Desalu, O.O., Adeoti, A.O., Fadeyi, A., Salami,A.K., Fawibe, A.E., Oyedepo, O.O., (2013). Awareness of the Warning Signs, Risk Factors, and Treatment for Tuberculosis among Urban Nigerians. *Tuberc Res Treat*. 2013:369717, 1-5.

[6] Gurp, M.G., Rood, E., Fatima, R., Joshi, P., Verma, S.H., Khan, A.H., Blok, L., (2020). Mergenthaler.C.; Bakker.I. Finding gaps in TB notifications: spatial analysis of geographical patterns of TB notifications, associations with TB program efforts and social determinants of TB risk in Bangladesh, Nepal and Pakistan. *BMC Infectious Diseases*. 20, 1-14.

[7] Ehsanul Huq, K.A.T.M., Moriyama, M., Zaman, K., Chisti, MJ., Long, J., Islam, A., Hossain, S., Hirin, H., Raihan, MJ., Chwdhury, S., Rahman, M.M., (2018). Health seeking behaviour and delayed management of tuberculosis patients in rural Bangladesh. *BMC Infect Dis*. 18-515, 1-9.

[8] National Tuberculosis Center, Department of Health Services, Ministry of Nepal, *National Strategic Plan for Tuberculosis prevention, care and control 2016-2021.*, (2018). Available online: https://nepalntp.gov.np/wp-content/uploads/2018/01/NSP-report-english-revised.pdf (accessed on 3 February 2021).

[9] National TB control center. Ministry of health and population. Government of Nepal. TB burden in Nepal. 24th March 2020. Available online: https://www.who.int/docs/default-source/nepal-documents/policy-brief.pdf?sfvrsn=37b5881c_2 (accessed on 3 February 2021).

[10] National Tuberculosis Center, Department of Health Services, Ministry of Nepal, National Tuberculosis Management Guidelines 2019 Available online: https://nepalntp.gov.np/wp-content/uploads/2019/10/National-Tuberculosis-Management-Guidelines-2019_Nepal.pdf (accessed on 3 February 2021).

[11] Huddart, H., Bossury, T., Pons, V., Baral, S., Pai, M., Delavallade, C., (2018). Knowledge about tuberculosis and infection prevention behavior: A nine city longtuginal study in India. *PLoS ONE*. 13(10): e0206245, 1-15.

[12] Naidoo, P., Simbayi, L., Labadarios, D., Ntsepe, Y., Bikitsha, N., Khan, G., Sewpaul, R., Rehle, T., (2016). Predictors of knowledge about tuberculosis: results from SANHANES I, a national, cross-sectional household survey in South Africa. *BMC Public Health*. 276 (2016), 1-12.

[13] Khan, A., Shaikh, BT., Bain, M.A., (2020). Knowledge, Awareness, and health seeking behavior regarding TB in Rural district of Khyber Pakhtunkhwa, Pakistan. *MioMed research international*. 1-6.

[14] Paul, S., Akter, R., Aftab, A., Khan, A.M., Barua, M., Islam, S., Islam, A., Husain, A., Sarker, M., (2015). Knowledge and attitude of key community members towards tuberculosis: mixed method study from BRAC TB control areas in Bangladesh. *BMC Public Health*. 31; 15:52, 1-8.

[15] Mishra, P., Hansen, E.H., Kafle, K.K., (2005). Socio-economic status and adherence to tuberculosis treatment: a case-control study in a district of Nepal. *Int J Tuberc Lung Dis.* 9(10), 1134–1139.

[16] Ten Asbroek, A.H., Bijlsma, M.W., Malla, P., Shrestha, B., Delnoij D, M.J., (2008). The road to tuberculosis treatment in rural Nepal: A qualitative assessment of 26 journeys. *BMC Health Serv Res*. 8-7, 1-10.

[17] Christian, C., Burger, C., Claassens, M., Bond, V., Burger, R., (2019). Patient predictors of health-seeking behaviour for persons coughing for more than two weeks in high-burden tuberculosis communities: the case of the Western Cape, South Africa. *BMC Health Serv Res*. 160 (2019), 1-8.

[18] Ministry of Health, Ramshah Path, Kathmandu Nepal. Nepal Demographic and Health Survey (NHDS)., (2016). Available online: https://www.dhsprogram.com/pubs/pdf/fr336/fr336.pdf (accessed on 1 February 2021).

[19] WHO. End TB strategy., (2014). Available online: https://www.who.int/tb/strategy/End_TB_Strategy.pdf (accessed on 16 February 2021).

[20] Li, J., Chung, P.H., Leung, C.L.K., Nishikiori, N., Chan, E.Y.Y., Yeoh, E.K., (2017). The strategic framework of tuberculosis control and prevention in the elderly: a scoping review towards End TB targets. *Infect Dis Poverty*. 1;6(1):70,1-12.

[21] Rauniyar, S.K., Rahman, M.M., Rahman, M.S., Abe, S.K., Nomura, S., Shibuya, K., (2020). Inequalities and risk factors analysis in prevarence and management of hypertension in India and Nepal: a national and subnational study. *BMC Public Health*. 20:1341, 1-11.

[22] Government of Nepal, Ministry of Health and Population Department of Health Services, National Tuberculosis Control Centre, National TB Prevalence Survey 2018/2019. Available online: http://impacttbproject.org/wp-content/uploads/2020/03/TBPS%20Summary%20Report_English_Final_21%20March%202020.pdf (accessed on 3 February 2021).

[23] Government of Nepal, Ministry of Health and Population Department of Health Services, National Tuberculosis Program Nepal Annual Report 2075/76 (2018/19). Available online: https://nepalntp.gov.np/wp-content/uploads/2020/04/NTP-Annual-Report-2075-76-2018-19.pdf (accessed on 1 February 2021).

[24] Marahhata, S.B., Yadav, R.Y., Giri, D., Lama, S., Rijal, K.R., Mishra, S.R., Shrestha, A., Bhattrai, P.R., Mahato, R.K., Adhikari, B., (2020). Barriers in the access, diagnosis and treatment completion for tuberculosis patients in central and western Nepal: A qualitative study among patients, community members and health care workers. *PLoS ONE*. 15(1), 1-18.

[25] Oxlade, O., Murray, M., (2012). Why Are the Poor at Greater Risk in India?. *PLoS ONE*. 7(11), 1-8.

[26] Adhikari, N., Joshi, L.R., Subedi, B., Acharya, D., Adhikari, M., Thapa, P., Sultana, R., Karki, K.B. , (2019). Tuberculosis in Nepal: Situation, Challenges and Ways Forward. *SAARC J. Tuberc. Lung Dis*. HIV/AIDS, 17, 34–40.

[27] Asian Development Bank, Country Poverty Analysis Nepal 2011. Available online: https://www.adb.org/countries/nepal/poverty (accessed on 1 February 2021).

[28] International Telecommunication Union (ITU), Global ICT Development Index 2017. *Measuring the Information Society Report 2017*. Available online: https://www.itu.int/en/ITU-D/Statistics/Pages/publications/mis2017.aspx (accessed on 1 February 2021).

[29] Laster, R., Park, J.J.H., Molten, L.M., Enjetti, A., Johnston, J.M., Schwartzman, K., Tilahun, B., Delft, A.M.V., Zachariah, R., (2019). Mobile phone short message service for adherence support and care of patients with tuberculosis infection: Evidence and opportunity. *J Clin Tuberc Other Mycobact Dis*. 16, 100-108.

[30] Choun, K., Achanta, S., Naik, B., Tripathy, J.P., Thai, S., Lorent, N., Khun, K.E., Griensven, J.V., Kumar, A.M.V., Zachariah, R., (2017). Using mobile phones to ensure that referred tuberculosis patients reach their treatment facilities: a call that makes a difference. *BMC Public Health*. 17:575, 1-7.

[31] GSMA Intelligence. Accelerating Affordable Smartphone Ownership in Emerging Markets 2017. Available online: https://www.gsma.com/mobilefordevelopment/wp-content/uploads/2018/08/Accelerating-

affordable-smartphone- ownership-in-emerging-markets-2017_we.pdf (accessed on 28 February 2021).

[32] Lee, V.L., Ho, M., Kai, C.W., Aguilera, X., Wilder-Smith, A., (2020). Epidemic preparedness in urban settings: new challenges and opportunities. *The Lancet*. 20-5, 527-529.

[33] Nomura, S., Siesjo, V., Tomson, G., Mohr, W., Fukuchi, E., Shibuya, K., Tangcharoensathien, V., Miyata, H., (2020). Contributions of information and communications technology to future health systems and Universal Health Coverage: application of Japan's experiences. Health Res. *Policy and Syst*. 18:73, 1-9.

[34] Japan International Cooperation Agency (JICA). *Project report of Tuberculosis and Pulmonary Health Project in Nepal 2005*. Available online: https://openjicareport.jica.go.jp/986/986/986_116_11831963.html (accessed on 1 February 2021).

[35] JICA. Outline of Cooperation in Nepal 2019. Available online: https://www.jica.go.jp/nepal/english/office/others/c8h0vm00009vyd39-att/brochure_12.pdf (accessed on 1 February 2021).

