School of Population Health

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Epidemiology of major infectious diseases in indigenous and ethnic minority peoples of the Asia Pacific region

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Declaration

To the best of my knowledge and belief, this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number #HRE2019-0581.

Signature:

Date: 25 August 2022

Abstract

The 2030 Sustainable Development Agenda sets the ambitious goal of eradicating poverty, protecting the planet, and ensuring peace and prosperity for all. The 2030 Agenda applies an equity lens to its goal and seeks to ensure equal opportunity for all, with an emphasis on those most vulnerable within society. Within its targets, sustainable development goal (SDG) 3.3 seeks to end acquired immunodeficiency syndrome (AIDS), tuberculosis (TB), malaria and neglected tropical disease (NTD) epidemics by 2030.

Fundamental to achieving these targets will be an understanding of the population groups that are at greatest risk of infection and inequitable health outcomes. Previous research shows indigenous and ethnic minorities to be a vulnerable population group in terms of both disease prevalence and health consequence. Although previous studies have evaluated disease prevalence and health consequence in discrete communities, these risks have not been considered within the context of these populations as a collective. To address this knowledge gap, this study sought to evaluate the prevalence of HIV, TB, malaria, and soil-transmitted helminth (STH) infections within indigenous ethnic minorities of the World Health Organization (WHO) South-east Asia (SEAR) and Western Pacific regions (WPR) and evaluate the relative risk of infection in indigenous ethnic minorities vs. comparative populations, where data were available. This study also sought to evaluate population status, as a risk factor, in the health outcomes of a drug susceptible TB (DS-TB) patient cohort.

To evaluate infection prevalence and the relative risk of infection, a series of systematic reviews and meta-analyses were undertaken. To evaluate population status as a risk factor within the health-care continuum, univariate and multivariate logistic regression models were run on a retrospective cohort of patients treated for DS-TB in Hunan Province, China between 2013 and 2018.

The study found a paucity of prevalence data across all infectious agents of interest for indigenous ethnic minority populations, even in countries that are classified as carrying a high burden of infection. There was a noticeable variation in the countries that were over or under-represented in the data, and this varied according to the disease of interest.

From the data available, results showed the prevalence of HIV, TB, malaria, and STH infection to be high in indigenous ethnic minority populations. A country's advanced socio-economic status did not confer its indigenous ethnic minority populations with lower STH prevalence. This finding emphasises that neglected tropical diseases (NTD) are a global issue, and not one limited to developing nations.

Within indigenous ethnic minority populations, results showed there to be no significant reduction in HIV, TB, malaria, or STH infection prevalence over time. In fact, the study identified an increasing trend in *Trichuris trichiura* prevalence, a finding that supports the call for a more effective treatment regimen. Within indigenous ethnic minority populations, *Plasmodium knowlesi* prevalence was high, with data originating from countries classified as 'malaria free'. Research shows the prevalence of zoonotic *Plasmodium spp*., to be increasing and the findings of this study support the argument for their inclusion in public health policy.

Where data were available on indigenous ethnic minorities and comparative populations, the prevalence of HIV, malaria, and STH infections were higher in minority indigenous ethnic populations. Comparative populations showed a significant reduction in HIV infection over time, but no improvement in prevalence was found in indigenous ethnic minorities. The reasons for this finding warrant further investigation and might suggest that health education is failing minority indigenous ethnic populations.

In assessing population status as a risk factor in health outcomes, the study found indigenous ethnic minorities to have significantly longer TB diagnosis delays than the reference majority population. Conversely, indigenous ethnic minorities had lower odds of a treatment delay, highlighting opportunities for improvements in healthcare provision across both population groups. Data showed an increasing trend in the likelihood of an unsuccessful TB treatment outcome over time, but that population status was not a risk factor for unsuccessful TB treatment outcomes.

To achieve SDG 3.3 and the broader objectives of the 2030 Agenda, vulnerable populations need to be identified and inequities addressed. To identify vulnerable populations, the challenges of data disaggregation and reporting by population status

need to be resolved and additional, detailed, linked, health and socio-economic data will be required to address inequities. If interventions seeking to address inequities are to be successful, a genuine intercultural approach will be required with an understanding of each populations' customs, traditions, and belief systems. Locally dominant populations should embrace the holistic approach to health and well-being that is fundamental to indigenous culture if they are to reverse health disparities.

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Acknowledgment of Country

We acknowledge that Curtin University works across hundreds of traditional lands and custodial groups in Australia, and with First Nations people around the globe. We wish to pay our deepest respects to their ancestors and members of their communities, past, present, and to their emerging leaders. Our passion and commitment to work with all Australians and peoples from across the world, including our First Nations peoples are at the core of the work we do, reflective of

our institutions' values and commitment to our role as leaders in the Reconciliation space in Australia.

Copyright Statement

List of Acronyms and Abbreviations

ACT	artemisinin-based combination therapies
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BCG	Bacille Calmette-Guérin
COVID-19	coronavirus disease 2019
CRF	circulating recombinant forms
DALY	disability adjusted life year
DR-TB	drug resistant TB
DS-TB	drug susceptible TB
GBD	global burden of disease
HIV	human immunodeficiency virus
HIV-1	HIV type 1
HIV-2	HIV type 2
IDU	injecting drug user
ILO	international labour organization
IRS	indoor residual spraying
LTBI	latent TB infection
MDA	mass drug administration
MDR/RR-TB	multidrug/rifampicin-resistant TB
MDR-TB	multi-drug resistant TB
MSM	men who have sex with men
MCT	mycobacterium tuberculosis complex
NAT	nucleic acid test
NTD	neglected tropical disease
PRISMA	preferred reporting items for systematic review and meta-analysis
PRISMA-P	preferred reporting items for systematic review and meta-analysis protocols
RDT	rapid diagnostic test
RTP	research training program
SDG	sustainable development goal
SDH	social determinants of health

SEAR	South-east Asia region
STH	soil-transmitted helminth
STI	sexually transmitted infection
TB	tuberculosis
TB/HIV	TB and HIV coinfection
UN	United Nations
UNAIDS	joint United Nations program on HIV and AIDS
UNIMAS	university of Malaysia, Sarawak
WASH	water sanitation and hygiene
WHO	World Health Organization
WPR	Western Pacific region
XDR-TB	extensively drug resistant TB.

Part I: Introduction

Chapter I: Thesis Overview

Research Objectives and Conceptual Framework

The 2030 Sustainable Development Agenda was endorsed by the United Nations (UN) 193 member states in 2015.[1] The Agenda builds on the Millennium Development Goals and seeks to eradicate poverty, protect the planet and ensure peace and prosperity for all.[2] The 2030 Agenda seeks '*a world of… equal opportunity permitting the full realization of human potential….. A just, equitable…….. and socially inclusive world in which the needs of the most vulnerable are met*'.[2] To achieve its goal, the 2030 Agenda has 17 inter-related and indivisible Sustainable Development Goals (SDG) and 169 targets.[2] SDG3 aims to ensure healthy lives for all, and within SDG 3.3 is the target of ending acquired immunodeficiency syndrome (AIDS), tuberculosis (TB), malaria and neglected tropical disease (NTD) epidemics by 2030.[2]

Fundamental to achieving the SDG targets is health equity and understanding the patterns of inequities within population groups.[3] Human immunodeficiency virus (HIV), TB, malaria and NTDs continue to take their greatest toll on population groups facing socio-economic disadvantage.[3] For some communities, inequities are further exacerbated by discrimination and stigma when accessing services.[3] ***'Pandemics thrive on inequalities and exacerbate inequities'.***[3]

Previous research shows indigenous ethnic minorities to be among the population groups often associated with higher burdens of disease and inequitable health outcomes.[4-9] It is these population groups and four of the diseases (HIV, TB, Malaria and NTD, -represented by soil-transmitted helminths (STH)) within SDG 3.3 that form the basis of this PhD thesis.

Although previous research has evaluated the prevalence of these infections within discrete indigenous ethnic minority communities, infection prevalence within this population group as a collective, and the infection risk relative to comparative populations have not been studied. Research objective I of this thesis aims to address

this knowledge gap by determining the prevalence of HIV, TB, malaria, and STH infection amongst indigenous ethnic minorities of the South-East Asia (SEAR) and Western Pacific regions (WPR) and evaluating the relative risk of infection vs. comparative populations.

In addition to understanding disease prevalence, is the need to identify the risk factors associated with inequitable outcomes in the subsequent health-care continuum. To address this need, research objective II of this thesis, evaluates indigenous ethnic minority status as a risk factor for diagnosis and treatment delay and for unsuccessful treatment outcomes in a drug- susceptible TB (DS-TB) patient cohort. The conceptual framework of the research objectives is presented in Figure 1.

To address research objective I, a series of systematic reviews and meta-analyses were undertaken, and the results are presented in chapters III, IV and V. To address research objective II, univariate and multivariate logistic regression models were run on a retrospective cohort of patients treated for DS-TB in Hunan Province, China between 2013 and 2018. The results for research objective II are presented in chapters VI and VII. Chapter VIII discusses the thesis findings in relation to the research objectives and the SDGs.

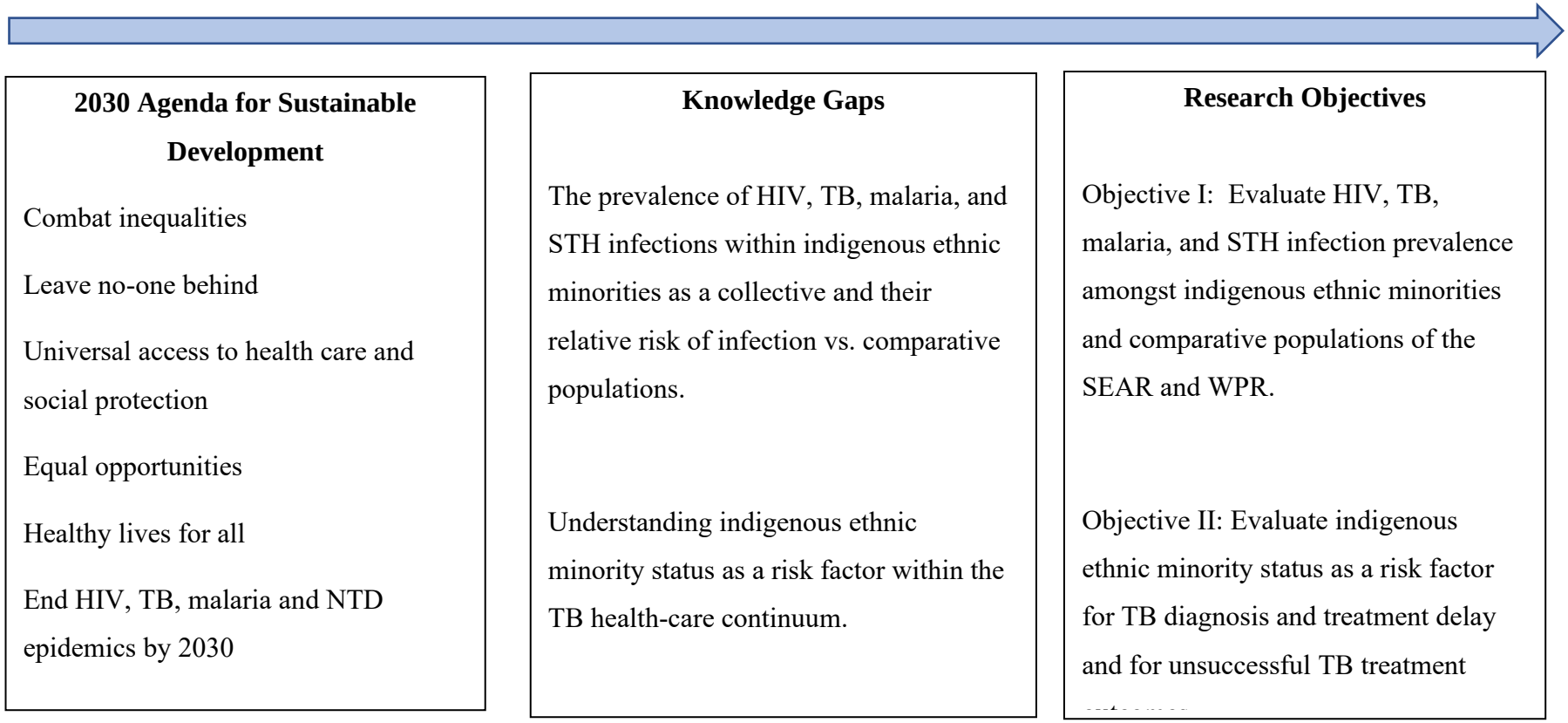

Figure 1: Conceptual framework of thesis in relation to research objectives

Thesis Structure

Table 1: Thesis structure

Section	Contents	Publications
PART I	**Introduction**	
Chapter I	Thesis Overview - Research objectives and conceptual framework - Thesis structure - Contribution statement - Methods summary	
Chapter II	Subjects of Study: study populations and diseases - Indigenous minorities - Ethnic minorities - HIV - TB - Malaria - STH	
PART II	**Prevalence of HIV, TB, malaria, and STH infections in indigenous ethnic minorities of the SEAR and WPRs**	
Chapter III	The prevalence of HIV infection in indigenous ethnic minority populations of the SEAR and WPR.	The prevalence of HIV infection in minority indigenous populations of SEAR and WPR: a systematic review and meta-analysis: Under review - *AIDS and Behaviour*

Chapter IV	Protocol for a systematic review of TB, malaria, and STH infection in indigenous ethnic minority people of the SEAR and WPR. The prevalence of TB and malaria in indigenous ethnic minority populations of the SEAR and WPR.	The prevalence of TB, malaria, and STH infection in minority indigenous people of SEAR and WPR: protocol for a systematic review and meta-analysis: Published in *BCM Systematic Reviews* The prevalence of TB and malaria in minority indigenous populations of SEAR and WPR: a systematic review and meta-analysis: Published in *Pathogens and Global Health*
Chapter V	The prevalence of STH infections in indigenous ethnic minority populations of the SEAR and WPR.	The prevalence of STH infections in minority indigenous populations of SEAR and WPR: a systematic review and meta-analysis: Published in *PLOS Neglected Tropical Diseases*
PART III	**Identification of touch points on the TB health-care continuum where indigenous ethnic minority status is a risk factor**	
Chapter VI	The impact of indigenous ethnic minority status on TB diagnosis and treatment delays in Hunan, China.	The impact of ethnic minority status on TB diagnosis and treatment delays in Hunan, China: Published in *BMC Infectious Diseases*
Chapter VII	Risk factors associated with poor tuberculosis treatment outcomes in Hunan, China.	Risk factors associated with poor tuberculosis treatment outcomes in Hunan, China: Published in *Tropical Medicine and International Health*

PART IV	**Discussion and conclusion**	
Chapter VIII	Study findings and considerations - HIV, TB, malaria, and STH disease burden and SDG objectives - The prevalence of HIV, TB, malaria, and STH infections within different populations of the SEAR and WPR - HIV, TB, malaria, and STH prevalence data availability for indigenous ethnic minority populations of the SEAR and WPR - Trends in HIV, TB, malaria, and STH infections in indigenous ethnic minority populations of the SEAR and WPR - Risk factors associated with TB diagnosis and treatment delays and unsuccessful treatment outcomes in Hunan Province, China - Study results and the SDGs - Strengths and limitations - Recommendations - Future research recommendations - Policy recommendations - Conclusions	

Contribution Statement

This thesis by compilation is based on the following six papers. The candidate's contribution is detailed in Table 2 and signed co-author attribution tables are included in Appendix 1. All analyses were undertaken by the candidate under the guidance of the supervisors.

Paper 1: Gilmour, B, Alene KA, Atalell KA, Clements ACA. The prevalence of HIV infection in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis. Under review with *AIDS and Behaviour.*

Paper 2: Gilmour B, Alene KA, Clarke N, Clements ACA. The prevalence of TB, malaria & STH infection in minority indigenous people of SEAR and WPR: protocol for a systematic review and meta-analysis. *BMC Systematic Reviews* 2021 Jul 10;10(1):203. doi: 10.1186/s13643-021-01753-y.

Paper 3: Gilmour B, Alene KA, Clements ACA. The prevalence of TB & malaria in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis. *Pathogens and Global Health* 2021 Dec 14;1-19. doi:10.1080/20477724.2021.2011579

Paper 4: Gilmour B, Alene KA, Clements ACA. The prevalence of STH infections in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis. *PLOS Neglected Tropical* Diseases November 10, 2021 https://doi.org/10.1371/journal.pntd.0009890

Paper 5: Gilmour B, Xu Z, Bai L, Alene KA, Clements ACA. The impact of ethnic minority status on tuberculosis diagnosis & treatment delays in Hunan Province, China. *BMC Infectious Diseases* (2022) 22:90 https://doi.org/10.1186/s12879-022-07072-4

Paper 6: Gilmour B, Xu Z, Bai L, Alene KA, Clements ACA. Risk factors associated with poor tuberculosis treatment outcomes in Hunan Province, China. *Tropical Medicine and International Health* 2022 Mar;27(3):290-299. doi: 10.1111/tmi.13720. Epub 2022 Feb 6.

Table 2: Candidates contribution to published papers

Manuscript title	Journal	Status	Number of co-authors	Candidate's position in authorship	Candidate's contribution				
					Conception + design	Acquisition of data + method	Data conditioning + manipulation	Analysis + statistical method	Interpretation + discussion
The prevalence of HIV infection in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis	*AIDS and Behaviour*	Under review	4	First	√	√	√	√	√
The prevalence of TB, malaria & STH infection in minority indigenous people of SEAR and WPR: protocol for a systematic review and meta-analysis	*BMC Systematic Reviews*	Published	4	First	√	√	√	√	√
The prevalence of TB & malaria in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis.	*Pathogens and Global Health*	Published	3	First	√	√	√	√	√
The prevalence of STH infections in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis	*PLOS Neglected Tropical*	Published	3	First	√	√	√	√	√
The impact of ethnic minority status on tuberculosis diagnosis & treatment delays in Hunan Province, China	*BMC Infectious Diseases*	Published	5	= First	√	√	√	√	√
Risk factors associated with poor tuberculosis treatment outcomes in Hunan Province, China	*Tropical Medicine and International Health*	Published	5	= First	√	√	√	√	√

Methods Summary

To address the research objectives of this thesis, systematic reviews, and meta-analyses as well as retrospective cohort studies were conducted among indigenous ethnic minorities and comparative population groups in the Asia Pacific regions. A summary of the methods used to address the research objectives is detailed in table 3. Detailed information on the methods is presented in the respective chapters.

Table 3: Methods summary

Research objective	**Study design**	**Study population**	**Data sources**	**Data analysis**
PART II				
Quantify the prevalence of HIV, TB, malaria & STH infections amongst indigenous ethnic minority populations of the SEAR and WPR. Where data are available, evaluate the relative risk of infection for indigenous ethnic minorities vs. comparative populations.	Systematic review and meta-analysis	Indigenous ethnic minorities Comparative populations	SCOPUS, Web of Science, Medline (Ovid), EMBASE (Ovid)	Random-effects meta-analysis and meta-regression
PART III				
Identify at which points along the TB health-care continuum, indigenous ethnic	Retrospective cohort	TB patients	TB patient data from the TB Control Institute of	Univariate and multivariate logistic

minority status presents as a risk factor.			Hunan (2013-2018)	regression models

Chapter II: Subjects of Study: Study populations and diseases

The following chapter gives background information on the study populations and the diseases that have been evaluated in this study.

The intent of this thesis was to study minority populations indigenous to their country. There is however no universal definition of 'indigenous' and each country has its own population classification system. China for example, does not officially use the term 'indigenous' but recognizes 55 ethnic minority peoples and likewise, India recognizes their 'indigenous peoples' as 'scheduled tribes'.[10 11] Therefore the population groups included within this study are a reflection of the respective country's terminology. Within this study, the term 'indigenous ethnic minority' is used with the intent of representing minority populations indigenous to their country.

Globally, indigenous ethnic minorities tend to experience a disproportionate burden of disease and poorer health outcomes than their majority population counterparts.[7-9] If the goals of the 2030 Sustainable Development Agenda are to be achieved, vulnerable populations that experience disparate disease burdens and healthcare inequities, need to be identified and appropriate interventions implemented.

Indigenous minorities

There are an estimated 370-500 million indigenous people[12] dispersed across 90 countries with 70% residing in the Asia and Pacific regions.[13] Although there is no universally accepted definition of 'indigenous' these populations are characterized by the following attributes:

- An individual and/or collective who self-identify as 'indigenous,'[13-16]
- Distinct populations who are descendants of the original or earliest known inhabitants of a country or geographical region who have historical continuity with societies pre-colonization,[6 13-16]
- Having strong links with their ancestral lands upon which they are reliant, [6 13 14 16]
- Having their own languages, cultures, and belief systems that are distinct from mainstream or dominant society,[13-16]

- Having their own distinct social, political, and economic systems,[14-16]
- Retaining a strong desire to maintain their unique identity and culture,[14 16 17]
- Non-dominant populations within society, [16 7]

The socioeconomic inequalities faced by minority indigenous people relative to their non-indigenous counterparts account, in part, for the significant health disparities they experience.[7 18] In addition to poverty and malnutrition, minority indigenous populations can experience poor living conditions, inadequate sanitation, low levels of educational attainment and limited access to healthcare services whilst often being exposed to prevalent infections and environmental contamination.[7] Across both industrialized and developing nations, minority indigenous people have a lower life expectancy at birth,[6] a greater incidence and burden of disease and higher rates of mortality and disability than their non-indigenous counterparts,[7] In addition to disparities in physical health, colonization has had a detrimental impact on the spiritual and mental well-being of traditional societies, [6 7] whose peoples are shown to have higher rates of mental health disorders and suicide.[19]

The lack of an official definition of 'indigenous' compounds the complexities in addressing the health disparities experienced by these populations. Differentiated data is not readily available and many countries do not officially recognise their indigenous peoples.[7 20] There is an urgent need for accurate and relevant data to be collated at all levels (internationally, nationally, regionally and locally) to facilitate the calculation of trends and to evaluate the impact of interventions.[7]

The viability of indigenous societies will be fundamental to the future of the planet and all its people. Although indigenous people are only estimated to represent just over six per cent of the global population, they are the guardians of 80% of the world's biodiversity and the custodians of 11% of the planet's forests.[6 13 14] Indigenous people have a distinctive place in the cultural heritage of mankind and possess unique and invaluable knowledge regarding the sustainable management of natural resources.[13 20]

Ethnic minorities

Ethnic minorities have many parallels with indigenous minorities. The definition of ethnicity is complex and imprecise. It is a self-claimed, socially construed identity

which may be linked to culture, religion, language, or place of origin.[21] In general, ethnic minorities are shown to experience poorer health outcomes, greater morbidity, and higher mortality than their non-minority counterparts.[5] Identifying the underlying reasons for these inequalities is complex and although socio-economic status has been shown to have a significant impact, when data are normalized, health disparities persist.[22] There are many variables from patient factors through to health care provider factors that can contribute to the health disparities that ethnic minorities experience.[23] The limitations in defining ethnicity and the fact that many countries fail to systematically record ethnicity data amplifies the complexity in identifying health inequities between population groups.[24 25]

HIV

HIV (human immunodeficiency virus) is an exogenous member of the Retroviridae family, classified within the *Lentivirus* genus.[26] Antigen and genetic characteristics differentiate the virus into type 1 (HIV-1) or type 2 (HIV-2) which have different zoonotic ancestories.[27 28] HIV-1 evolved from the simian immunodeficiency virus (SIV) that infects apes and HIV-2 evolved from the SIV that infects the sooty mangabey monkey.[28] HIV-1 is classified into four groups M-P, with group M further differentiated into subgroups A-D, F-H, J and K and HIV-2 is classified into groups A-H with circulating recombinant forms (CRF) increasing genetic diversity.[27 29] Each global region has a unique distribution of HIV classification, with HIV-1, group M, subgroup C being most prevalent worldwide.[30] Phylogenetic and epidemiological studies suggest that the virus entered the human population around 1920,[27] with the first case reported in 1981,[31] since which it has claimed 36.3 million lives globally.[32] At the end of 2020, it was estimated that 37.7 million people were infected with HIV globally, with the African region hardest hit followed by the Asia Pacific.[32 33]

HIV impairs immune function by infecting CD4-bearing cells.[26] Initial infection may result in acute syndrome typified by a range of symptoms, following which there is a long and variable asymptomatic period.[26] When immunodeficiency is advanced, the disease is classified as AIDS, which is characterized by a range of life-threatening opportunistic infections and neoplasms.[26 32]

As HIV is transmitted across mucosal surfaces, by percutaneous inoculation and vertically between mother and child, certain behaviours and population groups are at increased risk of infection.[34] Key high-risk population groups include injecting drug users (IDU), men who have sex with men (MSM), sex workers and the sexual partners of these key population groups.[35 36] Risk factors include unprotected sex, additional concurrent sexually transmitted infection (STI), sharing contaminated drug injecting equipment and receipt of contaminated transfusions.[32]

HIV infection can be diagnosed by antibody tests, antibody/antigen tests or by nucleic acid tests (NAT),[37] with HIV-2 diagnoses requiring the use of HIV-2 specific assays.[26] AIDS is diagnosed on the basis of a CD4 count <200/mm and opportunistic infections.[38]

HIV infection cannot be cured but control strategies include antiretroviral therapy (ART), education, and public health interventions.[26 32] ART reduces viral load and the risk of transmission whilst allowing the CD4 count to recover.[39 40] ART involves taking a combination of medicines that are classified into seven categories depending on their mode of action.[41] Although the successful uptake of ART has saved millions of lives, increasing drug resistance threatens progress.[42] The genetic diversity of HIV and CRFs contribute to drug resistance and present ongoing challenges to vaccine development.[30 42]

The UN Sustainable Development Agenda includes the goal of ending the global HIV/AIDS epidemic by 2030.[2] In seeking to achieve this target, the Joint United Nations Program on HIV and AIDS (UNAIDS) has set targets of 95% testing, treatment and viral suppression across all populations by 2025.[43] Both the SDG and UNAIDS apply an equity lens to the approaches recommended to achieve these goals.[2 44]

Tuberculosis

The genetically homogeneous etiological agents of TB are collectively categorized *Mycobacterium tuberculosis* complex (MTC) which is classified within the phylum Actinobacteria, order Actinomycetales, suborder Corynebacterineae, family *Mycobateriaceae* and genus *Mycobacterium.*[45] The MTC includes 11 species that affect a range of mammalian hosts; *Mycobacterium tuberculosis* (*Mtb*) is the most

significant to human health globally, with *Mycobacterium africanum* and *Mycobacterium canettii* emerging in Africa.[45 46 47] Species with zoonotic potential include *M.caprae,*[48] *M.microti,*[49] and *M.bovis* with the latter being most prolific of this group.[46] The potential of *Mtb* to transfer to animals that are in close contact with infected humans has been demonstrated.[47 50] It is estimated that the progenitor species from which *Mtb* has evolved may date back three million years.[51] Currently circulating strains of the pathogen are defined by six phylogeographic lineages that appear to have evolved with specific human populations.[52]

Over time, *Mtb* is thought to have caused more deaths than any other infectious agent,[53] a trend that continues today.[46] In 2019, an estimated 10 million people fell ill with the disease and 1.4 million people died, with the greatest burden befalling South East Asia followed by Africa and the Western Pacific Region.[46] The COVID-19 pandemic has had a significant impact on the TB figures reported for 2020, which show an 18% year on year reduction in case notifications.[54] A consequence of the reduction in TB diagnoses, has been an increase in the number of deaths, which are estimated at 1.5 million in 2020.[54] Although further research is required to understand activation from latency to active disease,[55] modelling studies suggest that latent TB infection (LTBI) is prevalent in just under one-quarter of the world's population.[56]

Mtb is an obligate intracellular bacterium, which, despite being capable of affecting any organ within the body, most commonly infects the lungs (pulmonary TB).[46 57] Infection is airborne and there is a 10% lifetime risk of active disease developing.[58 59] The development of active disease is more common following recent (within two years) infection and amongst those with compromised immune systems.[60] The symptoms of active disease are dependent upon the organs affected, those typically associated with pulmonary TB include chest pain, chronic coughing which may include haemoptysis, fever, fatigue, loss of appetite and weight loss.[59 61] In the absence of appropriate treatment, it is estimated that two-thirds of active TB infections will result in mortality.[59] The pathogenicity and virulence of *Mtb* are attributed to a complex cell wall envelope and its ability to impede macrophage development.[47 57] Chromosomal rearrangements and mutations facilitate the pathogens ability to develop drug resistance.[57]

Although *Mtb* is ubiquitous, it is a disease of poverty that fuels the cycle of marginalization.[46] The disease is most prevalent in adults in their productive years and is more common in males than females.[62] HIV and TB are syndemic, HIV increases the risk of primary TB infection and LTBI progressing to active disease.[63]

In 2019, 87% of new TB cases occurred within the 30 high TB burden countries,[64] a classification of 20 countries with the highest number of cases in absolute terms and 10 countries with the greatest per capita case rate that are not already captured within the initial 20 countries.[65] In 2019, two-thirds of the new cases occurred in eight countries: India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa.[64]

Conventional methods of identifying pulmonary TB include symptom assessment, sputum smear microscopy, chest radiography and culture, with the latter considered the gold standard.[66] Due to recent advances in molecular biology, rapid molecular assays are now the recommended diagnostic method for TB and drug-resistant TB (DR-TB),[67] but it is noted that resource constraints are a limitation for their implementation in many low-income countries.[68] Four first-line antimicrobial drugs are recommended for the treatment of drug-susceptible active disease- isoniazid, rifampicin, ethambutol and pyrazinamide.[69] Treatment regimens take 6-9 months to complete and protocols must be followed and completed to be successful and prevent the development of drug resistance.[69] Fundamental to the success of TB programs, is early case detection and prompt and appropriate treatment.[70] Delays in timely diagnoses and appropriate treatment leads to disease progression, poor treatment outcomes, TB dissemination and an increased risk of the emergence and transmission of drug-resistant strains.[70 71]

In addition to treatment regimes, preventative health care services are fundamental to combatting the disease; these services include pre-emptive treatment, transmission prevention and vaccination.[46] Preventative treatment involves the systematic treatment of high-risk populations- those living with HIV, household contacts of bacteriologically confirmed cases and those at clinical risk.[46] Transmission prevention measures include environmental and personal protection initiatives.[46] Bacille Calmette-Guérin (BCG) is the only licenced vaccine that can prevent severe

disease developing in children,[46] and work is underway to develop a vaccine for adults, with the candidate M72/AS01$_E$ showing potential.[46 72]

Multidrug-resistant TB (MDR-TB), which is defined as *Mtb* that does not respond to the most effective first-line antibiotics, isoniazid and rifampicin, is a growing health security threat.[64] Although MDR-TB may be treated with second-line chemotherapy, options are limited, the regime is protracted (up to two years) and the global success rate is only 57%.[64] MDR-TB, which is resistant to any of the fluoroquinolones and at least one of the second-line injectable drugs (kanamycin, amikacin or capreomycin), is classified as extensively drug-resistant TB (XDR-TB).[73] It is estimated that 6.2% of MDR-TB cases have XDR-TB which has a poorer prognosis for a successful treatment outcome and concerningly it is thought that MDR-TB and XDR-TB are as transmissible as *Mtb.*[73] The complex challenges of drug resistance are amplified in vulnerable population groups.[74]

The WHO's End TB Strategy and the UN SDG's that were adopted by the World Health Assembly and UN Member States in 2014 and 2015 respectively, seek to end the global TB epidemic.[46 75] The End TB Strategy milestones include a 95% reduction in the number of deaths and a 90% reduction in disease incidence by 2035 relative to 2015; and that by 2035, TB-affected families will not be burdened with catastrophic costs.[75] Globally, countries are not on track to achieve the interim 2020 milestone targets and the Coronavirus Disease 2019 (COVID-19) pandemic will further derail progress.[46]

Malaria

Malaria is a life-threatening disease caused by the obligate parasitic protozoan *Plasmodium spp.*[76 77] The genus is classified in the phylum Apicomplexa, order Haemosporida and family *Plasmodidae* and comprises an array of 270 species that infect a diverse range of vertebrate hosts.[77] The five species known to infect man include *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and the zoonotic species *Plasmodium knowlesi.*[78]

Plasmodium spp. have an incredibly complex multistage lifecycle, which occurs across vertebrate and invertebrate hosts.[79] The female mosquito of the *Anopheles* genus is the vector of human malaria and the definitive host in which the sexual

phase of the parasites' life cycle occurs.[80 81] The asexual phase of the life cycle occurs initially within the human liver followed by red blood cells where replication and subsequent cell destruction create the symptoms of malaria.[82] This life-cycle means that the parasite requires the ability to thrive in vertebrate and non-vertebrate hosts, in extracellular and intracellular environments, to infect numerous cell types and to avoid multiple immune systems.[79] The specialized protein expressions and metabolic pathways that enable the parasite to succeed, present challenges to the development of effective vaccines and therapeutic treatments.[79] The parasite has also evolved a mechanism to increase the probability of transmission as infection is mutually beneficial to both itself and the mosquito.[80]

This successful pathogen has shaped the course of history since ancient times and continues to be of significance today, with 40% of the world's population living in regions where *Plasmodium* is transmitted.[83]

In 2020, there were an estimated 241 million cases of malaria and 627,000 deaths, with the World Health Organization (WHO) African region carrying a disproportionate burden of the disease, followed by SEAR.[84 85]These infection and mortality metrics are however thought to be under-estimates because many cases go unreported and unregistered.[86]

P.falciparum the most pathogenic species in man,[87] accounts for the majority of malaria cases in the WHO Africa, South-East Asia, Eastern Mediterranean and Western Pacific regions.[81] The less pathogenic but still potentially life-threatening species, *P.vivax* dominates the Americas region.[81]

Malaria is more prevalent in the tropics with its distribution primarily governed by seasonal temperature patterns.[88] There is a strong correlation between regions where malaria prospers and poverty, with causality likely to be bidirectional.[88] Within a population, some groups have a greater probability of contracting malaria and of developing severe disease.[89] These population groups include infants, children under the age of 5 years, pregnant women, people living with AIDS/HIV and mobile populations who lack partial-immunity such as migrants and refugees.[89]

The symptoms of malaria include fever, headache, chills and fatigue and the destruction of red blood cells can result in anaemia and jaundice.[81 90 91] In the absence of rapid diagnosis and treatment, *P. falciparum* infection can lead to renal

failure, seizures, coma and death.[81 90] Prompt and accurate parasitological testing by microscopy or rapid diagnostic test (RDT) is important to ensure a correct diagnosis and effective treatment.[92] Accurate diagnosis prevents unwarranted treatment so limiting the development of drug resistance.[92] Artemisinin-based combination therapies (ACT) are recommended for the treatment of uncomplicated *P. falciparum* malaria.[92] ACT or chloroquine are recommended for the treatment of uncomplicated, *P. malariae*, *P. knowlesi*, *P. vivax* and *P. ovale* and primaquine may be administered to prevent malaria relapse in the latter two species.[92] ACT are not recommended for the treatment of uncomplicated malaria during the first trimester of pregnancy and alternate regimens may also be recommended in other high-risk population groups.[92] Artesunate used in conjunction with ACT is recommended for the treatment of severe malaria.[92]

In epidemics, complex emergencies and as a tool to achieve elimination, antimalarial drugs may be used in mass drug administration (MDA) programmes.[93] Routine treatments can also be used for chemoprophylaxis in travellers and can be intermittently administered in areas of high transmission to pregnant women and infants.[81 90] In some areas of Africa, chemoprevention is recommended for children under the age of 5 years in seasons of high transmission.[81] A growing threat to the control and treatment of malaria is drug resistance, which has developed in both *P.falciparum* and *P.vivax* and is shown to be extensive in some parts of the world.[90]

A key component to the control of malaria is prevention, with vector management through the use of insecticide-treated nets (ITNs) and indoor residual spraying (IRS).[90] Additional methods of larval control and the use of personal protective measures are also appropriate in some circumstances.[90] Although there is no currently approved vaccination, the RTS,S/AS01 (RTS,S) vaccine against *P. falciparum* has commenced pilot introduction in certain regions of Africa.[90 94]

In 2015, the World Health Assembly adopted the WHO Global Technical Strategy for Malaria 2016-2030.[86] The strategy includes the following global targets which are set relative to a 2015 baseline: a 90% reduction in malaria mortality and incidence rates by 2030; the elimination of disease within 35 countries by 2030 and the prevention of malaria resurgence in countries that are classified malaria- free.[86] Although significant progress has been made in combating the disease, this trend is

reversing for some countries due to funding gaps and the COVID-19 pandemic.[95] Diminishing resources emphasize the importance of accurate and relevant prevalence data to inform locally appropriate solutions.[95]

Soil-transmitted helminth infections

STHs are a group of parasitic worms belonging to the phylum Nematoda.[96] The main species associated with human infection are *Ascaris lumbricoides* (class Secernentea, order Ascarisisa, family Ascarididae); *Trichuris trichiura* (class Adenophorea, subclass Enoplia, order Trichocephalida, family Trichuridae); *Necator americanus* (class Secernentea, order Strongylida, family Uncinariidae); *Ancylostoma* duodenale (class Secernentea, order Strongylida, family Ancylostomidae); and to a lesser extent *Strongyoides stercoralis* (class Secernentea, order Rhabditida, family Strongyloididae).[97] The zoonotic species, *Ancylostoma ceylanicum* and *Ancylostoma caninum*, can also cause disease in man.