Chapter 4

Cost-benefit analysis of pre-entry tuberculosis screening policy: Nepalese and Japanese perspectives

4.1 Introduction

Respiratory infections are now a major health concern worldwide with the most serious recent lung infection coronavirus disease (COVID-19), declared by the World Health Organization (WHO) a public health emergency of international concern (PHEIC) in January 2020 [1]. Equally threatening, tuberculosis (TB), a respiratory tract infection [2], was declared a global health emergency in 1993 [3]. Up to 2019, TB remains the world's biggest infectious killer, taking more than 1.5 million lives in 2018 [4]. Despite efforts to eliminate TB, countries with low incidence of TB experience high concentrations of cases in at-risk groups as a result of cross-border migration related to globalization [5]. High-income countries are now concerned about TB morbidity and mortality, mainly the result of the arrival of individuals born in low income countries with high TB burden [6]. The WHO TB framework ***End TB*** by 2035 has identified migration by individuals infected with TB as a priority target for action in low incidence countries [7].

In the past few decades, Japan has been receiving increased numbers of migrants, including visitors, students, and workers from overseas. In 2019, the total number of migrant workers from Nepal in Japan was 91,770, making Nepalese third largest migrant group an increase of 12.5% over the previous year [8]. In 2019, Nepal was designated the first country to sign an agreement with Japan for specific-skilled migrant workers, aimed at greater transparency under Japan's immigration control and refugee recognition act [9]. Although good connections and friendship have been established through development projects for health, education, and tourism between Nepal and Japan [10], the number of migrant workers with TB has increased steadily in recent years [11]. In 2018, 1,667 foreign-born migrants with TB were reported in Japan, accounting for 10.2% of Nepalese migrant cases [12]. In fact, the yearly increase in number of Nepalese TB cases could increase the number of newly identified TB cases in the native Japanese population [13].

Studies indicate that to reduce the number of active TB cases among incoming migrants a pre-entry TB screening program is essential [14]. However, Japan has not implemented a mandatory pre-entry TB screening policy for applicant migrants as part of its visa application process, because a pre-entry screening requirement for all migrants would inflict an economic burden on migrants and their home countries, and could even damage the general population's health due to exposure.

Nevertheless, due to the seriousness of the issue of migrants with TB, the Japanese government finally decided to introduce a TB pre-entry screening requirement for middle- to long-term applicants from countries with a high number of TB cases (China, Indonesia, Myanmar, Nepal, the Philippines, and Vietnam), effective 2020 [15]. However, that action is insufficient in light of the estimated economic impact of the pre-entry TB screening policy on social cost. This study examined the expected cost and benefit of pre-entry TB screening policy on both Japan and Nepal for the period 2014–2018. The aim of that assessment is to support confidence-building and achieve mutual value for the partner countries.

4.2 Methods

4.2.1 Policy scenarios for analysis

Due to the increased number of TB patients in Japan from high-risk TB incidence countries, Japanese government policy requires pre-entry TB screening to identify migrants with TB [15]. TB screening for migrants is implemented as a mandatory part of the visa application procedure targeting five high-burden TB incidence countries, including Nepal [16]. In Figure 4.1, the left flow presents the with policy implementation scenario, where visa applicants should undergo TB screening in their country of origin. TB screening includes a general health check-up (health background check, physical examination, and chest radiography (CXR)), in line with the Japanese Pre-entry TB Screening (JPETS) procedure [17]. Mycobacterium tuberculosis analysis of three sputum smears and a culture examination are required if the results of the general health check-up suggest active TB. TB diagnosed applicants are not allowed entry into Japan until completion of TB treatment in line with WHO treatment guidelines, as well as the national TB protocol. Applicants are required to provide including appropriate certification that they are free of TB.

The right flow in Figure 4.1 presents the current without policy implementation scenario, where clinical TB screening of migrants is conducted within Japan. If the migrants present initial TB symptoms, they take a basic TB clinical examination as part of a general health check-up at clinic or hospital which ensure whether the patient has a suspected TB infection. The migrants must take a Mycobacterium tuberculosis examination of three sputum smears if TB infected.

If the sputum test or Polymerase Chain Reaction (PCR) perform positive and the migrants is diagnosed with TB, the physician sends the resident to a TB-specific medical facility or hospital for TB treatment to completion as specified in Japan's TB treatment protocol.

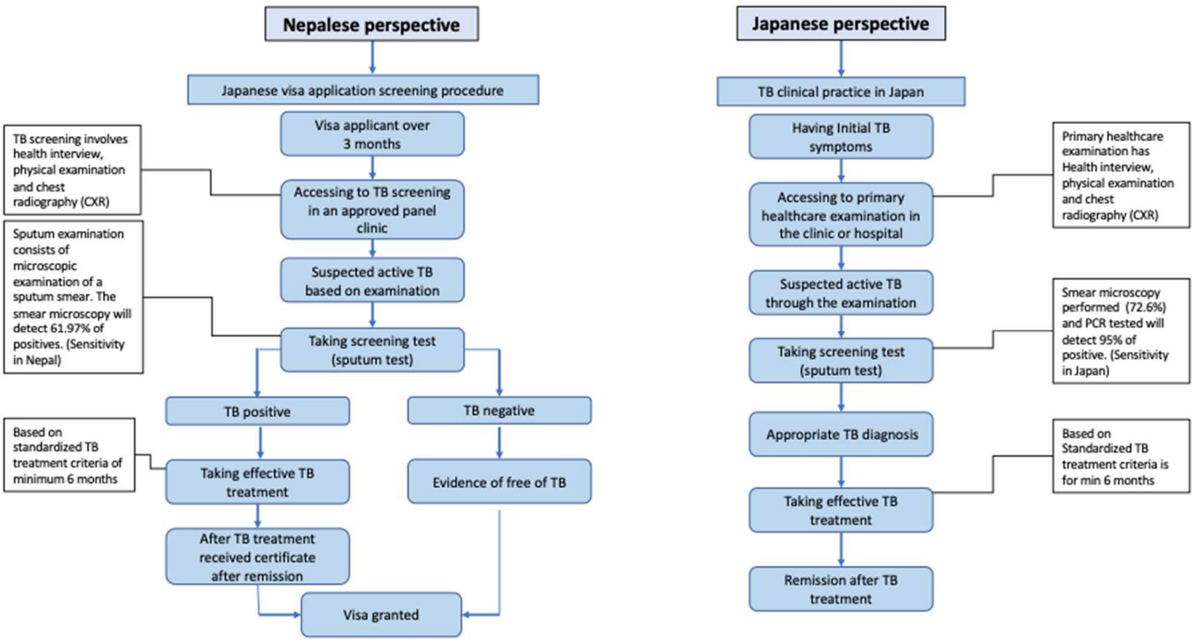

Figure 4.1 Policy scenario: TB screening procedure in Nepal and Japan

4.2.2 Analytical framework

The expected impacts of pre-entry TB screening policy were assessed using cost-benefit analysis approach. The analytical period was set within one year of each of 2014 to 2018, when the pre-entry TB screening policy still had not been introduced. In this CBA, total cost, total benefit and net benefit for Japan and Nepal were measured and these values for "*with pre-screening policy*" scenario and "*without pre-screening policy*" scenario are compared. Cost is measured as the fees for TB screening testing of migrants and TB treatment of patients with TB. Benefit is measured as the avoidance of capacity loss (wage × labor) of foreign migrants with TB through by means of incidence risk reduction. Finally, the sensitivity analysis is conducted by Monte Carlo simulation. From Japan's perspective, costs are covered by Universal Health Coverage (UHC), which provides effective coverage performance for improving health outcomes and reducing patients cost via equitable health services for all [18,19]. Japan publicly funded TB healthcare enables patients with independent residency and national health insurance status to access healthcare services, and the cost of TB-related healthcare services is fully subsidized [20,21]. On the other hand, in Nepal, individuals have to pay the full cost of health services because of insufficient coverage UHC, with some exceptions [22].

4.2.3 Estimation of active TB population

The target population of this study is foreign-born migrants who plan to acquire Foreign Resident status by first applying for a visa for middle- to long-term duration of stay in Japan [9]. The foreign residents with TB include those with permanent, study abroad, technical intern, migrant, accompanying family, Japanese spouse, and others Japanese residence status [12]. Data on foreign residents to Japan and on TB cases in Japan were collected from the Legal Affairs Bureau Japan and the Tuberculosis Surveillance Center Japan, respectively. TB Incidence data of Nepal are sourced from Nepal Demographic and Health Survey and Annual Report by Nepal's Department of Health Service (DHS) [23]. The cumulative incidence of TB as an annual figure was calculated by dividing the total population by the number of TB patients predicted under policy implementation during the study period.

For estimation of the active TB population in Japan under the policy of pre-entry TB pre-screening diagnostic tests, the screening test sensitivity ratio is a key prediction value. The ratio is defined to be the number of true positive cases divided by the number of all positive predictive cases (PPV). TB diagnosis depends on the result of sputum smear microscopy test, which can detect either smear-positive or non-infectious [24]. We estimate the predicted active TB population with the screening test sensitivity ratio. Kurumi et al. [25] found the screening test sensitivity ratio of sputum smear microscopy test in Nepal to be 62% in 2016. The sputum smear microscopy test is low cost and easy to perform, even in developing countries, while only a few PCR screening methods have been made available in Nepal's health facilities since 2015 [26]. On the other hand, the sensitivity of smear microscopy performance in Japan is around 72% [27] while the PPV of PCR is over 95% [28]. Thus, we adopted PCR as the test for Japan. Detailed statistical formula is described in supplementary Method 1-1.