Although the four most prevalent species of STH: *A. lumbricoides* (roundworm), *T. trichiura* (whipworm), *A. duodenale* and *N. americanus* (hookworms) are each unique, they are considered as a group due to similarities in their modes of transmission, methods of prevention and control interventions. [98 99] The four main species of STH have a similar lifecycle with the adult stage inhabiting the host intestine and reproducing sexually to produce eggs that are passed out in the faeces.[100] New *A. lumbricoides* and *T. trichiura* infections occur through direct faecal-oral transmission in contaminated environments.[101] *A. duodenale* and *N. americanus* infections are acquired by skin penetration of the infective filariform larva, and *A. duodenale* infection may also occur by oral and transmammary transmission.[102] *A. duodenale* has the ability to undergo hypobiosis within the host for several months.[98] STHs do not replicate within the host and so worm burden is a reflection of the extent of exposure to a contaminated environment over time.[100]

The primary causative agent of Strongyloides is *S. stercoralis* and to a lesser extent the zoonotic species *Strongyloides fuelleborni fuelleborni* and *Strongyloides fuelleborni kellyi.*[103] *S. stercorlais* has a number of characteristics that distinguish it from the other STHs, including a complex life cycle, which alternates between a free living and a parasitic phase that can be auto-infective.[103 104]

Nematodes are the most abundant multicellular organisms on the planet,[105] and it is estimated that the four main species of STH currently infect 1.5 billion people worldwide.[106] Due to a lack of epidemiological data for many regions, the current prevalence figure is considered to be an under-estimate;[107] a concept supported by modelling in 2010, that shows 77% of the world's population to live in areas at risk of stable transmission.[108] STH prevail in the tropics and subtropics,[106] and it is estimated that 67% of infections occur within Asia.[109]

STH are the most prevalent NTD.[99] NTDs are a group of diseases that are classified as such due to their disproportionate impact on the world's poorest and most impoverished populations.[110] In 2016, 3.4 million disability-adjusted life years (DALY) were lost due to STH infections,[111] with the majority of this figure attributable to morbidity rather than mortality.[112] STH morbidities can be hard to identify due to poverty, malnutrition and the presence of other infections, but sequelae include malnutrition, anaemia, impaired physical and cognitive development and reduced productivity,[106 112] with the quantum of morbidity directly related to the burden of infection.[106]

To date, the cornerstone of global health intervention has been the periodic administration of albendazole or mebendazole to high-risk population groups living in endemic areas.[113] High-risk groups include women of reproductive age, certain high-risk occupation groups, pre-school children and school-age children.[106] The latter group is targeted specifically, due to the impact of STH infection on growth and cognitive development and the logistical advantage of administering drugs through the school infrastructure.[113] This approach however recognises that it is only able to reduce the impact of infection and that it is not a solution to interrupting transmission and achieving elimination.[113] The age distribution of infection is STH species-specific and so the potential advantages of community-wide drug administration will be dependent upon the STH species and the baseline level of infection.[114] Although MDA may halt transmission in the short term, health education and appropriate water, sanitation and hygiene (WASH) provision are required to reduce the odds of re-infection and provide a sustainable outcome.[115]

Research and development are required to identify the next generation of anthelmintics as concerns are raised about the potential of drug resistance and in

recognition of an inadequate efficacy profile against some species.[116] Albendazole and mebendazole are shown to have low and variable efficacy against *T. trichiura* and hookworm respectively.[117] The efficacy of the benzimidazole drugs is also shown to have decreased over time.[117] Although ivermectin is the recommended drug of choice for the treatment of *S. stercoralis*, there is no consensus on the optimal dose.[118]

Knowledge gaps and research objectives

If SDG 3.3 is to be achieved, vulnerable population groups need to be identified within the context of the specific diseases of interest. Although studies have evaluated the prevalence of HIV, TB, malaria, and STH infection in discrete indigenous ethnic minority communities; the prevalence of these infections within this population group as a collective, and the infection risk relative to comparative populations, has not been evaluated. The first research objective of this thesis aims to address this knowledge gap.

In addition to identifying population groups that are more vulnerable to infection, is the need to identify population groups that face disparate health outcomes. Within the health-care system, population status may present as a risk factor, and it is this risk which is considered in the second research objective of this thesis. Research objective II evaluates indigenous ethnic minority status as a risk factor, within the timeframe from symptom onset to treatment outcome, within a discrete DS-TB patient cohort. The variables along the TB health-care continuum that are evaluated include diagnosis delay, treatment delay and unsuccessful treatment outcomes.

Part II: Prevalence of HIV, TB, malaria, and STH infections in indigenous ethnic minority populations of the SEAR and WPRs

Part II aligns with the first research question, which aims to evaluate the prevalence of HIV, TB, malaria, and STH infections in indigenous ethnic minority populations of the SEAR and WPR. Although studies have been undertaken on the prevalence of these infections within individual indigenous ethnic population groups, infection prevalence is not well understood within the context of indigenous ethnic minority people as a collective. The SEAR and WPR were chosen for this study as they capture a high proportion of the world's minority indigenous ethnic people,[14] whilst also providing an opportunity to compare data across countries with different levels of socio-economic development.

Chapter III: The prevalence of HIV in indigenous ethnic minority populations of the SEAR and WPR

This chapter addresses the objectives of Part II and evaluates the prevalence of HIV infection in indigenous ethnic minority populations of the SEAR and WPR. Chapter III also undertakes a comparative analysis of the prevalence of HIV infection in indigenous ethnic minority people vs. other population groups.

Although there have been calls for indigenous ethnic minorities to be recognized as a high-risk population group for HIV, they are not typically classified as such. Within the general population and traditional HIV high-risk populations (e.g., IDUs, MSM, sex workers), comparative analyses showed there to be no significant difference in HIV prevalence between indigenous ethnic minorities and other community members of these population sub-groups.

Within the WPR, the review found the odds of HIV infection to be significantly higher in indigenous ethnic minority peoples compared to other populations. Across the SEAR and WPR, there has been no significant reduction in HIV prevalence in indigenous ethnic minority populations over the years of data collection. Within other comparative populations however, there has been a significant reduction in HIV prevalence over time. Further research is required to understand the underlying causes of these findings.

It is noted that data on Chinese indigenous ethnic minorities represented a large proportion of the data analysed in this chapter. The lack of population-specific data for other countries within the SEAR and WPR highlights the need for improved data disaggregation and reporting.

Full details on the methods, analysis and findings for this chapter are presented in the following paper: Gilmour, B, Alene KA, Atalell KA, Clements ACA. The prevalence of HIV infection in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis *Under review: AIDS and Behaviour.*

Although this is the first infectious agent to be considered within the thesis, findings on HIV prevalence are the last to be published. It was hoped that fieldwork that was initiated before the COVID-19 pandemic could re-commence, but as this was not

possible, HIV was subsequently included within the scope of the thesis. As a result, HIV is not included in the protocol detailed in Chapter IV although the same design, definitions, data rules and methods were followed as registered with PROSPERO.

The prevalence of HIV infection in minority indigenous populations of the South-East Asia and Western Pacific Regions: a systematic review and meta-analysis.

Running Title: **HIV in minority indigenous populations**

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Abstract

A random effects meta-analysis was used to estimate the pooled prevalence of HIV infection within minority indigenous populations of the South-East Asia (SEAR) and Western Pacific Regions (WPR). Sub-group analyses were conducted where comparative data were available, and the sources of heterogeneity were explored through meta-regression using study characteristics as covariates.

The majority of studies were undertaken in high HIV risk subpopulations e.g., injecting drug users and men who have sex with men. There was a paucity of data for many countries with data from China representing 70% of the comparative studies. Within minority indigenous populations the pooled prevalence of HIV infection was 13.7% (95% CI: 8.9, 19) and 8.4% (95% CI: 6.3, 10.7) among other populations. The prevalence differential between populations was significant in the WPR (Adjusted Odds Ratio 1.1, 95% CI: 1.0, 1.2). Across both regions, in contrast to other populations, minority indigenous did not experience any significant reduction in HIV prevalence over the years of data collection. There was large heterogeneity in the prevalence of HIV across studies.

Keywords: HIV-AIDS, Indigenous Peoples, Minority, South-East Asia, Western Pacific, Systematic Review

Introduction

Human immunodeficiency virus (HIV) infection impairs the immune response thereby increasing susceptibility to opportunistic infections and certain cancers.(1) Although HIV infection cannot be cured, antiretroviral therapy is effective in preventing progression to acquired immunodeficiency syndrome (AIDS), which is defined when opportunistic infections are life-threatening due to the severity of immune response damage by HIV.(1, 2)

Since being recognized as a new disease in 1981, HIV/AIDS has claimed 36.3 million lives.(1, 3) In 2020, it is estimated that 37.7 million people were living with HIV globally, a 21% increase relative to 2010.(4) Of this 2020 global estimate, 3.7 million live in the South-East Asia region (SEAR) and 1.9 million in the Western Pacific region (WPR) which has seen an 8% increase in annual new diagnoses relative to 2010.(4) Although these regions have made progress in treating HIV, challenges remain regarding the stigma and prejudice

associated with the disease, and in ensuring that vulnerable populations have equitable access to key services.(5)

The Global AIDS Strategy 2021-2026, *End Inequalities End AIDS*, seeks to address the inequalities that exacerbate the pandemic.(6) Vulnerable populations are also a focus within the United Nations 2030 Sustainable Development Agenda that pledges 'no one is left behind'.(7) The Global AIDS Strategy 2021-2026 and the 2030 Sustainable Development Agenda both seek to end the AIDS epidemic by 2030.(6, 7) However, 2020 interim targets have not been met, and the Coronavirus disease (COVID-19) pandemic is likely to increase inequalities and erode progress in HIV/AIDS control.(6)

The mode of transmission of HIV across mucosal surfaces and by percutaneous inoculation,(8) puts key populations such as men who have sex with men (MSM), injecting drug users (IDU), sex workers and the sexual partners of these key populations, at greater risk of infection.(9, 10) Population groups vulnerable to infection include women, transgender people, migrants, youth, ethnic minorities and displaced, transient, and incarcerated populations. (9, 11, 12)

Social, economic, and cultural inequalities increase vulnerability to HIV infection and increase the probability of HIV progressing to AIDS.(6) Inequalities that impact HIV outcomes include education, income, occupation, discrimination, displacement, and access to health care services.(6) Minority indigenous populations are disproportionately impacted by poverty, face exclusion and discrimination, are disadvantaged in their access to education and healthcare services and are often displaced from their land. (13, 14). Cultural beliefs, religious traditions, and genetics have also been shown to impact the susceptibility of ethnic populations to HIV infection.(15-17)

If the goal of ending the AIDS pandemic by 2030 is to be achieved, the needs of all vulnerable population groups must be addressed. Although the mode of transmission of HIV has focused research on certain sub-population groups e.g., MSM, IDU, other sub-population groups may also be vulnerable to increased infection risk. Because indigenous minorities experience multiple inequalities that may elevate HIV infection risk, it is important that HIV prevalence is evaluated within this population group. Examples of inequalities that may amplify HIV infection risk include, poverty which leads to increased risk behaviours e.g., commercial sex work, plasma donation and migration; mental health disorders which result from colonization and that lead to risk behaviours such as IDU; low levels of educational attainment and limited access to healthcare services.(18-21) A significant proportion of the world's minority indigenous people live within the SEAR and WPR,(22) regions that contain a diverse range of countries with a broad spectrum of socio-economic strata. The aim of the current study was to quantify the prevalence of HIV/AIDS amongst minority indigenous people of the SEAR and WPR and to compare this to HIV/AIDS prevalence in other populations where data are available. Quantifying disease burden is an important starting point to understand the public health resources required to address HIV/AIDS in these vulnerable population groups.

Methods

Search strategy

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23) (Supplementary Data : PRISMA checklist) and a protocol registered with the international prospective register of systematic reviews (PROSPERO: CRD42021274382)(24). In summary, a systematic search was undertaken in four biomedical databases (Web of Science, Scopus, EMBASE (Ovid) and Medline (Ovid))

using the criteria detailed in ‘Supplementary Data: systematic review search terms’. In addition to the database search, Google Scholar, and reference lists from included studies were hand searched.

Study screening and selection criteria

Endnote X9 (Clarivate Analytics) was used to import studies that were identified from the systematic search and to delete duplicates. Studies were subsequently uploaded to Rayyan Qatar Computing Research Institute (QCRI)(25) and two authors (BG and KAAtalell) independently assessed titles and abstracts. The same two authors then independently screened the full-text articles of short-listed abstracts against the inclusion and exclusion criteria. Any discrepancies between the authors were discussed and advice was sought from a third author (KAAlene) if consensus could not be achieved. The corresponding author of the relevant study was contacted when further information or clarification was required.

Inclusion criteria

Studies were included in our systematic review if they were representative cross-sectional surveys that provided data to facilitate the calculation of HIV prevalence. Surveys were required to include minority indigenous participants within the World Health Organization (WHO) regions of South-East Asia or the Western Pacific.

Minority indigenous participants were defined when study populations met each of the following criteria:

- Descendants of the original or earliest known inhabitants of an area; people who have historical continuity with pre-invasion and pre-colonial societies.

- Distinct societies with languages, culture, customs, and social and political frameworks that vary significantly from those of the dominant population.
- Groups of people with strong cultural ties and dependence upon the environment and its resources for their survival.
- People self-identifying as indigenous.
- Groups who face relative disadvantage or discrimination in multiple areas of social existence including- success, education, healthcare, and employment.
- Numerically non-dominant groups in a country or area.

It is acknowledged that each country has its own classification or definition of 'indigenous'. For example, China does not officially use the term 'indigenous' but recognizes 55 ethnic minority peoples and likewise, India recognizes their 'indigenous peoples' as 'scheduled tribes'.(26, 27) The indigenous search terms that were used for each of the countries within the SEAR and WPR are detailed in 'supplementary data systematic review search terms'.

Exclusion criteria

Due to resource constraints, full-text articles not published in English were excluded. Articles were excluded if less than 90% of the study participants (or, for the comparative studies, the minority indigenous category) met the minority indigenous population criteria. Systematic and literature reviews; scientific correspondence e.g., letters to the editor, conference posters and abstracts; case studies and case series with less than 10 participants were excluded. Singapore was excluded from the search because it does not have any minority indigenous populations according to the criteria of this review.

Outcomes

The primary outcome of the study was to calculate the prevalence of HIV infection amongst minority indigenous populations within the SEAR and WPRs. Secondary outcomes were to quantify differences in HIV/AIDS prevalence between minority indigenous and other populations. The intent of the study is to determine whether minority indigenous population status is a risk factor for HIV infection. The identification of at-risk populations facilitates the opportunity to implement community appropriate interventions.

Data extraction and quality assessment

Microsoft Excel version 2016 (Microsoft, Redmond, Washington, USA) was used to record data extracted from shortlisted studies. The data extraction tool was piloted by BG and independently validated by KAAtalell. Following spreadsheet piloting and refinement, the following information was extracted from each included study: first author and year of publication, year of data collection, country of study, population group (minority indigenous or other), name of population group (e.g., Penan, Māori), sub-population group (e.g., drug users, MSM, commercial sex workers), study setting (e.g., health facility, community), diagnostic method, the mean or median age of the study population, study population size (n), and number of HIV positive study participants. Where studies undertook a comparison of infection prevalence across minority indigenous and other population groups, data were extracted for both to facilitate a comparison.

The quality of studies included within the analysis was evaluated using a modified version of the Newcastle-Ottawa Quality Assessment (QA) Scale (28) (Supplementary Data Table 1). Scores within the assessment tool range from 0 to 9. Scores between 1 and 4 were defined as low quality, scores between 5 and 7 were defined as medium quality, and scores between 8

and 9 were defined as high quality, as defined in the protocol registered at PROSPERO and used in other studies.(29)

Study Variables

Countries of study were classified according to the WHO region and mortality strata,(30) and these classifications were evaluated as study variables. Of the five WHO mortality strata classifications (A-E), three (A, B and D) are represented within the SEAR and WPR (A= very low child, very low adult mortality; B= low child, low adult mortality; D=high child, high adult mortality).(31) Other study variables used in the sub-group analysis included: country of study, year of data collection, sub-population group (e.g., drug users, MSM), study setting (e.g., health facility, related venue) and population group (minority indigenous vs. other). Population groups that were non 'minority indigenous' were described as 'other'.

Data Analysis

Meta-analysis was performed using a random-effects model to estimate the pooled prevalence of HIV infection. The Freeman-Tukey double arcsine transformation method was used to address variance instability and confidence limits outside the 0 to 1 range.(32) This method was executed in Stata using the *metaprop* command.(33) The summary effect estimates and 95% confidence intervals (CI) were represented with a forest plot.

Cochran's Q test and the index of heterogeneity squared (I^2) statistic with 95% confidence intervals (CI) was used to assess the heterogeneity between studies within each of the population groups.(34) Heterogeneity between studies was classified low, moderate and high when I^2 values were below 25%, between 25% and 75%, and above 75%, respectively.(34)

To investigate the high heterogeneity that was identified in both study populations, meta-regression was applied using the study characteristics as covariates. To manage non-independent effect sizes without information on the within-study covariance structure, the meta-regression was undertaken using the robust variance estimation (RVE) method.(35).

Potential publication bias was assessed using Funnel plots and asymmetry evaluated using Egger's method, bias was considered significant at $p < 0.05$.(36) Stata/MP version 17.0 (StataCorp, College Station, TX) was used to undertake the data analysis.

Results

Characteristics of the included studies

A total of 3,202 unique studies were identified from our search, from which 144 were shortlisted following title and abstract review. Following full-text screening, 57 studies were included in the final analysis, 43 of which reported HIV prevalence data for comparative minority indigenous and other populations (Supplementary Data Fig 1). A large number of studies were identified by the hand search, the majority of these were undertaken in China. Indigenous minorities are not typically classified as a high HIV-risk population group but China's routine reporting according to its population classification system enabled these articles to be identified despite reference to the population status not being detailed in the title and abstract. The characteristics of the studies included within the analysis are detailed in Table 1. Fifty-seven studies assessed the prevalence of HIV infection amongst minority indigenous populations of the SEAR and WPR.

Where authors reported participant age, all were adults (which was defined differently in different countries) with the exception of one community-based study that included participants >2 years. Of the 57 included studies, 53 detailed their method of HIV diagnosis

and 81% of these used additional confirmatory testing, with ELISA followed by Western Blot confirmation the most common.

Prevalence of HIV infection

The pooled prevalence of infection within minority indigenous populations across the 57 studies, representing 139,938 participants, was 10.8% (95% CI: 7.7, 14.2). There was high and significant (I^2=99.7 p=<0.001) heterogeneity between studies (Supplementary Data Fig 2).

Of the 57 studies, 43 provided HIV data for minority indigenous (n=101,300) and comparative other (n=667,328) populations. Within this dataset, the pooled prevalence of HIV infection was 13.7% (95% CI: 8.9, 19.3) among minority indigenous populations (Fig 1) and 8.4% (95% CI: 6.3, 10.7) among other populations (Fig 2) with both populations showing high and significant (I^2=99.7 p=<0.001) heterogeneity between surveys. The differential in HIV prevalence between the two populations groups was not found to be significant (p=0.103). Details on the pooled prevalence of infection and bivariate meta-regression across the study covariates for both population groups are detailed in Tables 2 and 3 respectively. Table 4 details bivariate meta-regression of HIV infection between populations groups analyzed within the study covariates.

Although the differential was not significant, within both population groups, there was a higher prevalence of HIV infection within the SEAR compared to the WPR. Between population groups, there was no significant difference in HIV prevalence between indigenous minority populations and other groups within the SEAR, but within the WPR, the odds of HIV infection were significantly higher in minority indigenous populations (Adjusted Odds Ratio (AOR) 1.1, 95% CI: 1.0, 1.2 p= 0.040).

There was a significantly higher prevalence of HIV infection in mortality strata B vs. mortality strata A for both minority indigenous (p=<0.001) and other (p=0.002) population groups. However, there was no significant difference in disease prevalence between population groups within the mortality strata.

Within both population groups, there were significant differences in HIV prevalence between countries. Within other populations, the odds of HIV infection in China and Thailand relative to Australia were AOR:1.1 (95% CI: 1.0, 1.2 p=0.001) and AOR: 1.3 (95% CI: 1.1, 1.6 p=0.010) respectively. Within minority indigenous populations an equivalent risk was observed between countries, with an AOR=1.2 (95% CI: 1.1, 1.3 p=<0.001) in China and an AOR= 1.2 (95% CI: 1.0, 1.5 p=0.030) in Thailand relative to Australia. Within China, there were significantly higher odds of HIV infection in minority indigenous populations (AOR:1.1, 95% CI: 1.0, 1.2 p=0.034) compared to other populations.

Within other populations, there was a significant reduction in HIV prevalence in 2000-2010 (p=0.034) and a marginally not significant reduction in 2010-2020 (p= 0.051) compared to 1990-2000. However, the drop in HIV prevalence within minority indigenous populations was not significant across the years of data collection. In 2000-2010, the comparative studies showed the odds of HIV infection to be significantly higher in minority indigenous populations (AOR: 1.1, 95% CI: 1.0, 1.2 p=0.031) than other populations.

Drug users had significantly higher odds of HIV infection than the general population in both minority indigenous (AOR:1.2, 95% CI: 1.1, 1.4 p=0.001) and other populations (AOR: 1.2, 95% CI: 1.1, 1.2 p= 0.002). Within the latter population group, MSM also had significantly higher odds of HIV infection (AOR: 1.1 95% CI: 1.0, 1.1 p= 0.006) than the general population. There was however no significant difference between minority indigenous and other populations within the population subgroups.

Within minority indigenous populations, the prevalence of HIV infection was significantly higher for participants recruited from the community (AOR: 1.2, 95% CI: 1.0, 1.4 *p*=0.027) compared to other recruitment venues. Within other populations, there were no significant differences in disease prevalence between participant recruitment settings.

Data from China represented 70% of the comparative studies and detail within the dataset provided an opportunity to undertake a country-specific analysis. Data on minority indigenous populations in China (Supplementary Data Table 2) found a range in HIV prevalence from 0.05% (95% CI: 0.0, 0.1) to 25.1% (95% CI: 19.5, 31.1) between different ethnic minority groups (Supplementary Data Table 3). Where sufficient studies were available to facilitate an analysis, the difference in HIV infection relative to the Zhuang, was significant for Yi (AOR: 1.1, 95% CI: 1.1, 1.2 *p*= 0.001), Uyghur (AOR: 1.3, 95% CI: 1.1, 1.6 *p*= 0.010) and 'other' ethnic groups (AOR: 1.2, 95% CI: 1.1, 1.4 *p*=0.002). Within the minority indigenous data for China, both MSM (AOR: 1.1, 95% CI: 1.0, 1.1 *p*=0.002) and drug user sub-populations (AOR: 1.3, 95% CI: 1.2, 1.5 *p*= <0.001) had significantly higher odds of HIV infection than the general population. The drop in HIV infection in minority indigenous populations of China was significant (*p*= 0.034) between 2000-2010 and 2010-2020 compared to 1990-2000.

Quality assessment

The average QA score across HIV studies was 5.9 out of a total possible score of 9 (Supplementary Data Table 4). Six studies were classified as low quality (score 1-4), 50 as medium quality (score 5-7) and one as high quality (score 8-9). The QA criteria with the lowest compliance was sample size justification which was only detailed in 7 of the 57 studies, followed by comparability between respondents and non-respondents which was detailed in 15 of the studies. Egger's regression test produced a bias co-efficient of 2.5 (95%

CI: 1.0, 4.0) *p*-value 0.001 indicating the existence of publication bias, which is represented graphically by the funnel plot (Supplementary data: Fig 3).

Discussion

Research shows indigenous minorities to have a higher incidence of HIV/AIDS and that these populations are disproportionately affected by the proximate determinants of infection, in comparison to their non 'minority indigenous' counterparts.(16, 37, 38) The results of this systematic review and meta-analysis show a high prevalence of HIV infection within minority indigenous study participants- the reasons for this, may in part, be attributable to the at-risk sub-population groups studied. In both minority indigenous and comparative 'other' populations, the heterogeneity in HIV prevalence between studies was significant. To evaluate this heterogeneity, sub-group analyses were undertaken, and the significance of study covariates were assessed between the two population groups and within each respective population group. Results show minority indigenous populations to have significantly higher odds of HIV infection than other populations within the WPR, but that any differential between population groups is not significant within the SEAR. The reason for this finding might be attributable to the countries for which data were available. Studies from China represented 69.8% of the comparative studies, and minority indigenous people within China were found to have significantly higher odds of HIV infection than other populations. The paucity of data for other countries may reflect the lack of systematic data collection by indigenous status.

Of the high-risk sub-population groups normally associated with increased HIV prevalence, drug users within minority indigenous populations and drug users and commercial sex workers within other populations were found to have a significantly higher risk of infection than their respective general populations. The review shows minority indigenous status did

not confer a significantly increased risk of infection within each of the respective high-risk sub-population groups, although some studies show that the impact of colonization and marginalization may increase high HIV-risk behaviours such as drug use.(39)

On the basis of data from the comparative studies, other populations have seen a significant reduction in HIV prevalence between 1990-2000 and 2000-2010, and the reduction in disease between 2000-2010 and 2010-2020 was only marginally not significant. Within minority indigenous populations however, none of the reductions in disease prevalence over time were significant. The non-significant reduction in HIV over time (in contrast to other populations), the higher prevalence of infection, and the slower uptake of antiretroviral therapy and biomedical HIV interventions within minority indigenous peoples, increase the risk profile of this population group.(40, 41)

Categorizing minority indigenous peoples as a collective however does not accommodate the significant cultural and socio-economic variations that occur between groups and the levels of disparity relative to their majority populations. Within our review, an analysis of the studies undertaken in China shows there to be a significant difference in HIV prevalence between minority indigenous population groups. There are many population and locally specific social determinants of health that increase HIV prevalence within minority indigenous populations. In some regions, the higher prevalence of infection within minority indigenous populations is attributed to their location along drug trafficking routes and the switch from opium to heroin as the drug of choice.(42) The disparate poverty experienced by minority indigenous populations,(43) can motivate high HIV risk behaviours e.g., commercial sex work, plasma donation and migration for work,(21) and limits their ability to access healthcare.(44) Social and cultural determinants e.g., limited access to infrastructure, language barriers, and cultural context, impact the ability of minority indigenous populations to access education and healthcare.(44, 45) Local beliefs, values and religious traditions are population specific and

also impact HIV risk behaviours.(46) The effectiveness of interventions that seek to reduce HIV infection risk, will be reliant upon understanding the underlying socio-economic and cultural factors associated with elevated infection risk within each discrete community. Although the nuances of different minority indigenous groups need to be taken into consideration, especially when informing culturally appropriate interventions, there have been calls for this population as a collective to be recognized as a high-risk HIV population group.(47) Throughout the HIV pandemic there have been waves of infection in high-risk sub-population groups all of whom experience social and economic marginalization.(38, 48) The COVID-19 pandemic will impact existing and emerging high-risk population groups as resource limitations, reduced mobility and increasing stigma compound.(49)

Although this systematic review summarizes HIV prevalence within minority indigenous populations of the SEAR and WPR, limitations are acknowledged. Analyses are constrained by data availability and data quality. The studies included within these analyses were of moderate quality and interrogation of the significant heterogeneity within study populations was limited to the study characteristics that were available. Due to resource constraints, data included within this review were limited to studies published in English, leading to the exclusion of 19 studies (Supplementary Data Fig 1). The translation and inclusion of these studies would provide additional data for analysis. Although the review specified criteria to describe minority indigenous peoples, there is no universal definition, and each country has its own population classification system. Global political and cultural complexities will challenge the goal of defining a universally accepted classification to specify the population group of interest. There will need to be changes to the understanding of the term indigenous which is currently based upon self-identification and community acceptance.(50) Data collection will also need to address issues such as data privacy, fear of exposing complex issues, definition complexities and perceived intent.(51, 52)

Conclusions

The prevalence of HIV infection among minority indigenous populations of the SEAR and WPR was high. In contrast to other populations, indigenous minorities did not experience a significant reduction in HIV prevalence over the years of data collection, which suggests a need for improved HIV prevention services within this population sub-group. The findings of the study should however be interpreted with caution, due to the significant heterogeneity between studies.

List of abbreviations:

AIDS: acquired immuno-deficiency syndrome; AOR: adjusted odds ratio; CI: confidence interval; COVID: Coronavirus disease; HIV: human immunodeficiency virus; IDU: injecting drug user; MSM: men who have sex with men; PRISMA: preferred reporting items for systematic reviews and meta-analyses; PROSPERO: international prospective register of systematic reviews; QA: quality assessment; QCRI: Qatar computing research institute; RVE: robust variance estimation; SEAR: South-east Asia region; WHO: World Health Organization; WPR: Western Pacific region.

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Table 1: Summary of HIV studies within minority indigenous populations in South-East Asia and the Western Pacific Region

							Minority Indigenous		'Other' Populations	
Study ID	First Author Year of Publication	Year of Data Collection*	WHO Region	WHO Mortality	Country	Study population+	Study Population (n)	Number Positive	Study Population (n)	Number Positive
1	Celentano, 1994[1]	1992	SEAR	B	Thailand	Commercial sex	37	20	149	105
2	Zhang, 2008[2]	2005	WPR	B	China	Drug users	280	129	13	1
3	Zhang, 2007[3]	2002	WPR	B	China	Drug users	439	178	259	37
4	Bao, 2012[4]	2009-2010	WPR	B	China	Drug users	59	5	1255	55
5	Dai, 2012[5]	2009	WPR	B	China	General population	2,077	2	2,418	0
6	Sarkar, 2018[6]	2016-2017	SEAR	B	India	Other	2,491	2	804	10
7	Srirak, 2005[7]	1992-2000	SEAR	B	Thailand	Drug users	137	8	63	6
8	Celentano, 1998[8]	1993-1995	SEAR	B	Thailand	Drug users	1,998	172	1,954	574
9	Razak, 2003[9]	1999-2000	SEAR	B	Thailand	Drug users	702	56	963	122
10	Ruan, 2004[10]	2002	WPR	B	China	Drug users	136	23	243	20
11	Cheng, 2010[11]	2006-2007	WPR	B	China	Other	218	6	871	13
12	Davies, 2012[12]	2000-2009	WPR	A	Australia	Other	371	0	53	0
13	Saxton, 2012[13]	2011	WPR	A	New Zealand	MSM	110	7	750	50
14	Butler, 2007[14]	2004	WPR	A	Australia	Detainees	71	2	320	1
15	Fu, 2011[15]	< 2011	WPR	B	China	General population	420	30	151	3
16	Des Jarlais, 2005[16]	2002	WPR	B	China	Drug users	212	40	82	8
17	Jia, 2008[17]	2004-2005	WPR	B	China	Drug users	285	163	390	190
18	Liu, 2012[18]	2009	WPR	B	China	Commercial sex	12	1	358	11
19	McAllister, 2008[19]	2005-2006	WPR	A	New Zealand	MSM	80	4	693	32
20	Pan, 2018[20]	2013-2014	WPR	B	China	MSM	92	16	275	19
21	Pratihar, 2015[21]	2008-2010	SEAR	B	India	General population	160	26	360	25
22	Shi, 2020[22]	2013-2016	WPR	B	China	General population	63,706	91	560,872	335
23	Wang, 2011[23]	2007	WPR	B	China	Drug users	161	44	1,872	15

24	Ward, 2011[24]	1998-2008∞	WPR	A	Australia	Drug users	1,380	13	14,752	131
25	Wu, 2010[25]	2008	WPR	B	China	Drug users	10	0	730	34
26	Xu, 2008[26]	2006	WPR	B	China	Commercial sex	173	7	259	7
27	Yin, 2007[27]	2004	WPR	B	China	Drug users	122	34	192	22
28	Zhang, 2020[28]	2008-2016∞	WPR	B	China	Drug users	4,199	158	52,483	761
29	Zheng, 1994[29]	1992	WPR	B	China	Drug users	205	120	77	19
30	Zhou, 2011[30]	2009	WPR	B	China	Drug users	221	83	166	48
31	Zhou, 2014A[31]	2012-2013	WPR	B	China	Commercial sex	308	15	473	22
32	Zhou, 2013[32]	2010	WPR	B	China	Commercial sex	5,092	64	7,442	60
33	Zhou, 2015[33]	2004-2012	WPR	B	China	Drug users	5,355	1,521	1,055	91
34	Zhou, 2014B[34]	2004-2012∞	WPR	B	China	Drug users	5,381	1,534	1,058	91
35	Dai, 2017[35]	< 2017	WPR	B	China	MSM	25	6	360	64
36	Griensven, 1995[36]	1992	SEAR	B	Thailand	Commercial sex	51	18	672	136
37	Guanghu, 2018[37]	2013-2015	WPR	B	China	MSM	1,517	149	4,141	337
38	Pan, 2015[38]	2013-2014	WPR	B	China	MSM	73	9	275	20
39	Swe, 2012[39]	2009-2010	SEAR	D	Myanmar	Drug users	135	42	255	57
40	Wu, 2017[40]	2012	WPR	B	China	Commercial sex	1,118	39	2,367	62
41	Yao, 2009[41]	2007	WPR	B	China	Drug users	63	42	251	146
42	Zheng, 2020[42]	2018	WPR	B	China	MSM	101	10	1,011	67
43	Zheng, 2012[43]	2013-2015	WPR	B	China	MSM	1,517	149	4,141	337
Studies on minority indigenous populations only										
44	Dong, 2014[44]	2010	WPR	B	China	General population	6,072	692		
45	Yang, 2018[45]	2010-2016	WPR	B	China	General population	4,897	264		
46	Beyrer, 1997[46]	< 1997	SEAR	B	Thailand	General population	1,000	16		
47	Anita, 2007[47]	2005	WPR	B	Malaysia	General population	2,364	7		
48	Anvikar, 2009[48]	2004-2005	SEAR	B	India	General population	526	0		
49	Estari, 2006[49]	2000-2002	SEAR	B	India	General population	1,556	168		
50	Mamidala, 2006[50]	2002-2004	SEAR	B	India	General population	390	26		
51	Mitra, 2019[51]	< 2019	SEAR	B	India	Other	317	39		
52	Pei, 2018[52]	2011-2016	WPR	B	China	General population	6,311	264		
53	Qin, 2014[53]	2012	WPR	B	China	General population	1,532	71		
54	Yang, 2017[54]	2011-2013	WPR	B	China	General population	4,371	284		

55	Apidechkul, 2019[55]	2016	SEAR	B	Thailand	General population	836	0	
56	Pei, 2020[56]	< 2020	WPR	B	China	General population	800	79	
57	Zhang, 2018[57]	2011-2015	WPR	B	China	General population	7,636	248	

Notes:
*Year of data collection: where the study does not identify the year of data collection, it is assumed to be < than the year of publication
[+] Study population: commercial sex= commercial sex workers + their clients; general population- includes specific study populations i.e., specific age groups, preganant women, blood donors; others= haemodialysis dependent population, TB patients, STD patients
[∞] The data collection timeframe spanned two of the timeframe categories used in the analysis (1990-2000; 2000-2010 or 2010-2020). Ward 2011, 1998-2008 was classified as 2000-2010; Zhang 2020, 2008-2016 was classified as 2010-2020 and Zhou 2014B, 2004-2012 was classified as 2000-2010.

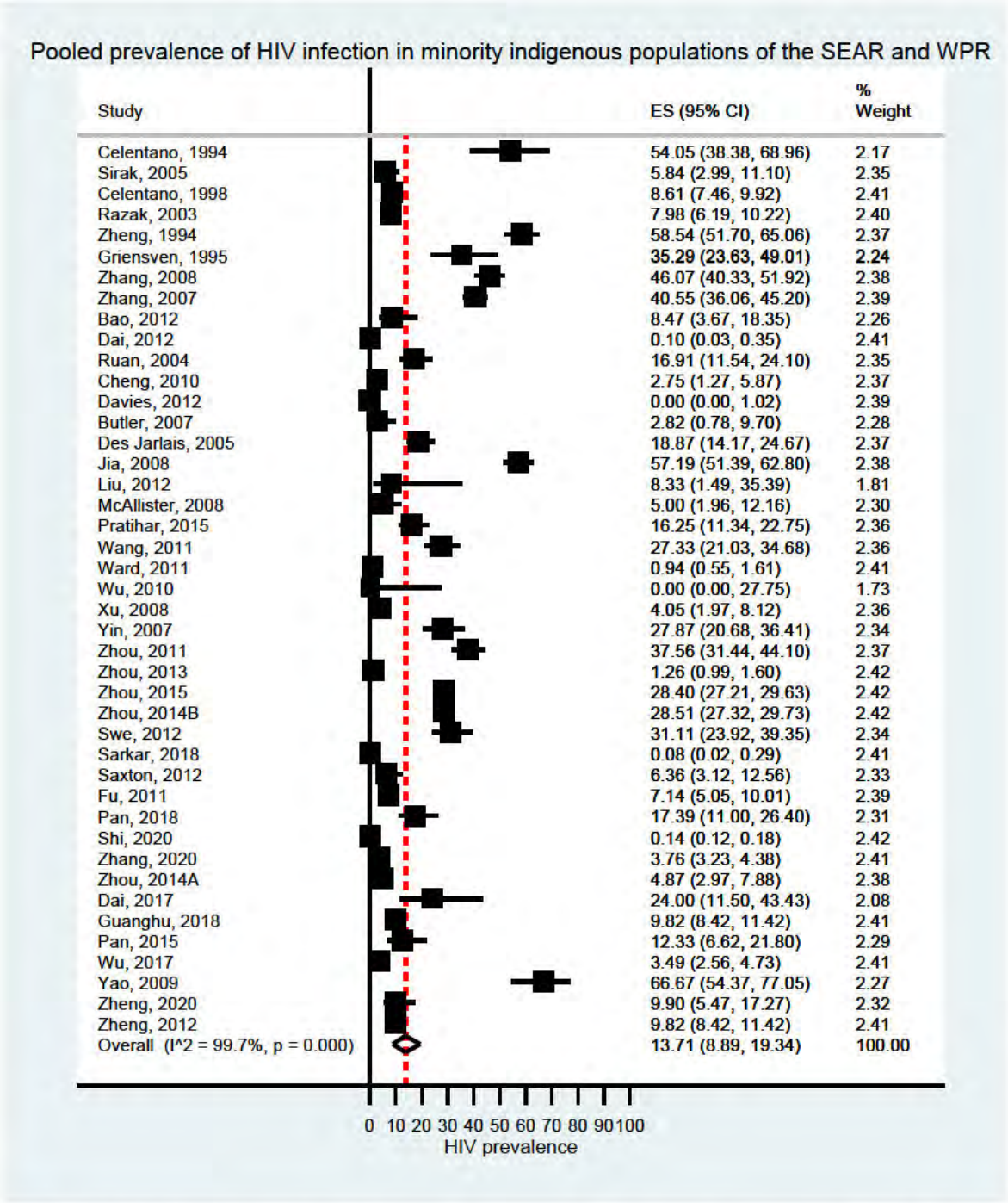

Fig 1: Pooled prevalence of HIV infection in minority indigenous popualations of the SEAR and WPR based on the 43 studies conatining comparative population data.