4.2.4 Present Condition

In our calculations of the population under the without-policy scenario (i.e. testing conducted in Japan) we used number incidence of TB based on data provided by the Tuberculous Research Institute. In the Japan with-policy scenario, total possible active TB population equals the number of TB false-negative cases in screening tests in Nepal. The difference in predicted active TB cases between with-policy and without-policy can be estimated as the number of active TB cases prevented by implementation of the policy.

Likewise, under the with-policy scenario (i.e. testing conducted in Nepal), the screening test sensitivity ratio was 62%, indicating that 62% of TB population could be detected without entering Japan; while 38% of the TB population was false negatives and was allowed entry to Japan. Our analysis predicts the total possible active TB population in Japan without policy by dividing the number of total TB cases detected in the screening tests by the screening test sensitivity ratio to estimate the number of TB patients in the active TB population (including false negatives). In the assumption of the transmission rate, there is no specific number for transmission rate, we thus calibrated from serial interval (SI), which is widely used in describing transmission of an infectious disease. The transmission 150% is computed from the average SI (1.5) from 56 publications, while removing the outliner [53,54].

From the Japanese perspective, the size of the active TB population is calculated as (Nepalese resident with TB in Japan／Screening test sensitivity ratio [95%]) × transmission rate [150%] in the without-policy scenario; and (Nepalese resident applicants to Japan×incidence rate in Nepal／Screening test sensitivity ratio [62%]－Nepalese resident applicants to Japan×Incidence rate in Nepal)× transmission rate [150%] in the with-policy scenario.

From the Nepalese perspective, there have been active Nepalese TB cases in Japan, and thus no direct benefit for Nepal in the without-policy scenario; the size of active TB population is calculated as (Nepalese resident applicants to Japan×incidence rate in Nepal／Screening sensitivity test ratio [62%]－False negative cases)×transmission rate [150%] in With-policy scenario.

4.2.5 Expected impact on the cost and benefit

The expected impact of the different hypothetical policy scenarios can be measured by comparing cost and benefit of "with policy" and "without policy" for both Japan and Nepal (Figure 4.2). There are two national perspectives, with-policy and without-policy. Thus, we have a prediction of the outcomes of the two scenarios, in terms of cost, benefit, and net benefit (benefit minus cost) monetized in local currency with consideration of inflation rate.

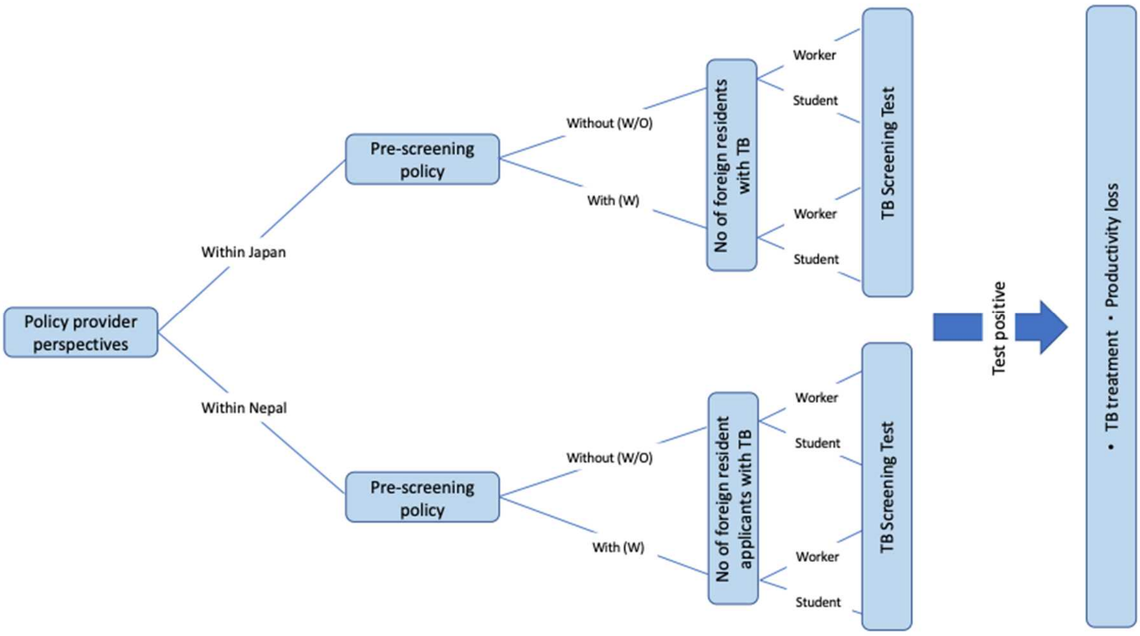

Figure 4.2 Policy scenario: Policy simulation algorithm

4.2.6 Cost of TB screening test

The full cost is presented as local prices in US dollars with inflation and the exchange rate of each year, according to Financial Statistics of the International Monetary Fund (IMF) [29]. All costs were reported within each year from 2014 to 2018 as total social cost from each national perspective. The data for Japanese local cost including cost of TB screening and treatment is taken from National Database (NDB) [30]. TB test prices in Nepal are drawn from the guidance for TB testing by UK [31], and treatment cost is quoted from Gurung et al. [32]. Costs of TB testing and treatment reflect the different approaches to screening and treatment under WHO guidelines for treatment criteria and National TB methodology. The screening cost consists of general health check-up, examination of three sputum smears, PCR, chest radiography, and standardized basic clinical TB examination. Indirect costs of transportation, caregiver or health worker time, etc. are not within the scope of our analysis [33].

4.2.7 Cost of TB treatment

The cost of the TB treatment drug regimen is calculated as the total number of tablets required for six months' treatment with the first-line drugs specified in both the WHO guideline and national TB methodology. The first-line drugs include Rifampicin (RFP), Pyrazinamide (PZA), Isoniazid (INH), and Rifabutin (RBT), as per the 2018 Japanese TB treatment guideline [34]. We calculated the cost of these drugs taken three times a day for six months; pre-treatment phase to the intensive period as the TB treatment in Nepal [32].

4.2.8 The benefit by avoidance of capacity loss

Cost of TB treatment includes medical expense, income and time loss resulting from undertaking TB treatment for a minimum of six months. The treatment requires that the patient be isolated, which would reduce the patient's income [35]. In that light, the assumption of benefit considers the avoidance of capacity loss by both patient and nation through incidence risk reduction via policy implementation. We estimate average monthly wages in Japan using sectoral data from the Ministry of Health, Labour, and Welfare in Japan [36], and in Nepal using monthly GNI per capita obtained from IMF [37] (constant LCU: local currency unit for one year).

Our primary estimation of the net present value (NPV) of implementation of the policy equals the difference between the present value of the social benefit (PVsb) and the present value of social cost (PVsc). From the Japanese perspective, NPV = 0－Total implement fee－Total capacity loss; while form the

Nepalese perspective, NPV = 0 − Incremental test fee − Total treatment fee − Total capacity loss. In that light, we need to estimate the impact of implementation of policy as an incremental net social benefit (NSB) = Net benefit in With-policy scenario − Net benefit in Without-policy scenario. We provide the statistical formula in more detail in supplementary Method 1-2.

4.2.9 Sensitivity analysis

The NPV is likely uncertain due to changes in the value of key input parameters, uncontrollable factors of epidemics, such as the chance of infecting other people could affect the benefit and cost that would be anticipated by the proposed policy. In Monte Carlo simulation of TB transmission impact, the probability of distribution in the population is a key input parameter for all essential uncertain quantitative estimations. For instance, the interval of sensitivity analysis in Cyprus presented 0–10% and 10–25% [14]. Given the fact of large economic impacts such as inflation, deflation and unemployment rate in Nepal and Japan, WHO key facts suggest that people carrying TB bacteria have a 5–15% chance of falling ill with TB [38]. We thus calibrate the parameters of increase and/or decrease of the incidence of TB probability over the intervals 0–15% and 15–30%.

4.2.10 Conceptualization toward burden sharing

The With-policy scenario requires Nepal to take on the additional costs of TB screening test of migrants to Japan. In high burden TB countries, out-of-pocket (OOP) expenditures have accounted for at least 45% of total health expenditures [39], and more than 50% in Nepal [40] due the absence of UHC [41]. They are suffering increased health-related financial difficulties in terms of OOP expenditure and access to healthcare. The catastrophic cost of healthcare (i.e. TB detection, care and treatment) in high TB burden countries called for affordable TB-specific interventions and sustainable mechanisms for financing those interventions, as well as progress under UHC [42]. Thus, it would be more equitable to develop a methodology of burden sharing so as to consider the net benefit of Japan and Nepal in calculations of appropriate share of investment transfer, so as to maximize Nepal's incentive to develop public health infrastructure for TB screening tests, care and treatment for disease prevention and control.