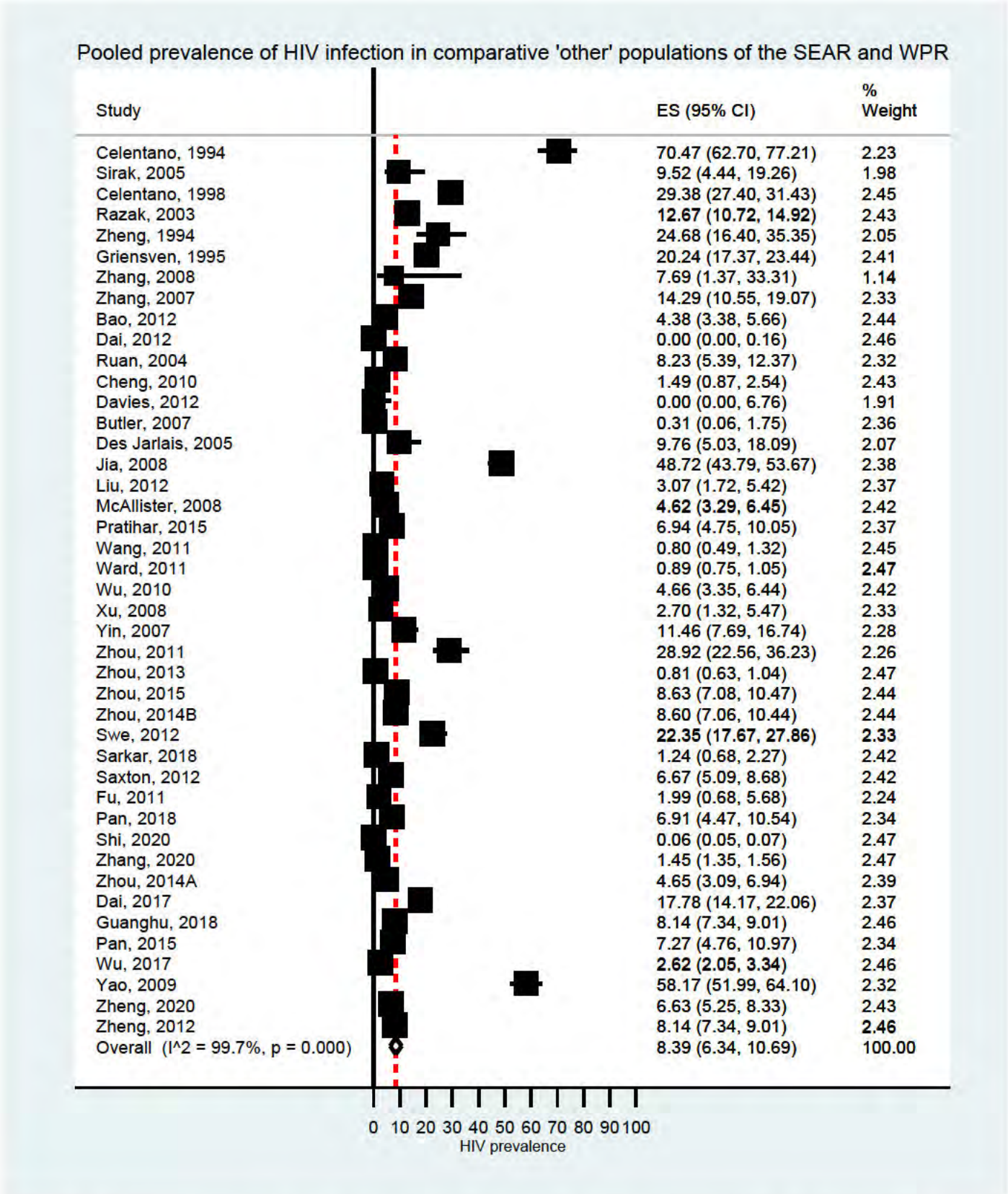

Fig 2: Pooled prevalence of HIV infection in comparative 'other' populations of the SEAR and WPR

Table 2: Pooled prevalance of HIV infection within minority indigenous and 'other' populations analyzed by study covariates.

	Studies (n)	Pooled Prevalence HIV Infection (95% CI) Minority Indigenous Populations	
Population group			
Minority indigenous populations	57	10.77 (7.73, 14.22)	
		Pooled Prevalence HIV Infection (95% CI) Minority Indigenous Populations	Pooled Prevalence HIV Infection (95% CI) 'Other' Populations
Comparative Studies	43	13.71 (8.89, 19.34)	8.39 (6.34, 10.69)
WHO regions			
SEAR	8	15.37 (6.62, 26.78)	18.74 (8.62, 31.60)
WPR	35	13.28 (7.84, 19.83)	6.49 (4.77, 8.43)
WHO Mortality Strata			
A	5	1.89 (0.22, 4.76)	1.94 (0.18, 5.11)
B	37	15.49 (9.92, 21.99)	9.28 (6.85, 12.03)
D	1	31.11 (23.92, 39.35)	22.35 (17.67, 27.86)
Countries			
Australia	3	0.53 (0.00, 2.17)	0.56 (0.42, 0.71)
China	30	15.90 (9.39, 23.68)	7.51 (5.42, 9.89)
India	2	0.16 (0.02, 0.39)[β]	2.52 (1.68, 3.51)
Myanmar	1	31.11 (23.92, 39.35)	22.35 (17.67, 27.86)
New Zealand	2	5.76 (2.77, 9.66)	5.64 (4.50, 6.90)
Thailand	5	16.49 (9.51, 24.85)	26.81 (14.87, 40.76)
Year of data collection			
1990-2000	6	24.50 (11.08, 41.02)	26.48 (15.66, 38.93)
2000-2010	23	14.19 (7.17, 22.99)	6.08 (3.74, 8.92)
2010-2020	14	8.69 (4.72, 13.65)	6.76 (4.18, 9.91)
Sub-population Group			
Drug users	20	23.42 (15.74, 32.08)	13.09 (8.74, 18.14)
Commercial sex[#]	7	9.81 (4.51, 16.64)	9.97 (3.46, 19.27)
MSM	8	9.79 (7.92, 11.83)	7.85 (6.39, 9.44)
General population[^]	4	3.13 (0.63, 7.30)	0.98 (0.05, 2.80)
Detainees	1	2.82 (0.78, 9.70)	0.31 (0.06, 1.75)
Others[$]	3	0.39 (0.00, 1.96)	1.07 (0.58, 1.67)

Recruitment Setting			
Community	8	27.73 (7.48, 54.58)	11.18 (0.88, 29.42)
Health facility*	15	9.32 (2.25, 20.20)	7.20 (2.20, 14.64)
Related venue[@]	12	10.36 (4.86, 17.40)	6.83 (3.36, 11.37)
Database[∞]	2	2.23 (1.94, 2.54)	1.36 (1.27, 1.45)
Multiple[Δ]	6	21.34 (12.20, 32.16)	16.57 (9.89, 24.55)
QA Grade			
Low	4	15.09 (0.12, 46.43)	8.21 (2.31, 17.21)
Medium	39	13.56 (8.84, 19.06)	8.41 (6.28, 10.81)

Notes:
[#] Commercial sex= commercial sex workers + their clients
^ General population- includes specific study populations i.e., specific age groups, preganant women, blood donors
[$] Others= haemodialysis dependent population, TB patients, STD patients
* Health facility: includes compulsory + voluntary detox centers, sexual health clinic, medical camps, blood donation centers, persons registered in the state harm reduction programmes
[@] Related venue: For commercial sex and MSM= bars, sex-on-site venues, massage parlours, gay community fairs; For detainees= prisons; For drug users= shooting places, needle + syringe exchanges
[∞] Database= National Dynamic Management + Control Database for Drug Users (NDMCDDU) or National Sentinel Surveillance (NSS)
[Δ] Multiple includes venue related, community, referral, social media, advertisments, outreach
[β] India- two studies ranging from 0.08 to 16.25% prevalence

Table 3: Bivariate meta-regression of HIV infections within minority indigenous and 'other' populations analyzed by study covariates (minority indigenous population data based on comparative studies only).

	Minority Indigenous Populations		'Other' Populations	
	95% CI	*p* value	95% CI	*p* value
WHO regions				
WPR	1.00		1.00	
SEAR	1.02 (0.89, 1.17)	0.754	1.13 (0.97, 1.32)	0.109
WHO Mortality Strata				
A	1.00		1.00	
B	1.18 (1.10, 1.26)	< 0.001	1.10 (1.04, 1.17)	0.002
Countries				
Australia	1.00		1.00	
China	1.20 (1.11, 1.30)	< 0.001	1.10 (1.05, 1.16)	0.001
Thailand	1.23 (1.02, 1.47)	0.030	1.32 (1.07, 1.63)	0.010
Year of data collection				
1990-2000	1.00		1.00	
2000-2010	0.91 (0.74, 1.11)	0.341	0.82 (0.69, 0.98)	0.034
2010-2020	0.85 (0.69, 1.05)	0.138	0.83 (0.69, 1.00)	0.051
Sub-population Group				
General population^	1.00		1.00	
Drug users	1.23 (1.09, 1.38)	0.001	1.15 (1.06, 1.24)	0.002
Commercial sex[#]	1.10 (0.93, 1.31)	0.261	1.13 (0.94, 1.36)	0.196
MSM	1.06 (0.98, 1.15)	0.166	1.06 (1.02, 1.11)	0.006
Others[$]	0.95 (0.88, 1.02)	0.185	0.99 (0.96, 1.02)	0.442
Recruitment Setting				
Health facility*	1.00		1.00	
Community	1.21 (1.02, 1.44)	0.027	1.06 (0.93, 1.21)	0.384
Related venue[@]	1.02 (0.91, 1.14)	0.773	1.01 (0.90, 1.14)	0.858
Multiple[Δ]	1.13 (0.93, 1.37)	0.225	1.11 (0.93, 1.31)	0.242
QA Grade				
Low	1.00		1.00	
Medium	0.99 (0.86, 1.14)	0.835	1.02 (0.93, 1.12)	0.675

Notes: Bivariate meta-regression analysis was only undertaken where there were 3 or more data sets
[α] the variation in effect size attributable to heterogeneity
[#] Commercial sex= commercial sex workers + their clients
^ General population- includes specific study populations i.e., specific age groups, preganant women, blood donors
[$] Others= haemodialysis dependent population, TB patients, STD patients
* Health facility: includes compulsory + voluntary detox centers, sexual health clinic, medical camps, blood donation centers, persons registered in the state harm reduction programmes
[@] Related venue: For commercial sex and MSM= Bars, sex-on-site venues, massage parlours, gay community fairs; For detainees= prisons; For drug users= shooting places, needle + syringe exchanges
[∞] Database= National Dynamic Management + Control Database for Drug Users (NDMCDDU) or National Sentinel Surveillance (NSS)
[Δ] Multiple includes venue related, community, referral, social media, advertisments, outreach

Table 4: Bivariate meta-regression of HIV infections between minority indigenous and 'other' populations analyzed by study covariates (minority indigenous population data based on comparative studies only).

Categories	95% CI	*p*	95% CI	*p*	95% CI	*p*	95% CI	*p*	95% CI	*p*
WHO Region	**WPR**		**SEAR**							
'Other' population	1.00		1.00							
Minority Indigenous	1.08 (1.00, 1.17)	0.040	0.98 (0.79, 1.21)	0.820						
WHO Mortality Strata	**A**		**B**							
'Other' population	1.00		1.00							
Minority Indigenous	1.00 (0.96, 1.04)	0.973	1.07 (0.99, 1.16)	0.103						
Country	**Australia**		**China**		**Thailand**					
'Other' population	1.00		1.00		1.00					
Minority Indigenous	1.00 (0.99, 1.01)	0.839	1.10 (1.01, 1.20)	0.034	0.93 (0.67, 1.28)	0.606				
Year Data Collection	**1990-2000**		**2000-2010**		**2010-2020**					
'Other' population	1.00		1.00							
Minority Indigenous	1.00 (0.74, 1.34)	0.981	1.10 (1.01, 1.20)	0.031	1.02 (0.91, 1.13)	0.774				
Sub-population group	**Drug users**		**Commercial sex**		**MSM**		**General population**		**Others**	
'Other' population	1.00		1.00		1.00		1.00		1.00	
Minority Indigenous	1.11 (0.99, 1.25)	0.071	1.00 (0.77, 1.29)	0.995	1.02 (0.99, 1.06)	0.183	1.02 (0.95, 1.10)	0.570	1.00 (0.97, 1.02)	0.754
Recruitment Setting	**Health facility**		**Community**		**Related venue**		**Multiple**			
'Other' population	1.00		1.00		1.00		1.00			
Minority Indigenous	1.03 (0.96, 1.11)	0.413	1.19 (0.96, 1.46)	0.101	1.03 (0.89, 1.20)	0.638	1.04 (0.80, 1.37)	0.738		

Notes: Bivariate meta-regression analysis was only undertaken where there were 3 or more data sets

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Chapter IV: The prevalence of TB and malaria infection in indigenous ethnic minority people of the SEAR and WPR

Chapter IV evaluates the prevalence of TB and malaria infection in indigenous ethnic minority people of the SEAR and WPR. This chapter comprises two publications- the first is the protocol for the systematic review of TB, malaria, and STH infection and the second is the systematic review of TB and malaria prevalence.

The protocol and the subsequent reviews were undertaken in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines respectively.[119 120] For each infectious agent, a systematic search was undertaken in four biomedical databases: EMBASE (Ovid), Medline (Ovid), Scopus and Web of Science. Countries within the SEAR and WPR were classified according to the WHO Global Burden of Disease (GBD) regional classification system.[121] Due to the lack of a universally accepted definition of 'indigenous', criteria were established on the basis of attributes described by the UN and the International Labour Organization (ILO) Indigenous and Tribal People Convention (#169).[16 122] The protocol includes information on the study selection, inclusion and exclusion criteria, data extraction, quality and bias assessment and quantitative analysis methods. Full details are included in the following paper: Gilmour B, Alene KA, Clarke N, Clements ACA. The prevalence of TB, malaria, and STH infection in minority indigenous people of SEAR and WPR: protocol for a systematic review and meta-analysis. *BMC Systematic Reviews* 2021 Jul 10;10(1):203. doi: 10.1186/s13643-021-01753-y.

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Systematic Reviews

PROTOCOL Open Access

The prevalence of tuberculosis, malaria and soil-transmitted helminth infection in minority indigenous people of Southeast Asia and the Western Pacific: protocol for a systematic review and meta-analysis

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Abstract

Background: Infectious diseases such as tuberculosis (TB), malaria and soil transmitted helminthiasis continue to impose a significant global health burden and socio economic impact. Globally, minority indigenous people are disproportionately affected by poverty and are shown to experience a disparate burden of disease and poorer health outcomes than the comparative majority population. Despite these inequalities, countries rarely systematically compile epidemiological data disaggregated by ethnicity to enable the extent of the differential to be quantified.

Methods: The systematic review will be reported in accordance with The Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) guidelines. Systematic searches will be conducted in EMBASE, Medline, Scopus and Web of Science for studies reporting data which enable the prevalence of TB, malaria, and/or soil transmitted helminth (STH) infections amongst minority indigenous populations within the Southeast Asia Region (SEAR) and Western Pacific Region (WPR) to be calculated.
Where studies provide data on disease prevalence for both minority indigenous and other populations within the same study, a comparative analysis will be undertaken. In addition to a narrative synthesis, where sufficient data are available, a random effects meta analysis will be conducted to obtain a pooled estimate value for each disease/ infection by country and mortality stratum.
Heterogeneity between studies will be examined using the Cochran's Q test and quantitatively measured by the index of heterogeneity squared (I^2) statistics. The methodological quality of the included studies will be assessed using a modified Newcastle Ottawa Scale.

Discussion: This systematic review aims to analyse the available data on the prevalence of TB, malaria and STH infections within minority indigenous populations of the SEAR and WPR.

Registration: Open Science Framework registration: osf.io/m6sqc

Keywords: Tuberculosis, TB, Malaria, Soil transmitted helminth, STH, Indigenous, Minority, Southeast Asia, Western Pacific, Systematic review

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Background

Despite impacting human health since ancient times [1–3], tuberculosis (TB), malaria, and soil-transmitted helminth (STH) infections continue to create a significant social and economic burden.

TB, an airborne bacterial disease caused by the bacterium *Mycobacterium tuberculosis* ranks in the top ten causes of death worldwide, killing more than 1.5 million people in 2018 [4]. TB is second to Coronavirus disease 2019 (COVID-19) as a leading cause of death due to a single infectious agent [5].

The protozoan parasite *Plasmodium* spp., transmitted via the female *Anopheline* mosquito vector, is responsible for causing malaria. In 2018, malaria is estimated to have caused 228 million cases of disease and 405,000 deaths worldwide [6].

STH infections are a neglected tropical disease (NTD) caused by parasitic nematode worms, including *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and *Necator americanus* and *Ancylostoma* spp. (hookworm). Together, these parasites are thought to infect more than 1.5 billion people [7], a figure which equates to 19% of the world's population. Although currently excluded from STH statistics, *Strongyloides stercoralis* is another pathogenic nematode of significance to human health.

Despite rarely causing mortality, STH infections are of major significance with respect to their burden of morbidity [8] and they are the most prevalent of the NTDs as defined by the World Health Organization (WHO) [9].

In 2016, 51.6 million disability adjusted life years (DALYs) were lost due to TB, 37.3 million DALYs were lost due to malaria and 3.4 million DALYs were lost due to STH infections globally [10]. These three diseases also have a substantial impact on the global economy. TB-related mortality was estimated to cause the loss of 616 billion USD between 2000 and 2015 and is projected to lead to a further loss of 984 billion USD between 2015 and 2030 [11]. Countries where severe malaria (malaria index > 0.5) is endemic are estimated to experience a 1.3% lower economic growth rate per annum [12]. The economic impact of STH infections is difficult to quantify, but mathematical modelling estimates the impact of hookworm infection to cost $2.5 to $138.9 billion per annum [13].

The organisms responsible for TB, malaria and STH infections are endemic in the tropics and are more prevalent amongst populations living in poverty [7, 14–17]. Globally, minority indigenous people are shown to be disproportionately affected by poverty, with their representation amongst the poor reaching 60–70% in some regions [18]. Minority indigenous people experience a disproportionate burden of disease and poorer health outcomes than their majority population counterparts [19–21].

In 2015, all member states of the United Nations endorsed the 2030 Agenda for Sustainable Development [22]. This is an ambitious agenda that calls on all countries to end poverty whilst achieving social, economic and environmental sustainability in an equitable manner [22]. A commitment of the Agenda is that "no one will be left behind" and that endeavours will be made to "reach the furthest behind first" [22].

The effective transformation of the Agenda goals into realistic interventions requires an accurate understanding of target populations and their relative disease burden [23]. At present, data and current indicators are rarely disaggregated to facilitate the identification of vulnerable groups [23].

Although studies have been undertaken on the prevalence of infectious diseases within individual indigenous groups, disease burden is not well understood within the context of minority indigenous people as a collective. Data on these vulnerable groups are crucial in facilitating achievement of the 2030 Sustainable Development Goals and enabling industrialized nations to narrow the health gap between their minority indigenous and majority populations.

A systematic review of disease prevalence in minority indigenous populations will provide a baseline and identify data gaps for this vulnerable population group as a collective.

This paper describes the protocol for a systematic review to determine the prevalence of TB, malaria, and STH infections among minority indigenous people of the WHO Southeast-Asia Region (SEAR) and Western Pacific Region (WPR). TB, malaria, and STH infections have been chosen as they are of major global health significance, and they have social determinants (such as poverty and health service inaccessibility) that make minority indigenous people particularly vulnerable to infection. The SEAR and WPR have been chosen to capture a significant proportion of the world's indigenous people [24] whilst also providing an opportunity to compare data across countries with differing levels of socio-economic development.

Methods/design

This protocol is reported in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines [25], the checklist for which is detailed in Additional file 1. If there is a need to amend this protocol, the date of each amendment and the reason for the change will be described.

Search strategy

A systematic search for epidemiological studies will be conducted in four biomedical databases: EMBASE (Ovid), Medline (Ovid), Scopus, and Web of Science. The search strategy has been developed with the help of a professional librarian and will be undertaken without restriction on the year of publication. Grey literature and regional databases will be included in the search and reference lists from relevant studies hand-searched. Forward and backward citation searching will be undertaken using Google Scholar to identify related articles. Authors of relevant papers will be contacted when there is a need for additional information.

The WHO Global Burden of Disease (GBD) regional classification system [26] will be used to define the countries within the SEAR and WPR. Singapore will be excluded as it does not have any minority indigenous people according to the definitions utilized by this review.

Although there is no universally accepted definition of 'indigenous status,' the United Nations (UN) and the International Labour Organization (ILO) Indigenous and Tribal People Convention (#169) utilise a number of attributes to define indigenous people [27, 28]. For the purposes of this review, the UN attributes will be included, and indigenous minorities will be defined as population groups who meet each of the following criteria:

- Descendants of the original or earliest known inhabitants of an area; people who have historical continuity with pre-invasion and pre-colonial societies [28 30]
- Distinct societies with languages, culture, customs, and social and political frameworks which vary significantly from those of the dominant population [18, 28 31]
- Groups of people with strong cultural ties and dependence upon the environment and its resources for their survival [21, 28, 29, 31]
- People self-identifying as indigenous [28]
- Groups who face relative disadvantage or discrimination in multiple areas of social existence success, education, healthcare, employment [19, 28, 32]
- Numerically non-dominant groups in a country or area [28]

In addition to universal indigenous terms, those relevant to each country will be used as detailed in Additional file 1. Country-specific indigenous terms have been derived from the World Directory Listing of Minorities and Indigenous People [33], Native Planet–Indigenous Mapping [34], and the International Working Group on Indigenous Affairs [35].

The following search terms will be used to identify studies on TB, malaria, and STH infections: "soil transmitted helminth*" OR STH OR *Ascaris* OR *Trichuris* OR *Nectator* OR *Ancylostoma* OR hookworm* OR *Strongyloides* OR malaria* OR *plasmodi** OR tuberculosis OR TB OR "*Mycobacterium tuberculosis*". The Plasmodium and helminth species that will be included within the review are detailed in the inclusion criteria. An example search strategy for Indonesia is detailed in Additional file 1.

Study selection

All articles identified from the systematic search will be uploaded into Endnote X9 (Clarivate Analytics) and duplicate articles removed. Two researchers (BG and KAA) will independently screen the titles and abstracts of the studies on Rayyan QCRI [36] and will then review the full text against the eligibility criteria. Any disagreements will be resolved through discussion and, in the event consensus cannot be achieved, agreement will be reached following discussions with a third author (ACAC).

Inclusion criteria

Studies are required to meet each of the following inclusion criteria:

- Studies that relate to human infection: for malaria, studies on *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium ovale,* and *Plasmodium malariae* which undergo human-to-human transmission and the zoonotic species *Plasmodium knowlesi*; for STH infections, studies on *A. lumbricoides* (roundworms), *T. trichiura* (whipworms), *N. americanus* and *Ancylostoma duodenale* (hookworms), *Strongyloides stercoralis* (threadworms), and the zoonotic hookworm species *Ancylostoma ceylanicum, Ancylostoma caninum,* and *Ancylostoma braziliense*
- Studies including minority indigenous populations
- Studies that report sufficient data to facilitate the calculation of TB, malaria, or STH prevalence
- Studies conducted within the SEAR or WPR as defined by the WHO regional classification system [26]
- Cross-sectional studies/ representative surveys
- Where studies undertake analyses pre and post intervention regimes, only pre-intervention baseline data will be recorded

Exclusion criteria

Studies will be excluded if they meet any of the following criteria:

- Case studies
- Case series with < 10 people
- Scientific correspondence, poster, and conference abstracts
- Systematic or literature reviews
- Due to resource constraints, articles not published in English will be excluded
- Papers where minority indigenous people comprise less than 90% of the group stated to be an indigenous minority population for the purpose of calculating prevalence in the indigenous minority group
- Studies on latent TB; diagnostic methods must be able to confirm active disease (i.e., studies utilizing Mantoux testing as the sole diagnostic will be excluded)

Data extraction

Data from the included studies will be independently extracted in a Microsoft Excel (version 2014) spreadsheet by BG and KAA. The data extraction spreadsheet will be piloted on five papers and then refined, if needed. Corresponding authors will be contacted by e-mail if relevant information is missing or unclear. If clarifications are not received within 4 weeks, the study will be excluded.

Where available, the following data will be extracted from each eligible publication: first author, year of publication, year of study, geographic location of study population (country, region), sample size, demographic factors (age group and sex), study design, bacteria/parasite species, number of people within sample population who are infected, diagnostic method utilised, number of samples taken and analyzed per participant, study population (minority indigenous/other), name of minority indigenous group, co-infection (name of infectious agent), and number of participants co-infected with multiple infectious agents.

Where studies undertake a comparison between minority indigenous and other population groups, data will be extracted for both groups to facilitate a comparison. A data extraction tool is provided in Additional file 1.

Quality and bias assessment

The methodological quality of the included studies will be assessed by two investigators (BG and KAA) using a modified version of the Newcastle-Ottawa Quality Assessment Scale [37] as detailed in Additional file 1. The quality assessment tool will be piloted on 10 randomly selected papers to increase agreement between the two reviewers, and any subsequent differences will be resolved through discussion with a third reviewer (ACAC). The QA tool has scores ranging from 0 to 9; scores between 1 and 4 will be defined as low quality, scores between 5 and 7 will be defined as medium quality, and scores between 8 and 9 will be defined as high quality. Sensitivity analyses will be performed to assess the impacts of methodological quality on the results of the review.

Funnel plots will be used to detect potential publication bias and small study effects. Egger's method will be used to assess asymmetry, with a P value < 0.05 considered to indicate statistically significant publication bias [38].

Quantitative analysis

The primary outcomes are the prevalence of TB, malaria, and STH infection among minority indigenous populations within the SEAR and WPR and across different mortality strata as defined by the WHO [26].

A random-effects meta-analysis will be used to obtain a pooled estimate value for each of the outcomes of interest. Where sufficient studies are available (three or more studies), subgroup analysis will be performed to assess the effects of each study characteristic on the primary outcomes of the study. A comparison will be made between minority indigenous and other population groups if sufficient data are available from studies that compare these groups directly. Heterogeneity between studies will be examined using the Cochran's Q test and quantitatively measured by the index of heterogeneity squared (I^2) statistics with 95% confidence intervals (CI) [39]. Heterogeneity between studies will be considered low, moderate, and high when I^2 values are below 25%, between 25% and 75%, and above 75%, respectively [39]. When there is evidence of significant heterogeneity, the sources of heterogeneity will be explored through meta-regression using study characteristics (e.g., country, mortality strata, diagnostic method) as covariates. The analysis will be conducted in Stata/MP version 18 (StataCorp, College Station, TX, USA).

Discussion

To address the issues of poverty, inequality, and the impact of infectious diseases such as TB, malaria, and soil-transmitted helminthiasis, several global goals and strategies have been endorsed. These include the 2030 Sustainable Development Agenda [22], the WHO 2016–2035 End TB Strategy [40], the WHO Global Technical Strategy for Malaria 2016–2030 [41], and the WHO 2030 targets for STH control programs [42].

Due to poverty, increased exposure to proximal determinants of disease, and living in remote and isolated locations, minority indigenous people have been shown to experience a disparate burden of TB, malaria, and STH infections [43–47].

These health inequalities are significant in all societies because, although minority indigenous people living in industrialized countries have a lower burden of disease

relative to those living in developing countries, the differential in disease burden between indigenous and majority populations has been shown to be greater in industrialized nations [44].

If the WHO targets and the 2030 Sustainable Development Agenda goals are to be accomplished, the prevalence of infectious diseases amongst vulnerable groups needs to be quantified. The WHO Constitution defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [48]. This definition highlights a holistic approach which more closely aligns with the harmonious lifestyle fundamental to indigenous culture [49]. To be successful, health systems need to respect indigenous culture [50] and embrace its positive attributes [51]. The findings of this systematic review will identify data gaps and provide information on the prevalence of disease burden which can be used to inform strengths based and community-led intervention.

Abbreviations

CI: Confidence Interval; DALY: Disability adjusted life year; GBD: Global Burden of Disease; I^2: Index of heterogeneity squared; ILO: International Labour Organization; NTD: Neglected tropical disease; PRISMA P: Preferred Reporting Items for Systematic Review and Meta Analysis Protocols; SEAR: Southeast Asia Region; STH: Soil transmitted helminth; TB: Tuberculosis; UN: United Nations; WHO: World Health Organization; WPR: Western Pacific Region

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643 021 01753 y.

Additional file 1 Appendix 1: PRISMA P 2015 Checklist. **Appendix 2:** Search Criteria. **Appendix 3:** Example search strategy for Indonesia. **Appendix 4:** Data extraction tool. **.Appendix 5:** Quality and bias assessment.

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Authors' contributions

BG, KAA, and ACAC conceived the study. BG developed the search strategy and drafted the protocol. BG, KAA, NEC, and ACAC critically revised the manuscript for methodological and intellectual content and have read and approved the final manuscript.

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The funders had no role in study design, decision to publish, or preparation of the manuscript.

Availability of data and materials

All the required information is available in the manuscript and supporting documents.

Declarations

Ethics approval and consent to participate

Ethics approval and participant consent will not be required as this study will be based upon a review of published work. The finalised report will be disseminated through publication in a peer reviewed scientific journal.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

The second section of Chapter IV evaluates the prevalence of TB and malaria in indigenous ethnic minority populations of the SEAR and WPR. For TB, the thesis presents its results in line with WHO guidelines that recommend symptom screening to identify the sample population.[123] Studies that relate to latent TB and those using Mantoux testing as their sole diagnostic were excluded from the analysis. For the malaria review, studies that undertook diagnoses within symptomatic populations only were excluded. Unlike for TB, there is no recognized pre-screening criteria recommendation for malaria testing.

The majority of studies included within the analysis were undertaken in the SEAR, with all SEAR TB studies undertaken in India. For both TB and malaria, only four studies were available for each infectious agent in comparative population groups.

The review found a paucity of data on TB in indigenous ethnic minority populations. On the basis of the data available, no improvement in TB prevalence was demonstrated over time and no prevalence differential was observed between population groups. The literature is conflicting regarding indigenous ethnic minority status as a risk factor for TB.[124] The findings of this review maybe impacted by the countries represented and the historic nature of the data.

The review showed there to be a high prevalence of malaria infection among indigenous ethnic minority populations and for these populations to be at greater risk of infection than comparative groups (although marginally not statistically significant). The locations inhabited by indigenous ethnic people may impact this finding and may also contribute to the observation that the prevalence of the zoonotic plasmodium *P. knowlesi*, was the second most prevalent amongst study participants, ahead of *P. vivax*.

For both TB and malaria, the review identified a paucity of data from countries that report a high burden of infection within their general populations. The findings highlight the need for current prevalence data that is disaggregated by indigenous/ethnic population status. Details of the review are included in the accepted manuscript titled ‘The prevalence of TB and malaria in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis’, that was published by Taylor and Francis in *Pathogens and Global Health* 2021 Dec 14;1-19

and is available online at:

https://www.tandfonline.com/doi/abs/10.1080/20477724.2021.2011579

The prevalence of tuberculosis and malaria in minority indigenous populations of South- East Asia and the Western Pacific Region: a systematic review and meta-analysis.

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Abstract

Infectious diseases have been shown to disproportionately affect indigenous populations. Tuberculosis (TB) and malaria continue to impose a significant burden on humanity and are among the infectious diseases targeted within the 2030 Agenda for Sustainable Development. A systematic review and meta-analyses were undertaken to evaluate the prevalence of TB and malaria infections within minority indigenous populations of the South-East Asia and Western Pacific Regions. The review was undertaken in accordance with The Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines following a published protocol. A random effects meta-analysis was used to calculate the pooled prevalence of TB and malaria. A meta-regression analysis was applied to quantify associations with study covariates and a sub-group analysis undertaken where studies provided comparative data between minority indigenous and other population groups. From the 3,275 unique publications identified, 24 on TB, and 39 on malaria were included in the final analysis. The pooled prevalence of TB was 2.3% (95% CI: 1.7, 2.9) and the pooled prevalence of malaria was 19.9% (95% CI: 15.9, 24.2). There was significant (p=0.000) heterogeneity (I^2) between studies. Significant difference was not observed in TB and malaria prevalence between minority indigenous and other population groups, although the odds ratio of malaria infection in minority indigenous populations was 1.15 (95% CI 0.99, 1.34: p-value 0.06) compared to other population groups. The review identified a paucity of data on TB and malaria in minority indigenous populations despite the significant prevalence and burden of these diseases within these regions.

Keywords: Tuberculosis, Malaria, Indigenous, Minority, South-East Asia, Western Pacific, Systematic Review.

Introduction

In 2015, the 193 member states of the United Nations (UN) adopted the 2030 Agenda for Sustainable Development.[1] Amongst other diseases, Sustainable Development Goal (SDG) 3.3 aims to end the epidemics of tuberculosis (TB) and malaria by 2030.[2] With respect to morbidity and mortality, TB and malaria are among the three most important infectious diseases affecting humankind, the other being Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Virus (AIDS).

In 2019, an estimated 1.4 million people died as a result of TB and although the burden of disease is falling, the decline is not occurring at a rate sufficient to achieve the milestones within the World Health Organization (WHO) End TB Strategy and the SDG TB related target.[3] In 2018, approximately 10 million people fell ill with the disease and 87% of new cases occurred within 30 high TB burden countries.[3] Of the 30 high TB burden countries, 11 fall within the WHO South-East Asia (SEAR) and Western Pacific Region (WPR)[4] where 44% and 18% of 2018 new cases occurred respectively.[3]

In 2018, there were an estimated 228 million cases and 405,000 deaths due to malaria, with the burden of disease in the SEAR second only to that occurring within the African Region.[5] Although the incidence of malaria is decreasing, the decline is not occurring at a rate sufficient to achieve the milestones of the Global Technology Strategy for Malaria 2016-2030[5] and the SDG target.

Mycobacterium tuberculosis, the bacterium responsible for TB, is globally ubiquitous.[3] The distribution of malaria caused by the protozoan parasite *Plasmodium* spp. is governed by seasonal temperature patterns and the distribution of

the mosquito vector, *Anopheles* spp.[6, 7] For both TB and malaria, research shows the prevalence of disease to be higher in populations living in poverty.[8-10] Indigenous people are disproportionately affected by poverty[11] and may be unduly impacted by TB and malaria in terms of both incidence and proximate determinants. [12-16] Access to health care provision for indigenous populations is inequitable due to social and cultural barriers, and the fact that they often live in remote locations.[17] These factors compound the health inequalities that are observed between indigenous and non-indigenous populations in both developing and industrialized nations.[18] The SEAR and WPR were chosen for this review to provide an opportunity to compare disease prevalence across countries with differing levels of socio-economic development whilst also capturing a significant proportion of the world's minority indigenous people.[19]

If health targets and the commitment of the 2030 Agenda for Sustainable Development that "no one will be left behind" [20] are to be met, the prevalence of disease among vulnerable populations will need to be quantified so that effective interventions can be implemented. This systematic review analysed available data to quantify the prevalence of TB and malaria in minority indigenous populations within the SEAR and WPR. The review also estimated the risk of infection in minority indigenous people relative to other populations groups from studies where direct comparative data were available.

Methods

Search strategy and selection criteria

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table 1: PRISMA

Checklist).[21] The full details of the search and selection criteria are available in a published protocol[22] (Open Science Framework registration: osf.io/m6sqc).

In summary, a systematic search for epidemiological studies was undertaken in Q4 2020 in four biomedical databases: Web of Science, Scopus, EMBASE (Ovid) and Medline (Ovid), without restriction on year of publication, using the search terms detailed in Appendix 1. In addition to the search results from the biomedical databases, reference lists from relevant studies were hand searched.

Screening

Articles identified from the search were uploaded into Endnote X9 (Clarivate Analytics) and duplicates were removed. Once the duplicates were removed, all remaining articles were uploaded into Rayyan Qatar Computing Research Institute (QCRI) software [23] and two authors (BG and KAA) independently screened the titles and the abstracts. The same authors independently screened the full text articles against the inclusion and exclusion criteria.

Any disagreements regarding the inclusion/exclusion of a study were resolved by discussion and when consensus could not be achieved, the third author (ACAC) was consulted. Where required, further clarification was sought from the corresponding author of relevant studies.

Inclusion criteria

To be included, studies were required to: relate to human infection, include minority indigenous populations within the SEAR or WPR and be representative surveys that reported sufficient data to enable the prevalence of disease to be calculated. Where

studies reported on the impact of intervention regimes, only pre-intervention baseline data were recorded.

As detailed in the protocol,[22] minority indigenous population groups where defined when each of the following criteria were met:

- Descendants of the original or earliest known inhabitants of an area; people who have historical continuity with pre-invasion and pre-colonial societies, [24-26]
- Distinct societies with languages, culture, customs, and social and political frameworks that vary significantly from those of the dominant population, [24-28]
- Groups of people with strong cultural ties and dependence upon the environment and its resources for their survival, [24, 26, 28, 29]
- People self-identifying as indigenous, [26]
- Groups who face relative disadvantage or discrimination in multiple areas of social existence- success, education, healthcare, employment, [26, 30, 31]
- Numerically non-dominant groups in a country or area.[26]

Exclusion criteria

Due to resource constraints, articles published in languages other than English were excluded. Studies were excluded if less than 90% of study participants in the study (or, for the comparative analyses, the minority indigenous category) were minority indigenous participants. Case studies and case series with less than 10 people, literature or systematic reviews, conference abstracts or posters and scientific correspondence e.g., letter to the editor, were excluded. Studies on latent TB were

omitted from the analysis (i.e., those utilizing Mantoux testing as the sole diagnostic). Studies were excluded if only symptomatic participants were tested and details on the total population screened were not included.