4.3 Results

The predicted numbers of active TB cases and NSB for workers/students

(2014 to 2018) in Japan and Nepal are shown in Table 4.1. For Japan, the predicted number of active TB cases increased for both with- and without-policy. Still, the percentage of active TB cases among students is higher than that among workers. Significantly, the outcome of fewer cases of active TB in the With-policy case constitutes reduction of active TB incidence risk. In addition, increased worker NPV under the TB screening policy in 2014 was estimated at USD 1.12 million and increased to USD 3.00 million in 2018. In turn, the result of the increase of student NPV was a positive, USD 1.92 million in 2014, and grew substantially to USD 2.90 million in 2018. The increase in NPV was greater than zero, which implies that the implementation of the TB screening policy in Japanese society could produce a significant benefit in terms of prevention of increased number of cases of active TB. For Nepal, the predicted number of Nepalese with active TB increased, with student incidence greater than that for workers. Student NPV decreased from −USD 3.93 million in 2014 to −USD 8.11 million in 2018, where pre-entry TB screening policy was implemented. Total NPV for Nepal was negative due to the total cost being higher than the benefit (capacity loss), which indicates the imposition of the burden of direct cost, including testing and treatment costs, on Nepalese society.

Table 4.1 Number of predicted active TB cases and net social benefit for workers/students in Japan and Nepal

Perspective within Japan

TB pre-screening Policy (Worker)		Population (Active TB Cases)	Total cost	Total benefit	Net benefit	Incremental net benefit (With - Without)
without policy (Current)	2014	45.71	USD 621,528	USD -929,572	USD -1,551,100	USD NA
	2015	71.45	USD 847,293	USD -1,285,992	USD -2,133,285	USD NA
	2016	80.84	USD 1,068,189	USD -1,597,162	USD -2,665,351	USD NA
	2017	120.32	USD 1,541,281	USD -2,328,357	USD -3,869,637	USD NA
	2018	114.16	USD 1,485,082	USD -2,254,007	USD -3,739,088	USD NA
with policy (Proposed)	2014	12.68	USD 172,443	USD -257,910	USD -430,353	USD 1,120,747
	2015	14.89	USD 176,625	USD -268,076	USD -444,701	USD 1,688,584
	2016	16.86	USD 222,791	USD -327,831	USD -543,827	USD 2,040,236
	2017	19.64	USD 251,536	USD -376,097	USD -627,633	USD 3,242,004
	2018	22.31	USD 290,189	USD -440,438	USD -730,627	USD 3,008,462

TB pre-screening Policy (Student)		Population (Active TB Cases)	Total cost	Total benefit	Net benefit	Incremental net benefit (With - Without)
without policy (Current)	2014	91.58	USD 1,245,203	USD -1,862,355	USD -3,107,557	USD NA
	2015	96.32	USD 1,142,207	USD -1,733,602	USD -2,875,809	USD NA
	2016	129.47	USD 1,710,771	USD -2,557,955	USD -4,268,726	USD NA
	2017	134.21	USD 1,719,276	USD -2,597,248	USD -4,316,525	USD NA
	2018	150.00	USD 1,951,353	USD -2,961,696	USD -4,913,049	USD NA
with policy (Proposed)	2014	34.82	USD 473,500	USD -708,178	USD -1,181,678	USD 1,925,879
	2015	40.90	USD 484,984	USD -736,091	USD -1,221,075	USD 1,654,734
	2016	46.30	USD 611,746	USD -914,687	USD -1,526,433	USD 2,742,294
	2017	53.92	USD 690,675	USD -1,043,377	USD -1,734,052	USD 2,582,473
	2018	61.25	USD 796,809	USD -1,209,370	USD -2,006,179	USD 2,906,869

Perspective within Nepal

TB pre-screening Policy (Worker)		Population (Active TB Cases)	Total cost	Total benefit	Net benefit	Incremental net benefit (With - Without)
without policy (Current)	2014	NA	0	0	0	0
	2015	NA	0	0	0	0
	2016	NA	0	0	0	0
	2017	NA	0	0	0	0
	2018	NA	0	0	0	0
with policy (Proposed)	2014	20.73	USD 3,094,977	USD -2,970	USD -3,097,947	USD -3,097,947
	2015	24.25	USD 3,953,348	USD -3,397	USD -3,956,745	USD -3,956,745
	2016	27.45	USD 4,782,953	USD -3,660	USD -4,786,612	USD -4,786,612
	2017	32.00	USD 5,922,683	USD -4,673	USD -5,927,356	USD -5,927,356
	2018	36.51	USD 6,575,916	USD -5,290	USD -6,581,205	USD -6,581,205

TB pre-screening Policy (Student)		Population (Active TB Cases)	Total cost	Total benefit	Net benefit	Incremental net benefit (With - Without)
without policy (Current)	2014	NA	0	0	0	0
	2015	NA	0	0	0	0
	2016	NA	0	0	0	0
	2017	NA	0	0	0	0
	2018	NA	0	0	0	0
with policy (Proposed)	2014	56.93	USD 3,929,613	USD -8,155	USD -3,937,768	USD -3,937,768
	2015	66.60	USD 4,932,007	USD -9,328	USD -4,941,335	USD -4,941,335
	2016	75.36	USD 5,883,405	USD -10,049	USD -5,893,454	USD -5,893,454
	2017	87.87	USD 7,264,374	USD -12,830	USD -7,277,204	USD -7,277,204
	2018	100.24	USD 8,100,501	USD -14,524	USD -8,115,025	USD -8,115,025

Note: Exchange rates based on the average rate according to IMF Statistics

We applied 0–15% and 15–30% sensitivity analysis in a Monte Carlo simulation as the secondary transmission rate on incremental NPV for both perspectives in order to address parameter difference uncertainty. The NPV for Japan increased depending on the TB incidence rate in each interval on the transmission scale. When a high 15% increase in TB transmission rate might indicate a high risk of becoming infected, the output would increase student NPV from USD 2.07 million to USD 3.12 million for 2018 (Table 4.2). In contrast, the negative value of NPV distribution among Nepalese students increased to －USD 8.72 million in 2018 (Table 4.3)—very costly when the risk of transmission rates increased by more than 30%. We provide calculation formula and results in Figure S4.1 and Figure S4.2 in more detail in Supplement section.

Table 4.2 Sensitivity analysis of net present value in Japan (Unit: USD)

Worker		**(−) 30%**	**(−) 15%**	**0%**	**(+) 15%**	**(+) 30%**
Incremental net benefit (With - Without)	**2014**	869,669	1,039,732	1,120,747	1,206,542	1,374,137
	2015	1,310,295	1,566,522	1,688,584	1,817,849	2,070,357
	2016	1,632,969	1,952,296	2,104,416	2,265,514	2,580,206
	2017	2,515,707	3,007,652	3,242,004	3,490,188	3,974,993
	2018	2,334,484	2,790,991	3,008,462	3,238,767	3,688,648

Student		**(−) 30%**	**(−) 15%**	**0%**	**(+) 15%**	**(+) 30%**
Incremental net benefit (With - Without)	**2014**	1,494,430	1,786,665	1,925,879	2,073,310	2,361,303
	2015	1,284,028	1,535,120	1,654,734	1,781,408	2,028,855
	2016	2,127,945	2,544,063	2,742,294	2,952,223	3,362,302
	2017	2,003,928	2,395,796	2,582,473	2,780,167	3,166,347
	2018	2,255,651	2,696,743	2,906,869	3,129,397	3,564,087

Table 4.3 Sensitivity analysis of net present value in Nepal (Unit: USD)

Worker		(−) 30%	(−) 15%	0%	(+) 15%	(+) 30%
Incremental net benefit (With - Without)	2014	-2,403,006	-2,875,395	-3,097,947	-3,330,523	-3,796,234
	2015	-3,069,156	-3,672,498	-3,956,745	-4,253,794	-4,848,608
	2016	-3,712,864	-4,442,748	-4,786,612	-5,145,963	-5,865,530
	2017	-4,597,713	-5,501,542	-5,927,356	-6,372,346	-7,263,400
	2018	-5,104,889	-6,108,420	-6,581,205	-7,075,283	-8,064,630

Student		(−) 30%	(−) 15%	0%	(+) 15%	(+) 30%
Incremental net benefit (With - Without)	2014	-3,054,436	-3,654,884	-3,937,768	-4,233,392	-4,825,353
	2015	-3,832,879	-4,586,356	-4,941,335	-5,312,301	-6,055,127
	2016	-4,571,416	-5,470,076	-5,893,454	-6,335,900	-7,221,857
	2017	-5,644,759	-6,754,419	-7,277,204	-7,823,533	-8,917,508
	2018	-6,294,637	-7,532,052	-8,115,025	-8,724,253	-9,944,177

The scenario results show that the implementation of pre-entry TB screening for applicants for Japanese visas could involve significant cost for Nepal (Figure 4.3). We provide Table A.1 and Figure A.1 in more detail in supplementary Result 2-3.

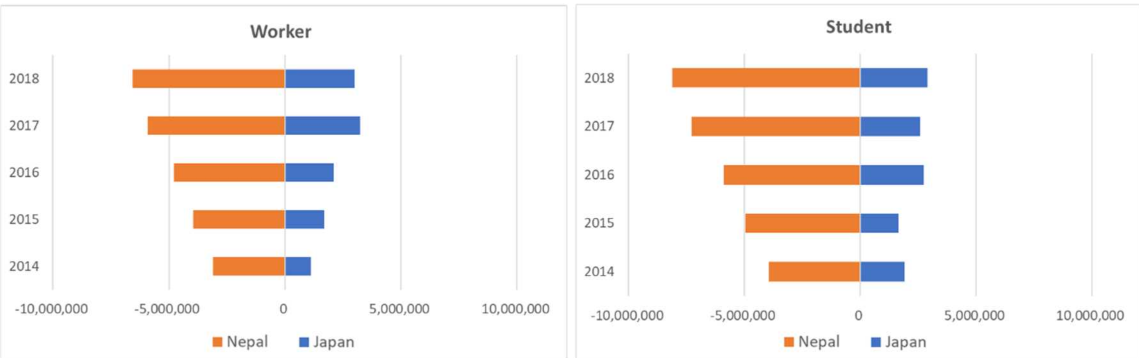

Figure 4.3 Net present value for Nepalese workers and students in Nepal and Japan (Unit: USD)

As shown above, Nepal bears a much heavier burden than Japan. Significantly, the difference in NPV is counterbalanced by the burden of cost allocation, which is accentuated by the huge economic gap between two countries. Level of fiscal burden should be taken into consideration under a fair sharing mechanism between collaborating countries. Although, methods for determining burden-sharing rate for global health aid projects have not yet been developed, our net benefit scenario results could be considered as a net benefit contributing to health equality.

4.4 Discussion

4.4.1 Policy implications

Assessment of Nepal's and Japan's expected costs and benefits of resulting from Japan’s pre-entry TB screening policy implementation for prospective Nepalese residents of Japan should be conducted with consideration of social value in terms of monetization. Our multi-dimensional evaluation simulates empirically scenarios reflecting both perspectives, so as to examine the potential outcome of implementation of the new policy design in Japan. Specifically, our approach measures the social values of pre-entry TB screening strategy. The simulation suggests that pre-entry TB screening would have prevented about 181 active TB cases in Japan for 2018, and would in turn have reduced TB screening costs and worker capacity loss—welcome outcomes from the Japanese perspective. This encores that the appropriate pre-entry TB screening policy for that group has been discussed [43], would contribute to the prevention, and eventually elimination, of TB in Japan.

Overseas LTBI screening and treatment for refugees and foreign-born residents in the US could serve as a model for the reduction of active TB by domestic health prevention management [44]. Current TB cross-border management issues are inadequate for TB incidence risk reduction, infection control, collaboration, and the sharing of global data [45]. The reduction of risk of TB incidence is recommended as a policy-based practice within public health emergency management at every level. National health prevention and disease control could serve as health emergency management instruments in neighboring countries *vis*-à-*vis* trans-border migration.

Due to weak public and global health emergency management and the increasing number of foreign residents with TB worldwide, cross-border infectious disease transmission is now a major human security concern, even threatening international peace and security [46]. Human security is now recognized in Japan as a central concern; Japan must promote social resilience through international health cooperation [47]. Our scenario results estimate that pre-entry TB screening testing within Nepal could have been identified 137 TB cases among 42,346 visa applicants from Nepal in 2018; those individuals could have undergone TB treatment in Nepal until issued TB-free certificates.

Although pre-entry TB screening strategy could contribute to the establishment of aggressive TB screening and treatment in Nepal, it could have a negative impact on TB-related expenditure for households with insufficient healthcare coverage [48]. WHO's End TB strategy identified reduction of TB-affected household expenditures as a priority means of preventing catastrophic economic costs of TB in low income countries [49]. The implementation of TB screening pre-entry to Japan would reduce TB incidence risk, and early TB diagnosis prior to entry to Japan would ensure elimination of a substantial proportion of detected TB cases.

In Japan, there remains little evidence of sufficient awareness within the target population (Nepal) of TB control, prevention and treatment. The target population diagnosed with TB could be subjected to considerable disease-related burden, including loss of income, discretionary time for TB care, and treatment cost difficulties related to lack of health coverage. Fair sharing of net benefits as public goods is likely to improve health equity, assuming cooperation by developing countries [50]. According to some empirical studies, the burden-sharing required to achieve the global health target will call for large efforts by multi-stakeholders [51]. The outbreak of the Covid-19 global pandemic has confirmed that policy implementation reflecting migrant home and destination is indispensable for a resilient public health system and infrastructure for financing holistic health diplomacy development [52].

4.4.2 Limitations and future perspective

TB has been designated an infectious disease by law in Japan, with provision of full coverage of treatment costs. In the absence of such system for Nepal, measures of willingness to pay and shadow price to estimate the value of a statistical life (VSL) are not applied in this study. Moreover, due to the lack of precise reference for the TB transmission rates in Nepal and Japan, the rough assumption in this study may constrain the accuracy of consequences.

Nevertheless, this study clarifies the relationship between economic impact and Japanese pre-entry TB screening policy aimed at the elimination of

TB. The empirical estimates elucidate the spillover effect from health system reinforcement through international collaboration, while technology application is expected to enhance the interpretation of the change from the value chain in the both countries.

Regarding the public health impact of infectious disease exacerbated by cross-border issues, implementation of the policy would enhance the effect of TB incidence risk reduction and cost-saving by foreign born residents of Japan. Migrant nations subject to the implementation of the policy, especially low-income countries, would bear the cost of TB testing and treatment. Hence, establishing a burden-sharing mechanism would generate a spillover effect on population health and reduce vulnerability to financing shock for the migrant county, in turn deepening the interdependence between Nepal and Japan in terms of inclusive development for the elimination of TB.

4.5 Conclusion

This study estimated the expected policy implementation costs and benefits of pre-entry TB screening testing and treatment targeting Nepalese born residents of Japan, a high TB burden country. In order to give consideration to the different perspectives on the policy implementation scenarios, we calculated the risks of TB incidence related to cost and benefit with transmission risks, as measures of policy effectiveness in each country. We reason that effective TB infection control could help reduce the output value of capacity loss, which would in turn lead to cost-saving the implementation of pre-entry TB screening policy in Japan. By identifying an optimal combination of expected cost and benefit, it possible to give stakeholders various options for TB countermeasures both nationally and internationally. Policy makers understand that it is vital to provide information and guidance regarding the recognized impacts, considering different perspectives, of this policy setting process. It should be noted that the simulation framework could also be applied to the design of Covid-19 countermeasures.

4.6 Ethical and conflict of interest statement

We used secondary health data from the Nepal Demographic and Health Survey and the Nepal Department of Health Services (DHS) Annual Report [23]; and from Japan's Legal Affairs Bureau and Tuberculosis Surveillance Center. It is not possible to identify individual health information of participants from the data, so this study did not require ethical approval or conflict of interest statements.

4.7 Supplement

4.7.1 Formula of target population

Fomula1: Target population (Japanese perspective)

Without policy (current, TB testing done in Japan)

$$POP_{t,i}^{TB,wo} = \underbrace{(POP_{t,i}^{TB}/Screening\ test\ sensitivity\ ratio)}_{\textit{Total predicted newly diagnosed TB cases*}} \times T$$

Where *p* = policy implementation (*w*: with policy / *wo*: without policy)

t = year

POP^{TB}= foreign resident with newly diagnosed TB

i = Resident type of Nepalese resident in Japan (*s*: student / *em*: worker)

Screening test sensitivity ratio = 95%

T=Transmission rate = 150%

* False negative cases included

($POP_{t,i}^{TB}$= Nepalese resident with TB in Japan, sourced from Tuberculosis Surveillance Center Japan)

With policy (screening done in Nepal, costs borne by Nepal)

$$POP_{t,i}^{TB,w} = \overbrace{\left(\underbrace{POP_{t,i} \times \frac{incidence\ \ rate\ \ in\ \ Nepal}{Screening\ \ test\ \ sensitivity\ \ ratio}}_{\text{Predicted newly diagnosed TB cases of applicants}} - POP_{t,i} \times incidence\ \ rate\ \ in\ \ Nepal\right)}^{\text{Total predicted newly diagnosed TB cases}} \times T$$

Where *p* = policy implementation (*w*: with policy / *wo*: without policy)

t = year

i = Resident type of Nepalese resident in Japan (*s*: student / *em*: worker)

POP^{TB}= foreign resident with newly diagnosed TB

POP = foreign resident applicants to Japan

Screening test sensitivity ratio = 62%

T = Transmission rate = 150%

*False negative cases included

(With 62% TB Screening test sensitivity ratio in Nepal, false negative cases will be entering to Japan, and taking the test and treatment)

Formula 2: Target population (Nepalese perspective)

Without policy (current)

There have been active Nepalese TB cases in Japan, therefore there is no direct benefit for Nepal.