Data extraction and quality assessment

Data were extracted into a Microsoft Excel 2014 spreadsheet (Microsoft, Redmond, Washington, USA) by one of the researchers (BG) and cross-checked by the second author (KAA).The data extraction spreadsheet was pilot tested and refined before subsequent extraction of the following data: first author; year of publication; year of data collection; country in which the study was undertaken; population group (whether minority indigenous or other population); infectious agent (for *Plasmodium* species); diagnostic methods; size of study population (n); age; sex; size of the disease positive population (n) and screening method (for TB studies). Where studies undertook a comparison between minority indigenous and other population groups, data were extracted for both groups to facilitate a comparison.

The quality of the included studies was assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale[32] the results of which are detailed in Appendix 2.

Data Analysis

For both TB and malaria, a random effects meta-analysis with 95% confidence intervals (CI) was used to estimate the prevalence of infection. For the prevalence of both diseases, a meta-regression model was used to quantify associations of population type and study characteristics with infection status. Where direct

comparative data were available for minority indigenous and other population groups, sub-group analyses were undertaken to calculate the relative risk of infection between the two population groups.

Infection status (positive/negative) was derived using the case definitions used within each study.

Cochran's Q test, utilized to measure heterogeneity between studies, was quantitatively assessed by the index of heterogeneity squared (I^2) statistics with 95% CI.[33] As a result of the high heterogeneity (I^2 >75%)[33] identified, meta- regression was undertaken using the study characteristics as covariates. Where differentials in disease prevalence were identified across covariates, or between population groups, bivariate meta-regression was used to test significance (p <0.05) when three or more studies were available for each comparison.

Potential publication bias was assessed utilizing funnel plots and asymmetry was evaluated with Egger's method using a p <0.05 to indicate significant bias.[34]

Stata/MP version 16 (StataCorp, College Station, TX) was used to undertake the analyses.

Results

The search identified 3,275 unique publications and 233 articles remained after the title and abstract screening. After full text review, 63 were included in the final analysis. The PRISMA summary of the systematic review shortlisting process is detailed in Figure 1. Analysis of publication bias for the included studies is detailed in Figures 2 and 3. No publication bias was observed for the malaria studies (Fig 3),

however asymmetry of the funnel plot (Fig 2) and a p=0.003 for Egger's regression test indicated publication bias for the included TB studies.

Characteristics of the included studies

The characteristics of the included studies are presented in Tables 2 and 3.

A total of 24 studies on TB, representing 337,677 minority indigenous participants, met the review criteria and were included in the analysis. Within the 24 studies, four [35-38] undertook a comparison between minority indigenous and other population groups. These four studies represented 17,895 and 7,547 minority indigenous and non 'minority indigenous' participants, respectively.

Eighteen TB studies [35-37, 39-52] where undertaken in the SEAR, all in India (WHO mortality stratum D).[53] Six TB studies were identified in the WPR; two in Australia [54, 55] (mortality stratum A);[53] three studies where undertaken in Malaysia [38, 56, 57] (mortality stratum B)[53] and one study in the Solomon Islands[58] (mortality stratum B).[53] Nineteen minority indigenous population groups were represented across the four countries- Table 4.

For malaria, a total of 39 studies representing 98,249 minority indigenous participants were included in the analysis. Within the 39 studies, four studies[59-62] undertook a comparison between minority indigenous and other populations, representing 4,841 and 747 participants, respectively.

Within the 39 studies, 26 were undertaken in the SEAR, and of these seven were within mortality stratum B[53] (two in Indonesia[63, 64] and five in Thailand [65-69]) and 19 within mortality stratum D[53] (one in Bangladesh[60] and 18 in India[70-87]). Thirteen studies were undertaken in the WPR, all within mortality stratum B[53] (eight in

Malaysia[61, 88-94], one in the Philippines[62], one in the Solomon Islands[58] and three in Vietnam[59, 95, 96]). Thirty-three minority indigenous population groups were represented across the eight countries- Table 5.

Prevalence of TB

Within minority indigenous populations, the pooled prevalence of TB was 2.3% (95% CI 1.7, 2.9); ranging from 0.3% (95% CI 0.2, 0.4)[46] to 32.0% (95% CI 24.6, 40.5).[43] These data are represented in a Forest Plot -Fig 4, which shows the significant heterogeneity between studies. The pooled prevalence of TB in minority indigenous people between study populations and across study covariates is detailed in Table 6 and associations with covariates are detailed in Table 7.

In the four studies that undertook a comparison between population groups,[35-38] no difference in TB prevalence was observed between minority indigenous (5.0% 95% CI 1.7, 9.9) and non 'minority indigenous' participants (5.0% 95% CI 0.3, 14.2).

Within minority indigenous populations only, there were no significant differences in TB prevalence between the regions (SEAR and WPR), WHO mortality strata, countries of study, year of data collection, sex of study participants, diagnostic method, or method of population screening. Insufficient studies were available to examine age as a covariate.

Prevalence of malaria

The prevalence of malaria across the study covariates is detailed in Table 8 and the analysis of associations between malaria and covariates is detailed in Table 9.

The pooled prevalence of malaria across minority indigenous participants was 19.9% (95% CI 15.9, 24.2), ranging from 0.5% (95% CI 0.1, 2.8)[92] to 85.9% (95% CI 79.7, 90.4).[93] These data are represented in a Forest Plot (Fig 5). Where the species of plasmodium was identified by the study, the most prevalent was *Plasmodium falciparum* (12.9%, 95% CI 9.4, 16.9) followed by *Plasmodium knowlesi* (7.5%, 95% CI 5.1, 11.0) and *Plasmodium vivax* (4.8%, 95% CI 3.2, 6.6).

Across the four studies[59-62] that undertook a comparison between population groups, the prevalence of malaria was 21.5% (95% CI 7.8, 39.4) in minority indigenous people and 8.2% (95% CI 4.9, 12.2) in the non 'minority indigenous' population. The difference was not significant at the 5% level, but only marginally not so (p= 0.06), with an odds ratio of 1.15 (95% CI 0.99, 1.34).

Prevalence of malaria in minority indigenous populations was found not to be significantly different for the regions (WPR and SEAR), nor for the mortality strata, country of study, or year of data collection.

The difference in malaria prevalence between studies using microscopy 17.2% (95% CI 13.2, 21.6) and spleen palpitation (40.2% (95% CI 23.9, 57.7)) was found to be significant (p= 0.035).

Discussion

This systematic review highlights the paucity of TB data for minority indigenous populations within the high TB burden countries of the SEAR and WPR as defined by the WHO. From these high TB burden countries, data were only available for India. From the studies that are available, no improvement in disease prevalence was

observed over time. The disease is a global problem that continues to prevail across all mortality strata.

The review only found four studies for each disease that undertook a direct comparison of disease prevalence between minority indigenous and other population groups. Based on the data from these four studies, there was no difference in TB prevalence between the population groups. The literature is conflicting regarding the impact of indigenous status on TB prevalence[13] highlighting the need for further research. It has been suggested that the isolation of some tribal communities from cultural contact has provided a safeguard from TB disease.[58, 97] Where disease prevalence is comparable between population groups, research has shown indigenous populations to be at an increased risk of TB as they transition to a more modern lifestyle.[39] The risk factors associated with lifestyle transition include increased exposure to both the disease and its proximate determinants.[14, 39, 98]

The review identified a high prevalence of malaria among minority indigenous peoples and comparative studies showed these populations to be at greater risk of disease relative to other groups (although marginally not statistically significant). The environments that minority indigenous people inhabit put them at increased risk of infection with malaria[59] and due to their geographic isolation, these populations can present one of the last barriers to disease elimination.[99] The human population interface with alternate hosts of zoonotic *Plasmodium spp.,* may also impact the prevalence of disease. Notably *P.knowlesi,* a zoonotic malaria parasite, was the second most prevalent amongst study participants, ahead of *P.vivax*. The review includes a study published in 2016 showing a high prevalence of malaria in minority

indigenous peoples of Malaysia, a country which was classified as malaria free in 2017.[100] This finding maybe due to the exclusion of zoonotic species from the definition of "malaria free"[101] and although the definition is complex,[102] data on all *Plasmodium spp.,* infections will be required to effectively combat the disease.

Although light microscopy is the recommended gold standard for malarial parasite detection,[103] its ability to detect asymptomatic infections is low in comparison to molecular techniques.[104] Data from the systematic review showed a wide range in malaria prevalence across the diagnostic methods. Although splenomegaly has many potential causes and low sensitivity for a definitive malaria diagnosis, the results of the review recommend further diagnostics be used when an enlarged spleen is identified in malaria endemic areas.

The review demonstrated high heterogeneity in the prevalence of TB and malaria between studies and within and across co-variates. This variation in disease prevalence highlights the need for targeted and relevant data to inform effective control strategies. The review identified a paucity of data for minority indigenous populations in countries that report a high prevalence of infection across their total population. Where studies were available, the data were often historic making current conclusions difficult to draw.

Although progress has been made in reducing the prevalence of these diseases over recent decades, achievements may be derailed by the Coronavirus Disease 2019 (COVID-19) pandemic as control and treatment programmes are disrupted and resources are re-allocated. [105] [106, 107] [108] Modelling suggests that over a five-year

period in high TB and malaria settings, the COVID-19 pandemic could result in a 20% and 36% increase in TB and malaria deaths respectively.[109] To date empirical evidence regarding the impact of the COVID-19 pandemic on TB and malaria is limited[106, 110].The interrelationship between the diseases is geospatially and temporally complex but the pandemic is likely to further exacerbate the TB and malaria epidemics in vulnerable population groups.[106, 110, 111]

There were several limitations to the current study. Publication bias and reliance on the use of secondary data are limitations of the systematic review process. Due to resource constraints, the review restricted studies to those published in English. Studies on small sample populations may decrease the accuracy of estimating disease prevalence. The implementation of treatment and intervention programs have not been taken into consideration, which may impact disease prevalence over time. There is no universal definition of minority indigenous peoples, and each country has its own definition.

The review shows the prevalence of malaria to be higher in minority indigenous than comparative populations, but for there to be no difference for TB. The reason for this finding may be the limited number of comparative studies and the relatively small size of the study population groups.[13] The different findings for TB and malaria , may also be partly attributable to the very different ecologies of the two diseases, and how these ecologies have interfaced with indigenous lifestyles over time. The year of data collection for the comparative TB studies may have impacted the findings of the systematic review. Recent results from countries that disaggregate data by ethnicity, show indigenous populations to carry a significant and disproportionate burden of

TB.[112] Time may be an important factor as increased exposure of indigenous people to the social and proximate determinants of the disease occurs as they move away from their traditional lifestyles.[14]

The results show however, that further research and current data are required, if the burden of TB and malaria are to be accurately quantified in vulnerable populations and appropriate and effective interventions are to be developed.

Conclusions

The review shows there to be a paucity of recent data on TB and malaria prevalence within minority indigenous populations of the SEAR and WPR, despite the significant burden of these diseases within these regions. If SDG 3.3 is to be achieved, accurate and current data on the prevalence of TB and malaria within vulnerable population groups is required.

List of Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; CI: Confidence Interval; COVID-19: Coronavirus Disease 2019; ES: Effect Size; GBD: Global Burden of Disease; HIV: Human Immunodeficiency Virus; IFS: Indirect Fluorescent Antibody; PCR: Polymerase Chain Reaction; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses; QA: Quality Assessment; QCRI: Qatar Computing Research Institute; RDT: Rapid Diagnostic Test; SDG: Sustainable Development Goal; SEAR: South-East Asia Region; TB: Tuberculosis; UN: United nations; WHO: World Health Organization; WPR: Western Pacific Region.

Declarations

Ethical approval and consent to participate: Ethics approval and participant consent was not required for this study as it was based upon a review of published work.

Consent for publication: Not applicable

Availability of data and materials: All required information is available in the manuscript and supporting documentation.

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Authors' contributions: BG, KAA, and ACAC conceived the study. BG undertook the search, analysis and drafted the manuscript. BG, KAA, ACAC critically revised the manuscript for methodological and intellectual content and have read and approved the final manuscript.

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Table 1: PRISMA Checklist[21]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	36
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	31
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	24-26
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	37-39
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	34-35
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	27, 29
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	32, 33

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	28, 30
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

Table 2: Summary of TB studies

Study ID	First Author Year of Publication	Year of Data Collection^	WHO Region	WHO Mortality Strata	Country	Diagnostic Method*	Population Screened# (n)	TB +ve (n)	Screening Method≠	Screened Population % Male
1	Bhat, 2009	2007-2008	SEAR	D	India	Culture	22,284	83	Chest symptoms	48.6
2	Bhat, 2015	2012-2013	SEAR	D	India	Culture	19,409	494	Chest symptoms	
3	Bhat, 2017	2013	SEAR	D	India	Culture	12,123	348	Chest symptoms	
4	Bolton, 1975	1961-1971	WPR	B	Malaysia	Smear	71,748	249	X-ray	
5	Chakma, 1996	<1996	SEAR	D	India	Culture	11,097	142	Chest symptoms	
6	Damon, 1974	1968	WPR	B	Solomon Is	Clinical	850	21	No pre-screening	
7	Datta, 2001	1989	SEAR	D	India	Culture	16,017	126	Chest symptoms +/or x-ray	60.2
8	Haddad, 2012	<2012	SEAR	D	India	Smear	1,660	346	Chest symptoms	
9	Hussain, 2020	2015-2017	SEAR	D	India	Culture	5,145	35	Chest symptoms	
10	Kashyap, 2013	<2013	SEAR	D	India	Culture	128	41	No pre-screening	
11	Kerketta, 2009	<2009	SEAR	D	India	Clinical	314	12	No pre-screening	43.0
12	King, 1951	1950	WPR	A	Australia	Clinical	3,209	15	Mantoux test	
13	Macken, 1952	1949-1951	WPR	A	Australia	Clinical	5,472	177	Mantoux test	
14	Murhekar, 2004	2001-2002	SEAR	D	India	Smear	10,570	77	Chest symptoms	
15	Purty, 2019	2015-2017	SEAR	D	India	Smear	6,898	18	Chest symptoms	47.8
16	Rao, 2010A	2008	SEAR	D	India	Culture	1,390	6	Chest symptoms	
17	Rao, 2010B	2007-2008	SEAR	D	India	Culture	11,116	166	Chest symptoms	
18	Rao, 2011	2007-2008	SEAR	D	India	Culture	9,538	133	Chest symptoms	47.6
19	Rao, 2015	2012-2013	SEAR	D	India	Culture	9,653	318	Chest symptoms	46.5
20	Rao, 2019	2013	SEAR	D	India	Culture	9,756	293	Chest symptoms	
21	Roy, 1969	1968	WPR	B	Malaysia	Smear	1,055	108	X-ray	
22	Sharma, 2010	2006-2007	SEAR	D	India	Smear	50,000	266	Chest symptoms	
23	Vyas, 2019	2014-2015	SEAR	D	India	Smear	65,230	964	Chest symptoms	
24	Yano, 1974	1972	WPR	B	Malaysia	Clinical	562	12	No pre-screening	

Notes: ^If the study has not detailed the year of data collection, it is assumed < year of publication

*Diagnostic method: Smear= smear or uncategorized sputum methodology. Clinical= current TB treatment, self-report, X-ray. If a paper uses multiple methods, it is classified according to the most sensitive method according to the following descending order: culture, smear and clinical (e.g. if smear + culture classified as culture, if x-ray and smear classified as smear)

Population figures are inclusive of non-indigenous participants in the comparative studies

≠ Where studies utilize a screening method to determine the population to be tested, this is detailed. Chest symptoms include-persistent cough, chest pain, fever, haemoptysis.

Table 3: Summary of malaria studies

Study ID	First Author Year of Publication	Year of Data Collection^	WHO Region	WHO Mortality Strata	Country	Diagnostic Method *	Population tested#	Malaria positive $	Tested Population % Male
1	Abe, 2009	2006	WPR	B	Vietnam	Microscopy	552	38	
2	Chaturvedi, 2017	2013-2014	SEAR	D	India	Microscopy	6,761	2,094	
3	Choubisa, 1992	<1992	SEAR	D	India	Microscopy	250	30	64
4	Chourasia, 2017a	2013-2014	SEAR	D	India	Microscopy	293	81	
5	Chourasia, 2017b	2016	SEAR	D	India	PCR	437	103	42.8
6	Damon, 1974	1966 +1968	WPR	B	Solomon Is	Microscopy + Enlarged Spleen	1,542	734	
7	Das, 2000	1998	SEAR	D	India	Microscopy	435	109	53.8
8	Das, 2005	2001	SEAR	D	India	Microscopy	179	30	58.1
9	Das, 2017	2014-2016	SEAR	D	India	RDT	1,192	342	
10	Dev, 2006	1991-1993	SEAR	D	India	Microscopy	15,093	3,101	
11	Erhart, 2005	2003	WPR	B	Vietnam	Microscopy	3,932	1,385	
12	Ganguly, 2013	2012	SEAR	D	India	PCR	963	81	
13	Gordon, 1991	<1991	WPR	B	Malaysia	Microscopy	268	60	
14	Haque, 2011	2009	SEAR	D	Bangladesh	RDT	1,400	161	
15	Jiram, 2016	<2016	WPR	B	Malaysia	PCR	306	82	52.3
16	Kaur, 2009	<2009	WPR	B	Malaysia	Microscopy	520	126	49.6
17	Luxemburger, 1996	1991-1992	SEAR	B	Thailand	Microscopy + Enlarged Spleen	677	61	
18	Mak, 1987	1984	WPR	B	Malaysia	Microscopy	191	17	
19	Marasabessy, 2019	2019	SEAR	B	Indonesia	Microscopy	84	3	60.7
20	Marchand, 2011	2010	WPR	B	Vietnam	Microscopy	624	49	
21	Nakabayashi, 1973	1970	WPR	B	Philippines	Microscopy	65	10	
22	Nithikathkul, 2003A	2002	SEAR	B	Thailand	Microscopy	119	4	46.2
23	Nithikathkul, 2003B	<2003	SEAR	B	Thailand	Microscopy	195	2	42
24	Norhayati, 2001	<2001	WPR	B	Malaysia	Microscopy	310	34	
25	Pichainarong, 2004	2001-2002	SEAR	B	Thailand	Microscopy	417	191	68.1
26	Rahmah, 1997	1996	WPR	B	Malaysia	Microscopy	200	1	
27	Rajagopalan, 1989	1986-1988	SEAR	D	India	Microscopy + Enlarged Spleen	29,932	3,501	
28	Roy, 2001	1997	SEAR	D	India	Microscopy	163	22	
29	Sahu, 2013	2009	SEAR	D	India	Microscopy	12,045	1,983	48.6
30	Sharma, 2004	2001	SEAR	D	India	Microscopy	6,136	525	

31	Sharma, 2006	2001-2003	SEAR	D	India	Microscopy	14,860	1,214	
32	Singh, 1989	1987-1988	SEAR	D	India	Microscopy + Enlarged Spleen	10,558	4,817	
33	Singh, 1998	1995-1996	SEAR	D	India	Microscopy	456	96	0
34	Singh, 2001	1999	SEAR	D	India	Microscopy + Enlarged Spleen	349	205	
35	Srivastava, 2000	1995	SEAR	D	India	Microscopy	833	217	
36	Stafford, 1980	<1980	SEAR	B	Indonesia	Microscopy	316	19	52.8
37	Thomas, 1981	<1981	WPR	B	Malaysia	Microscopy + Enlarged Spleen + IFA$^{\Delta}$	163	140	
38	Tipmontree, 2009	<2009	SEAR	B	Thailand	Self-report	192	66	
39	Wharton, 1963	1960-1962	WPR	B	Malaysia	Microscopy	1,244	283	

Notes: $^{\wedge}$ If the study has not detailed the year of data collection, it is assumed < year of publication

***** Where studies utilized multiple diagnostic methods, Rapid Diagnostic Test (RDT) + microscopy were classified as microscopy and RDT + microscopy + Polymerase Chain Reaction (PCR) were classified as PCR.