With policy (screening done in Nepal, costs borne by Nepal)

$$POP_{t,i}^{TB,w} = \underbrace{\left(POP_{t,i} \times \frac{incidence\ \ rate\ \ in\ \ Nepal}{Screening\ \ test\ \ sensitivity\ \ ratio} - False\ \ negative\ \ cases\right)}_{\text{Total predicted newly diagnosed TB cases*}} \times T$$

Where *p* = policy implementation (*w*: with policy / *wo*: without policy)

t = year

i = Resident type for Nepalese resident in Japan (*s*: student / *em*: worker)

POP^{TB}= foreign resident with newly diagnosed TB

POP = foreign resident applicants to Japan

Screening test sensitivity ratio = 62%

T = transmission rate = 150%

* False negative cases excluded

(False negative cases will enter Japan and take the test and treatment in Japan)

4.7.2 Formula of cost and benefit

Formula 3: Cost and benefit (Japanese perspective)

$$Net\ \ benefit_t^{w,wo} = 0 - \Big[\overbrace{\sum_i \sum_t \big(POP_{i,t}^{TB} \times F_{te}\big)}^{\textit{Test fee}} + \overbrace{\sum_i \sum_t \big(POP_{i,t}^{TB} \times F_{tr}\big)}^{\textit{Treatment fee}}\Big] - \overbrace{POP_{i,t}^{TB} \times (-Wage) \times 6}^{\textit{Capacity loss}}$$

$$\Rightarrow Net\ \ benefit_t^{w,wo} = 0 - \underbrace{\sum_i \sum_t \big[POP_{i,t}^{TB} \times (F_{te} + F_{tr})\big]}_{\textit{Total implement fee}} - \underbrace{POP_{i,t}^{TB} \times (-Wage) \times 6}_{\textit{Total capacity loss}}$$

Where *p* = policy implementation (*w*: with policy / *wo*: without policy)

t = year

POP^{TB}= foreign resident with newly diagnosed TB

i = Resident type for Nepalese resident in Japan (*s*: student / *em*: worker)

F = fee of (*te*: test / *tr*: treatment)

Wage = monthly wage

Formula 4: Cost and benefit (Nepalese perspective)

$$Net\ \ benefit_t^{wo} = N.A.$$

(There have been active Nepalese TB cases in Japan, with all costs borne by Japan.)

$$Net\ \ benefit_t^{w} = 0 - \overbrace{POP_t \times F_{te}}^{\textit{Incremental test fee}} - \underbrace{\sum_i \sum_t \left[POP_{i,t}^{TB} \times (F_{tr})\right]}_{\textit{Total treatment fee}} - \overbrace{POP_{i,t}^{TB} \times (-Wage) \times 6}^{\textit{Total capacity loss}}$$

Where *p* = policy implementation (*w*: with policy / *wo*: without policy)

t = year

POP^{TB}= foreign resident with newly diagnosed TB

i = Resident type for Nepalese resident in Japan (*s*: student / *em*: worker)

F = fee for (*te*: testing / *tr*: treatment)

Wage = monthly wage

4.7.3 Sensitivity test result in Japan (Unit: USD)

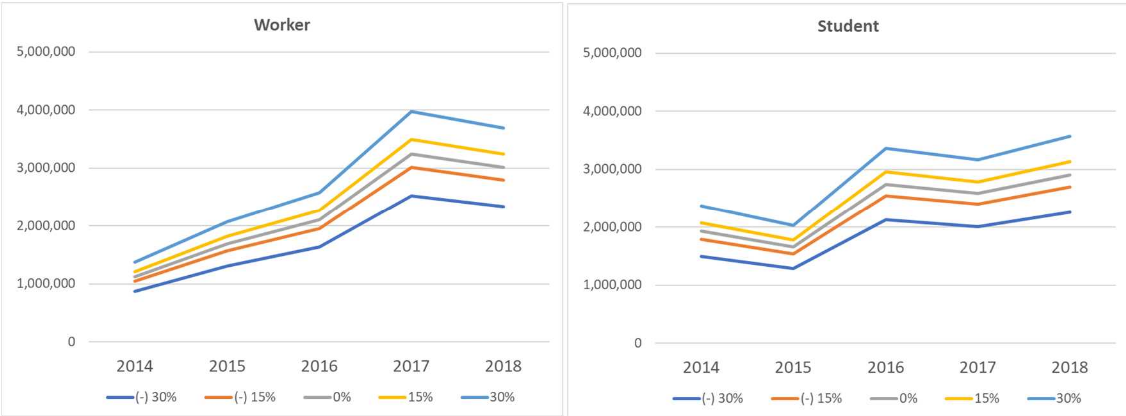

Figure S4.1 Sensitivity test of net present value for workers/students in Japan

4.7.4 Sensitivity test result in Nepal (Unit: USD)

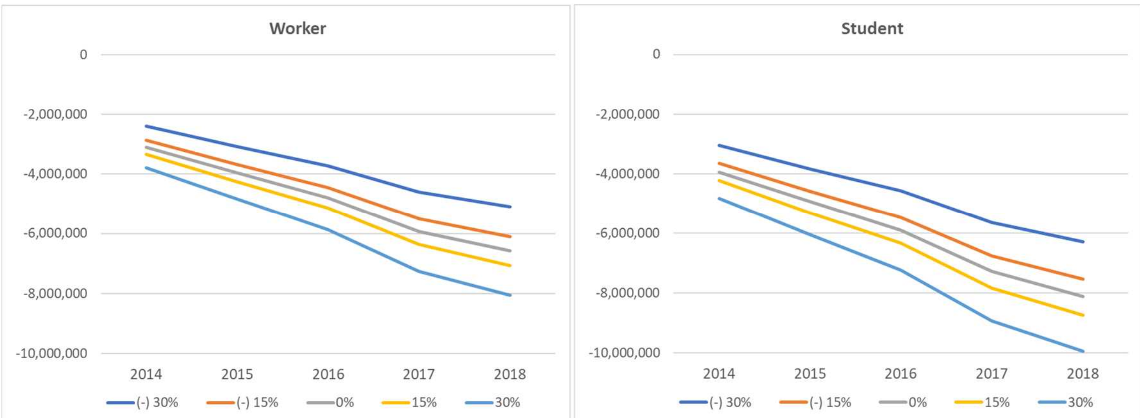

Figure S4.2 Sensitivity test of net present value for workers/students in Nepal

4.8 Reference

[1] World Health Organization., (2005). Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)'. Newsroom detail, 30 January 2020. Available from https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov). [Accessed January 28 2021].

[2] Brown, J.S., Lipman, M.C., Zar, H.J., (2012). What's new in respiratory infections and tuberculosis 2008-2010. *Thorax*. 67:350-354.

[3] WHO Global Tuberculosis Programme., (1994). TB: a global emergency, WHO report on the TB epidemic. World Health Organization. Available from: https://apps.who.int/iris/handle/10665/58749. [Accessed January 28 2021].

[4] WHO., (2019). Global Tuberculosis Report', Fact sheets on Tuberculosis. Available from: https://www.who.int/tb/publications/factsheet_global.pdf?ua=1. [Accessed January 28 2021].

[5] Lönnroth, K., Migliori, G., Raviglione, M., (2014). Toward tuberculosis elimination in low-incidence countries: reflections from a global consultation. *Ann Intern Med*. 12014;61(9), 670-671.

[6] Pareek, M., Greenaway, C., Noori, T., Munoz, N., Zenner, D., (2016). The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. *BMC Med*. 14, 48-57.

[7] Nathavitharana, R., Friedlead, J.A., (2015). Tale of two global emergencies: tuberculosis control efforts can learn from the Ebola outbreak. *Eur Respir*. 46, 293-296.

[8] Ministry of Health, Labour and Welfare (MHLW), Japan. Employment for foreign worker situation report in Japanese. Available from: https://www.mhlw.go.jp/content/11655000/000590309.pdf. [Accessed January

28 2021].

[9] Immigration Services Agency of Japan. Initiatives to Accept New Foreign Nationals and for the Realization of Society of Harmonious Coexistence 2019. Available from: http://www.moj.go.jp/content/001308076.pdf. [Accessed January 28 2021].

[10] Sharmila, T., (2018). <Fieldwork News>Diplomatic Practices in Nepal-Japan Relations: A Comparative Study Based on Regime Chang. *Asian and African Area Studies*. 18(1), 100-106.

[11] Hoshino, H., Ohmori, M., Okada, M., (2010). Trends in tuberculosis infection among foreigners in Japan according to work status. *Kekkaku*. 85(9), 697-702.

[12] Tuberculosis Surveillance Center, Japan. Tuberculosis in Japan -Annual Report 2019, Viewed February 2019. Available from < https://www.jata.or.jp/rit/ekigaku/en/statistics-of-tb/>. [Accessed January 28 2021].

[13] Kawatsu, L., (2017). Tuberculosis infectious disease originating overseas entering the country in Japanese. *Infectious Agents Surveillance Report (IASR)*. 2-17;38(12), 234-235. Available from: <https://www.niid.go.jp/niid/images/idsc/iasr/38/454.pdf>. [Accessed January 28 2021].

[14] Zannetos, S., Talias, M., (2016). A Cost-benefit Analysis of a Proposed Immigrant Latent Tuberculosis Infection Screening Program for Cyprus. *Mater Sociomed*. 28(6), 464-467.

[15] MHLW. Japan Pre-Entry Tuberculosis Screening" in Japanese 2020, Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou03/index_00006.html. [Accessed January 28 2021].

[16] MHLW. Japan Pre-Entry Tuberculosis Screening Guideline" in Japanese 2020. Available from <https://www.mhlw.go.jp/content/000613443.pdf>.

[Accessed January 28 2021].

[17] Tuberculosis and Infectious Disease Control Division Health Service Bureau, Ministry of Health, Labour and Welfare, Government of Japan 2020, 'Japan Pre-Entry Tuberculosis Screening - TECHNICAL INSTRUCTIONS' Version 1, Available from: https://www.mhlw.go.jp/content/000613445.pdf. [Accessed January 28 2021].

[18] GBD 2019 Universal Health Coverage Collaborators., (2020). Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 396, 1250-1284.

[19] Ikegami, N., (2019). Japan: achieving UHC by regulating payment. *BMC Globalization and Health*. 15(Suppl 1), 72-77.

[20] Ikegami, N., (2014). Universal health coverage for inclusive and sustainable development: lessons from Japan'. A World Bank study. World Bank, Washington, DC2014.

[21] Katsuda, N., Hirosawa, T., Reyer, J., Hamajima, N., (2015). Roles of Public Health Centers (Hokenjo) in Tuberculosis control in Japan. *Nagoya J. Med. Sci*. 77, 19-28.

[22] Mishra, S.R., Khanal, P., Dhimal, M., (2016). Nepal's quest for Universal Health Coverage. *Journal of Pharmacy Practice and Community Medicine*. 2(4), 104-106.

[23] Department of Health Services, Ministry of Health and Population, Government of Nepal Annual Report 2074-75. Available from: https://dohs.gov.np/category/annual-report/. [Accessed January 28 2021].

[24] Dowdy, D., Dye, C., Cohen, T., (2013). Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list. *Int J Tuberc Lung Dis*. *17*(7), 866–877.

[25] Kurumi, R., Rauniyar, R., Manandhar, K.D., Gupta, B.P., (2016). Evaluation of the XpertMTB/RIF for the Diagnosis of Pulmonary Tuberculosis Among the Patients Attending DOTS Center Parsa District of Nepal. *Nepal journal of biotechnology*. 4(1), 26-32.

[26] Joshi, B., Lestari, T., Graham, S., Baral, S., Verma, S., Ghimire, G., Bhatta, B., Dumre, S., Utarini, A., (2018). The implementation of X-pert MTB/RIF assay for diagnosis of tuberculosis in Nepal: A mixed-methods analysis. *PLoS One*. 13(8): e0201731.

[27] Aono, A., Chikamatu, K., Yamada, H., Murata, H., Yuki, A., Misawa, S., Oguri, T., Mitarai, S., (2012). External Quality Assessment for Direct Acid-Fast Bacilli Smear Microscopy' in Japanese, The Journal of the Japanese Society for Clinical Microbiology. 22(4), 279-283. <http://www.jscm.org/journal/full/02204/022040279.pdf> .

[28] The Japanese Society for Tuberculosis and Non-tuberculosis Mycobacteriosis. Japanese TB diagnosis 2014 in Japanese., (2014). *Kekkaku*. 89(4), 1-6. Available from: https://www.kekkaku.gr.jp/books-basic/pdf/2.pdf. [Accessed January 28 2021].

[29] International Monetary Fund (IMF), Exchange Rate Archives by Month. Available from < https://www.imf.org/external/np/fin/data/param_rms_mth.aspx. [Accessed January 28 2021].

[30] MHLW 2019, National Data Base (NDB) open-data Japan 5th edition. [Accessed January 28 2021].

[31] United Kingdom (UK) help and service in Nepal. Tuberculosis test clinics for UK visa, Guidance of TB test, Government of UK. Available from <https://www.gov.uk/government/publications/tuberculosis-test-for-a-uk-visa-clinics-in-nepal/tuberculosis-testing-in-nepal>. [Accessed January 28 2021].

[32] Gurung, S., Dixit, K., Rai, B. et al., (2019). The role of active case finding in reducing patient incurred catastrophic costs for tuberculosis in Nepal. *Infect Dis Poverty*. 8, 99-113.

[33] Wilkinson, T., Bozzani, F., Vassall, A., Remme, M., Sinanovic, E., (2019). Comparing the Application of CEA and BCA to Tuberculosis Control Interventions in South Africa. *Journal of Benefit-Cost Analysis*. 10(S1), 132-153.

[34] Kekkaku., (2014). TB treatment guideline in Japanese. The Japanese Society Tuberculosis and Non-tuberculosis Mycobacteriosis. *Kekkaku* book.Ver. 4. Published December 2014.

[35] Gurung, G., Chhetri, P., Jha, N., (2012). Economic impact of pulmonary tuberculosis on patients and their families of Dharan municipality, Nepal. *Nepal Med Coll J*. 14(3), 196-198.

[36] MHLW Statistics and Information Department, Monthly Labour Survey. Available from:https://www.mhlw.go.jp/english/database/db-l/monthly-labour.html. [Accessed January 28 2021].

[37] IMF, Databank Microdata in Nepal. Available from: https://data.worldbank.org/country/nepal. [Accessed January 28 2021].

[38] WHO., (2020). Key facts, 14 October 2020, Tuberculosis. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis. [Accessed January 28 2021].

[39] WHO., (2017). Global Tuberculosis Report 2017, Available from: https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf?ua=1. [Accessed January 28 2021].

[40] Mahato, P., Paudel, G., (2015). Access to free health-care services for the poor in tertiary hospitals of western Nepal: a descriptive study. *WHO South East Asia J Public Health*. 4(2), 167-175.

[41] Swe, K., Rahman, M., Rahman, M., Saito, E., Abe, S., Gilmour, S., Shibuya, K., (2018). Cost and economic burden of illness over 15 years in Nepal: A comparative analysis. *PLoS One*. 13(4): e0194564.

[42] Floyd, K., Glaziou, P., Zumla, A., Raviglione, M., (2018). The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. *Lancet Respir Med*. 6(4), 299-314.

[43] Kawatsu, L., Uchimura, K., Ohkado, A., Kato, S., (2017). Pulmonary tuberculosis and non-recent immigrants in Japan - some issues for post-entry interventions. *Western Pacific surveillance and response journal: WPSAR*. *8*(4), 13-19.

[44] Wingate, L., Coleman, M., de la Motte, C., Semple, M., Zhou, W., Cetron, M., Painter, J., (2015). A cost-benefit analysis of a proposed overseas refugee latent tuberculosis infection screening and treatment program. *BMC Public Health*. 15, 1201-1215.

[45] Dara, M., Sulis, G., Centis, R., D'Ambrosio, L., de Veries, G., Douglas, P., Garcia, D., Jansen, N., Zuroweste, E., Migliori, G.B., (2017). Cross-border collaboration for improved tuberculosis prevention and care: policies, tools and experiences. *Int J Tuberc Lung Dis*. 21(7), 727-736.

[46] United Nations., (1945). Charter of the United Nations. Available from: https://www.un.org/en/sections/un-charter/introductory-note/index.html. [Accessed January 28 2021].

[47] Nomura, S., Sakamot, H., Sugai, M., Nakamura, H., Sakurai, K., Lee, S., Ishizuka, A., Shibuya, K., (2020). Tracking Japan's development assistance for health, 2012–2016. *BMC Global Health.* 16, 32. <https://doi.org/10.1186/s12992-020-00559-2>.

[48] Dixit, K., Rai, B., Prasad, T., Mishra, G., de Siqueira-Filha, N., Paudel, P., Levy, J., Rest, J., Gurung, S., Djotal, R., Biermann, O., Vinet, K., Lonnroth, K., Squire, S., Caws, M., Wingfield, T., (2020). Research protocol for a mixed-methods study to characterise and address the socioeconomic impact of accessing TB diagnosis and care in Nepal [version 2; peer review: 2 approved with reservations]. *Wellcome Open Res*. 5:19.

[49] WHO., (2015). Global Tuberculosis report 2015. Global strategy and targets

for tuberculosis prevention, care and control after 2015[a], The official text approved by sixty seventh World Health Assembly, 14 March 2014. Available from: https://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1. [Accessed January 28 2021].

[50] Kaul, I., Faust, M., (2001). Global public goods and health: taking the agenda forward, *Bulletin of the World Health Organization*. 79, 869-874.

[51] Shekar, M., Kakietek, J., D'Alimonte, M., Rogers, H., Eberwein, J., Akuoku, J., Pereira, A., Soe-Lin, S., Hecht, R., (2017). Reaching the global target to reduce stunting: an investment framework. *Health Policy Plan*. 32(5), 657-668.

[52] Shimizu, K., Kondo, T., Tokuda, Y., Shibuya, K., (2020). An open letter to Japan’s new Prime Minister. *The Lancet*. 396: e57.

[53] Ma, Y., Horsburgh, C., White, L., Jenkins, H. (2018) Quantifying TB transmission: a systematic review of reproduction number and serial interval estimates for tuberculosis, *Epidemiol Infect.* 146(12): 1478–1494.

[54] Kitahara, R., Otsuki, T. (2014) A study on Living Environment of Bangladesh Nationality Foreign Residents in Kita-Ku, Tokyo", *Journal of Architecture Planning*, 79(698): 873-882.

Chapter 5

Conclusion

5.1 Concluding remarks

The pandemic of COVID-19 has increased societal interest in epidemiology and global health. TB remains threatening under the intensified circumstances and insufficient detective or treatment in developing countries. The capture of the research trend is of helpfulness for identify the scope with information for inclusive input or academic collaboration. In addition, the understanding of utilization of ICT appliances at the local base demonstrated a compact visualization for stakeholders to strengthen the policy more effectively. Finally, the TB screening policy must be implemented in immigrant country to ensure the control of TB inspection and the following medical treatment. With the support of destination country, possible cases could be diagnosed at the pre-entry stage to prevent the transmission risk. The global collaboration is essential for the control and elimination of TB.

To specify the contribution of each chapter, we evaluated scientific studies that have contributed to the achievement of global health in the context of TB eradication in the past two decades to better understand the trend of research. In addition, we conducted a topic modeling analysis of qualitative article data to obtain a comprehensive understanding of the characteristics of Japanese TB scientific research in the context of national health policy, comparing with 15 countries. The results provide evidence that Japan has the most influential academic publications of clinical research and medical trials related to patient health care and treatment. Interestingly, a science mapping of topic communities and country clusters, visualizing the characteristics and priorities of TB research worldwide, revealed the strong independence of TB research in Japan in particular. The mapping actually revealed some weaknesses of TB research in Japan, while we could identify weaknesses in Japanese TB research regarding the interrelationships between social factors that could influence health-seeking behavior and the broader health care system and dynamics. In the future, it would be desirable to improve the performance of analytical systems for the identification of trends in medical titles in order to obtain higher validation results from text mining studies.

The ICT-based TB awareness survey shed light on demographic and socioeconomic factors associated with TB awareness at national and subnational levels in Nepal. The regression results show that socioeconomic determinants such as wealth quintile, education level, and mobile phone ownership are significantly associated with TB awareness regardless of urban or rural levels. The high level of awareness of TB at the community level emphasizes the need to develop strategies to increase awareness of TB. Most of all, the use of cell phones could be an effective strategy element for increasing awareness of TB in rural townships or villages, which implies that implementing policy regarding a mobile-oriented approach to health care infrastructure could effectively and inexpensively increase TB awareness and access to treatment. The findings provide stakeholders with valuable support for the need for further research on the contribution of ICT use to TB awareness in Nepal. Further research is required to achieve a full understanding of the mechanisms that could influence the underlying determinants of TB awareness in the Nepalese context, to support the work to promote and support TB elimination in Nepal.

Cost-benefit analysis of 2014–2018 TB diagnosis data for Japan estimates that net present value (NPV) for Nepalese students increased from US$1.9 million to US$2.9 million; and for Nepalese workers increased from US$1.1 million to US$3.0 million. The increase in NPV is significantly greater than zero, and the implementation of this policy will benefit Japan in preventing an increase in the number of new TB cases. The facts indicate that the implementation of this policy may benefit Japan in terms of preventing an increase in new TB cases. The projected number of newly diagnosed Nepalese TB cases among foreign applicants for migration has increased. Nepal's NPV was negative because the total costs exceeded the benefits, suggesting an increased burden from the direct costs of TB. We thus conclude that implementing a pre-entry TB screening policy for foreign migrants entering Japan from Nepal, which has a high TB rate, could serve to reduce the number of newly diagnosed cases of TB, including those at risk of infection through transmission, and achieve both efficiency and cost reduction.

To sum up, the topic modelling method contributed our understanding of how research could consolidate endowment in global health and national health services. The most influential clinical research and medical trails in Japan can be of fundamental value, and surely applicable, as they directly address clinical problems and the provision of quality health services. Moreover, an understanding of the determinants of public TB awareness in Nepal could accelerate public sector identification of affordable and effective intervention for

TB infection control, which would in turn prevent people from falling into poverty. Finally, given the increasing interdependency of human resources across borders, global collaboration may substantially strengthen resilience under epidemic threats. Hence, newly developed evaluation methods can translate into enhancement of global health policymaking practice, and in turn into the flow of benefits and positive impacts to society.

For TB control, it is essential to combine medical, public health targets, and socioeconomic interventions along with research and innovation that embraces country-specific strategies for prioritizing TB research capacity. Understanding the TB research priority help set up and strengthen a coordinating body for collaborative TB research activities functional at global and national levels. On the other hand, unfolding the social determinants of TB awareness and access to TB assistance could significantly help stakeholders of the local community identify the needs for medical support and thus effectively reduce the diagnosis risk. Likewise, an evidence-based estimate on diagnostic service with adequate health assisting networks and radiography, technology requirements, and human resources is vitally important along with the international mobility growth. To prevent the inadequate provision of medical treatment and specific TB service packages with quality standards could lead an effective TB control across countries. The cost-benefit analysis of the current state of health financing system could reinforce UHC and its healthcare frameworks that substantially contribute to the accuracy of ex-ante resource allocation. It is indispensable to ensure that populations at high risk for TB reach early in the roll-out of schemes.

As indicated in the introduction chapter, for the final analysis, research results focused on these three perspectives, to create knowledge of medical care and drug development; to raise the awareness of prevention, diagnosis, and treatment information to the general public; and to have effective boarder measures to prevent the international spread of the infectious disease.

5.2 Research limitation and future prospects

Although we used three approaches to evaluate recent TB research, these methods contain limitations in the scope of analysis. Systematic errors in the combined dataset used for bibliometric evaluation might have affected the results due unbalanced database merging and errors in translation into English. Given that the purpose of this study was to assess Japan's contribution to TB research, the combined data set did enable a full, more holistic, grasp of trends.

However, it is challenging to classify the data into five categories, given the insufficient quality of medical and scientific terms used in the individual datasets. Different approaches could enhance the reliability of the primary analysis, which was aimed at determining the general characteristics of the progress of TB research in Japan.

Regarding the regression analysis using household survey data, exclusion of the data for study participants whose information is incomplete is essential, although that could lead to an overestimation of the TB awareness of the population. Moreover, TB awareness is likely to be influenced by several factors, including distance from health facilities, service provider attitude, and factors related to TB complications, for which not data are available. We acknowledge that several TB awareness programs, implemented in different parts of Nepal, may have influenced local awareness.

Since there is still no full coverage and treatment system for TB in Nepal, our cost-benefit analysis does not apply willingness-to-pay or shadow price measures to estimation of the statistical value of life (VSL). However, pre-entry TB screening policy aimed at TB elimination was examined empirically. Further empirical estimates and incorporation of technology into the methodology are expected to enhance the interpretation of changes in the value chains of both countries, in turn generating spillover effects of international cooperation to the strengthening of the health care system. In addition, a thorough location-based analysis of the TB programs would make the findings of this study more comprehensive.

During the breakout of the COVID-19 pandemic, global health systems have undergone substantial reforms with regard to international collaboration. For instance, the Pandemic Preparedness Partnership (PPP), launched by the UK, Europe and some Asian countries in 2021, conducted a mission to develop and deploy high quality vaccines for new diseases and reduce the development period from 300 to 100 days. The intensive support plan is backed by additional financial support of the global vaccine supply work of Global Fund, Global Vaccine Alliance (Gavi) and the Coalition for Epidemic Preparedness Innovations (CEPI) [1]. The CEPI mechanism operated in a public-private partnership, bringing together industry, international organizations, and leading experts. The export panel provided recommendations for delivering on the ambitious targets of faster development of vaccines, therapeutics and diagnostics, through greater global co-operation on research and development, manufacturing, clinical trials and data-sharing. The global response to COVID-19 and other potential epidemiologic threats (AIDS, TB and malaria) has demonstrated that such joint countermeasures could be most successful, thanks to synergy between scientists, businesses, and governments, and collective action through multilateral institutions [2].

Furthermore, WHO has developed its Global Action Framework for TB Research to strengthen TB research by means of adequate domestic funding and interaction with key stakeholders at the national and global levels. High TB burden countries, especially in LMICs, require considerable support and facilitation for intensification of and innovation in TB research [3]. For this reason, it is essential that stakeholders to emphasize the importance of public-private and international partnerships to prevent future disease and another global pandemics, so as to contribute equitable recovery and the strengthening of collaboration on pandemic preparedness. Under such circumstances, the evaluation of the implementation of the policy framework is necessary to ensure that the reinforcement work with the national strategy and TB research plan [4]. The above demonstrates that our evaluation research provides an effective emanation of policymaking process in global health collaboration. Clearly there is a need for research with a broader scope, including pandemic preparedness, information sharing and provision of an assistance platform for dissemination of the results of evaluation research at both the domestic and global levels.

5.3 References

[1] The Government of UK (2021) New global partnership launched to fight future pandemics <https://www.gov.uk/government/news/new-global-partnership-launched-to-fight-future-pandemics> Accessed on 10 Oct. 2021

[2] The Cabinet Office (2021) Toward Japan's Global Health Strategy Making <Task Force Meeting) <https://www.kantei.go.jp/jp/singi/kenkouiryou/global_health/tf_dai1/siryou3-1.pdf> Accessed on 10 November 2021. (In Japanese)

[3] WHO 2015. A Global Action Framework for TB Research-in support of the third pillar of WHO's End TB Strategy. <https://apps.who.int/iris/rest/bitstreams/872635/retrieve> Accessed on 20 November 2021.

[4] WHO 2015. The Implementing the End TB strategy: The essentials. <https://www.who.int/publications/i/item/implementing-the-end-tb-strategy> Accessed on 10 November 2021