$^{\#}$ Population figures are inclusive of non-indigenous participants in the comparative studies

$^{\$}$ Where multiple diagnostic methods were used in the same study, the method which gave the greatest number of malarial cases was used to determine the number of cases.

$^{\Delta}$ Indirect Fluorescent Antibody (IFA)

Table 4: Minority indigenous population groups represented in the TB studies analyzed

Country	# Minority Indigenous Study Participants	Minority Indigenous Population	Minority Indigenous Population % Representation
Australia	8,681	Aborigine	100.0
India	254,901	Saharia	55.5
		Sahariya + Bhil	19.6
		Tribal	13.5
		Malayaali	6.3
		Car Nicobarese	4.1
		Bharia	0.5
		Paniyas + other scheduled tribes	0.3
		Langia Saora, Paudi Bhuiyan, Kutia Kondh + Dongria Kondh	0.1
Malaysia	73,245	Orang Asli	98.0
		Murut	1.4
		Iban	0.6
Solomon Islands	850	Nasioi, Kwaio, Lau + Baegu	100.0

Table 5: Minority indigenous population groups represented in malaria studies analyzed

Country	# Minority Indigenous Study Participants	Minority Indigenous Population	Minority Indigenous Population % Representation
Bangladesh	1,043	Marma, Tripura, Tonchonga, Khiang + Chakma	100.0
India	85,679	Aboriginal tribes	88.2
		Baiga	7.9
		Munda ,Oraon, Lohra, Bedia, Baraik + Kachhap	1.4
		Gond	1.3
		Gond, Halba + Muria	0.5
		Santhals + Adivasis	0.5
		Jarawas	0.2
Indonesia	400	Nuaulu	21.0
		Torajans	79.0
Malaysia	3,074	Orang Asli	100.0
Philippines	30	Palawano	100.0
Solomon Islands	1,542	Nasioi, Kwaio, Lau + Baegu	100.0
Thailand	1,600	Karen	61.9
		Hill Tribe	26.1
		Karen + Mon	12.0
Vietnam	4,881	Rag Lays	75.9
		Raglai	12.8
		Steing	11.3

Table 6: Pooled prevalence of TB within population groups and across study covariates within minority indigenous populations

	Studies (n)	Pooled[α] Prevalence TB (95% CI)
Study Population		
Minority indigenous populations	24	2.27 (1.69, 2.92)
Comparative Studies		
Non 'minority indigenous' populations	4	4.96 (0.32, 14.23)
Minority indigenous populations	4	5.04 (1.72, 9.93)
Analysis on indigenous populations only		
WHO regions		
SEAR	18	2.23 (1.61, 2.95)
WPR	6	2.31 (0.65, 4.91)
WHO Mortality Strata		
A	2	1.93 (1.65, 2.23)
B	4	2.77 (0.08, 8.78)
D	18	2.23 (1.61, 2.95)
Countries		
Australia	2	1.93 (1.65, 2.23)
India	18	2.23 (1.61, 2.95)
Malaysia	3	2.87 (0.00, 11.99)
Solomon Islands	1	2.47 (1.62, 3.75)
Year of data collection		
1945-1970	4	2.46 (0.46, 5.95)
1971-1995	4	1.44 (0.81, 2.24)
1996-2020	16	2.44 (1.72, 3.28)
Age		
<15 years	1	13.64 (7.34, 23.93)
≥15 years	15	2.40 (1.55, 3.41)
Sex		
Female	9	1.01 (0.53, 1.63)
Male		2.89 (1.56, 4.59)
Diagnostic methods		
Clinical	7	2.05 (1.34, 2.89)
Culture	12	2.08 (1.28, 3.08)
Smear	8	2.18 (1.34, 3.22)
Screening Method		
Chest symptoms	16	1.76 (1.2, 2.41)
Mantoux skin test	2	1.93 (1.65, 2.23)
No pre-screening	4	6.86 (1.37, 15.91)
X-ray	2	0.37 (0.33, 0.42)

Note: [α] Prevalence pooled when >1 data set, otherwise result is presented from a single study

Table 7: Bivariate regression between TB study covariates

	Pooled prevalence of TB infection	
	95% CI	*p*-value
Comparative Studies		
Non 'minority indigenous' populations	1.00	
Minority indigenous populations	1.00032 (0.85, 1.18)	0.996
WHO regions		
SEAR	1.00	
WPR	0.99 (0.95, 1.04)	0.783
WHO Mortality Strata		
B	1.00	
D	1.00 (0.95, 1.06)	0.985
Countries		
India	1.00	
Malaysia	1.00 (0.94, 1.07)	0.895
Year of data collection		
1945-1970	1.00	
1971-1995	0.98 (0.94, 1.03)	0.380
1996-2020	1.00 (0.95, 1.06)	0.863
Sex		
Female	1.00	
Male	1.02 (0.99, 1.05)	0.218
Diagnostic methods		
Clinical	1.00	
Culture	1.01 (0.98, 1.04)	0.581
Smear	1.02 (0.97, 1.07)	0.468
Screening Method		
Chest symptoms	1.00	
No pre-screening	1.06 (0.94, 1.19)	0.354

Note: Bivariate meta-regression analysis was only undertaken where there were 3 or more data sets

Table 8: Pooled prevalence of malaria within population groups and across study covariates within minority indigenous populations

Categories	Pooled[α] prevalence of malaria*	
	Studies (n)	Pooled Prevalence (95% CI)
Population group		
Minority indigenous populations	39	19.87 (15.89, 24.16)
Comparative Studies		
Non 'minority indigenous' populations	4	8.20 (4.89, 12.22)
Minority indigenous populations	4	21.50 (7.81, 39.42)
Analysis on indigenous populations only		
WHO regions		
SEAR	26	18.37 (13.93, 23.27)
WPR	13	23.11 (14.27, 33.32)
WHO Mortality Strata		
B	20	18.71 (11.72, 26.86)
D	19	21.03 (15.67, 26.94)
Countries		
Bangladesh	1	13.23 (11.31, 15.42)
India	18	21.51 (15.93, 27.67)
Indonesia	2	5.36 (3.29, 7.85)
Malaysia	8	23.21 (11.41, 37.61)
Philippines	1	26.67 (14.18, 44.45)
Solomon Islands	1	47.60 (45.12, 50.10)
Thailand	5	14.84 (2.29, 35.27)
Vietnam	3	15.20 (1.23, 40.35)
Infectious agent[$]		
P.falciparum	22	12.90 (9.37, 16.90)
P.falciparum + P.malariae	2	0.00 (0.00, 0.003)
P.falciparum +/or P.vivax	13	5.04 (2.81, 7.84)
P.falciparum +/or P.vivax +/or P.malariae	3	0.91 (0.42, 1.58)
P.knowlesi	1	7.52 (5.06, 11.03)
P.malariae	8	0.61 (0.23, 1.14)
P.vivax	22	4.75 (3.16, 6.63)
P.vivax + P.malariae	1	1.12 (0.38, 3.24)
Plasmodium spp	14	27.47 (17.21, 39.10)
Year of data collection		
1960-1980	5	36.44 (15.98, 59.82)
1981-2000	14	19.21 (12.58, 26.85)
2001-2020	20	16.89 (12.28, 22.07)
Diagnostic methods^		
Enlarged spleen	6	40.17 (23.90, 57.68)
IFA	1	85.89 (79.72, 90.41)
Microscopy	33	17.19 (13.19, 21.59)
PCR	3	18.70 (7.52, 33.41)
RDT	2	20.93 (19.27, 22.65)
Self-report	1	34.38 (28.02, 41.34)

Notes: [α] Prevalence pooled when >1 data set, otherwise result from single study

*All species consolidated to give malaria prevalence, where a study uses different diagnostic methods on the same study population, the result from the method which gives the highest number of positives is taken as the number of malaria cases.

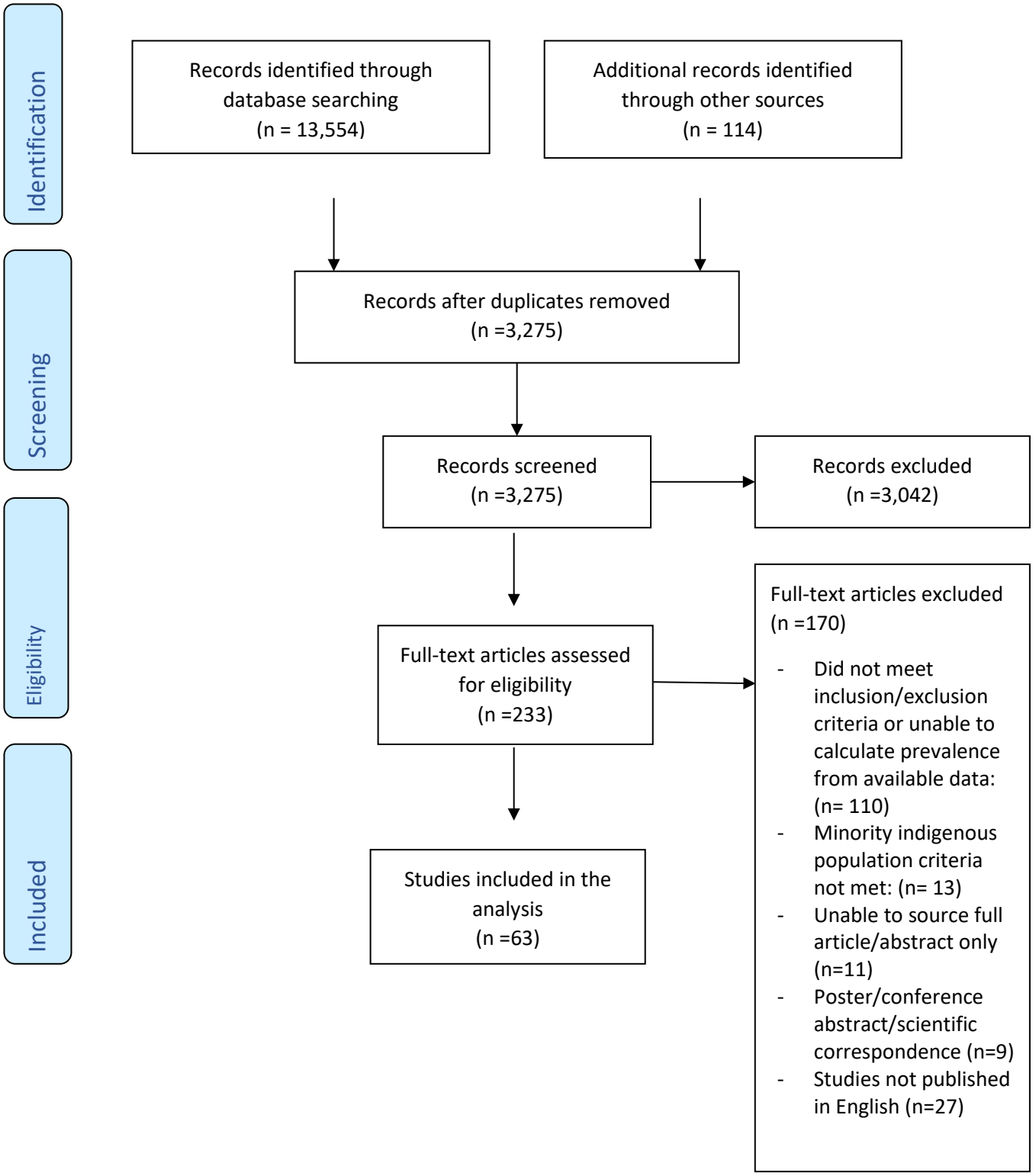
[$] P falciparum + P.vivax and P.falciparum or P.vivax classified together as P.falciparum +/or P.vivax.

^ RDT + microscopy classified as microscopy; RDT + microscopy + PCR classified as PCR

Table 9: Bivariate regression between malaria study covariates

Categories	Pooled prevalence of malaria	
	95% CI	*p* value
Comparative Studies		
Non 'minority indigenous' populations	1.00	
Minority indigenous populations	1.15 (0.99, 1.34)	0.063
Analysis on indigenous populations only		
WHO regions		
SEAR	1.00	
WPR	1.05 (0.92, 1.21)	0.433
WHO Mortality Strata		
B	1.00	
D	1.003 (0.90, 1.12)	0.963
Countries		
Thailand	1.00	
Vietnam	0.98 (0.76, 1.28)	0.896
Malaysia	1.07 (0.82, 1.40)	0.601
India	1.04 (0.85, 1.26)	0.704
Year of data collection		
1960-1980	1.00	
1981-2000	0.844 (0.64,1.11)	0.223
2001-2020	0.82 (0.63, 1.08)	0.158
Diagnostic methods		
Microscopy	1.00	
Enlarged spleen	1.25 (1.02, 1.53)	0.035
PCR	1.00 (0.90, 1.12)	0.954

Note: Bivariate meta-regression analysis was only undertaken where there were 3 or more data sets



From Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 1: PRISMA summary of systematic review study selection process

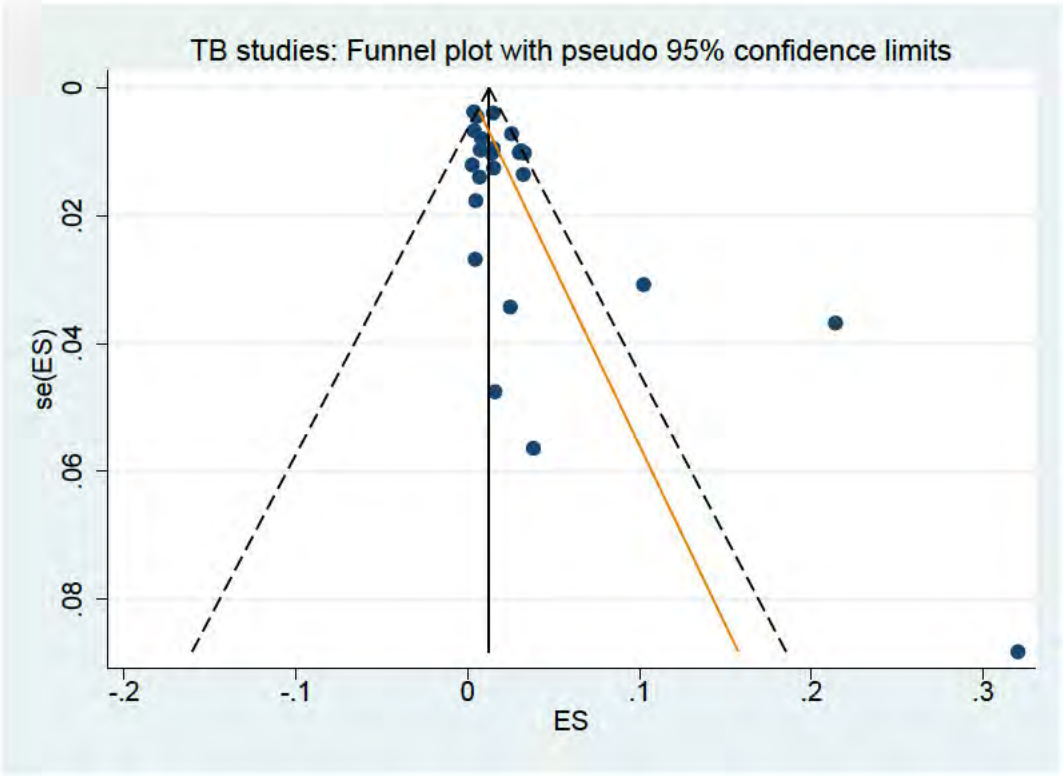


FIG 2: Funnel plot with pseudo 95% confidence limits for TB studies

Egger's test for small study effects gave a bias coefficient of 1.78 (95% CI 0.66, 2.91) *p*-value 0.003 indicating significant publication bias.

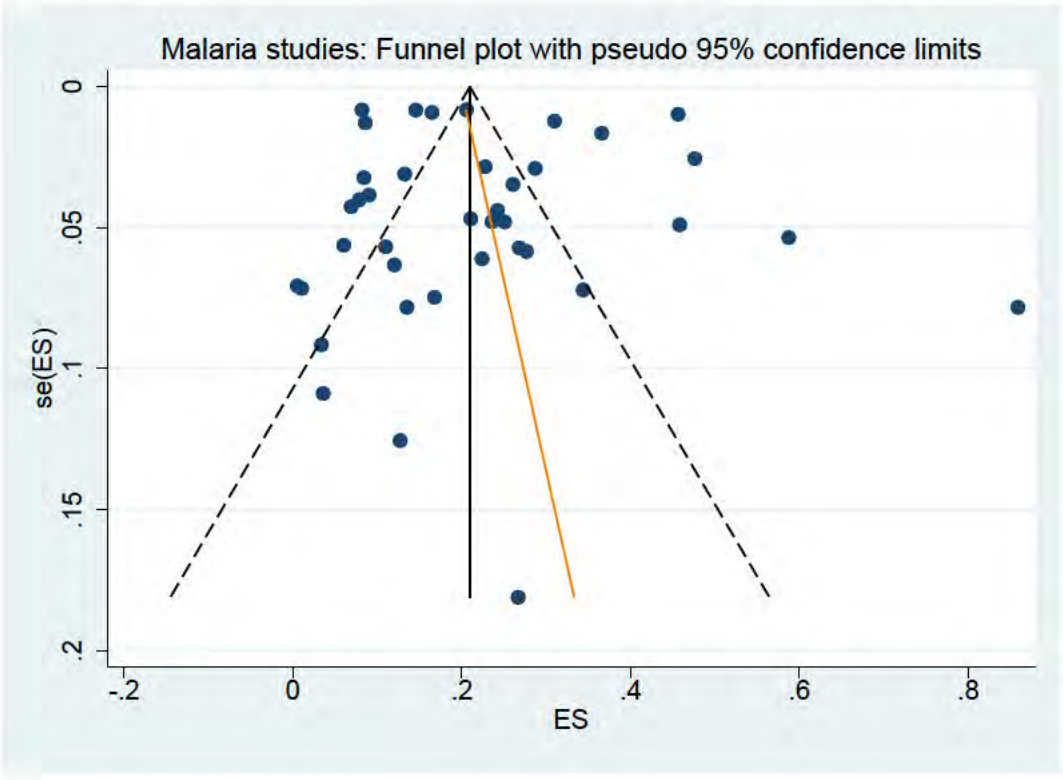


FIG 3: Funnel plot with pseudo 95% confidence limits for malaria studies

Egger's test for small study effects gave a bias coefficient of 0.74 (95% CI -2.33, 3.81) and a *p*-value of 0.63 indicating no significant publication bias.

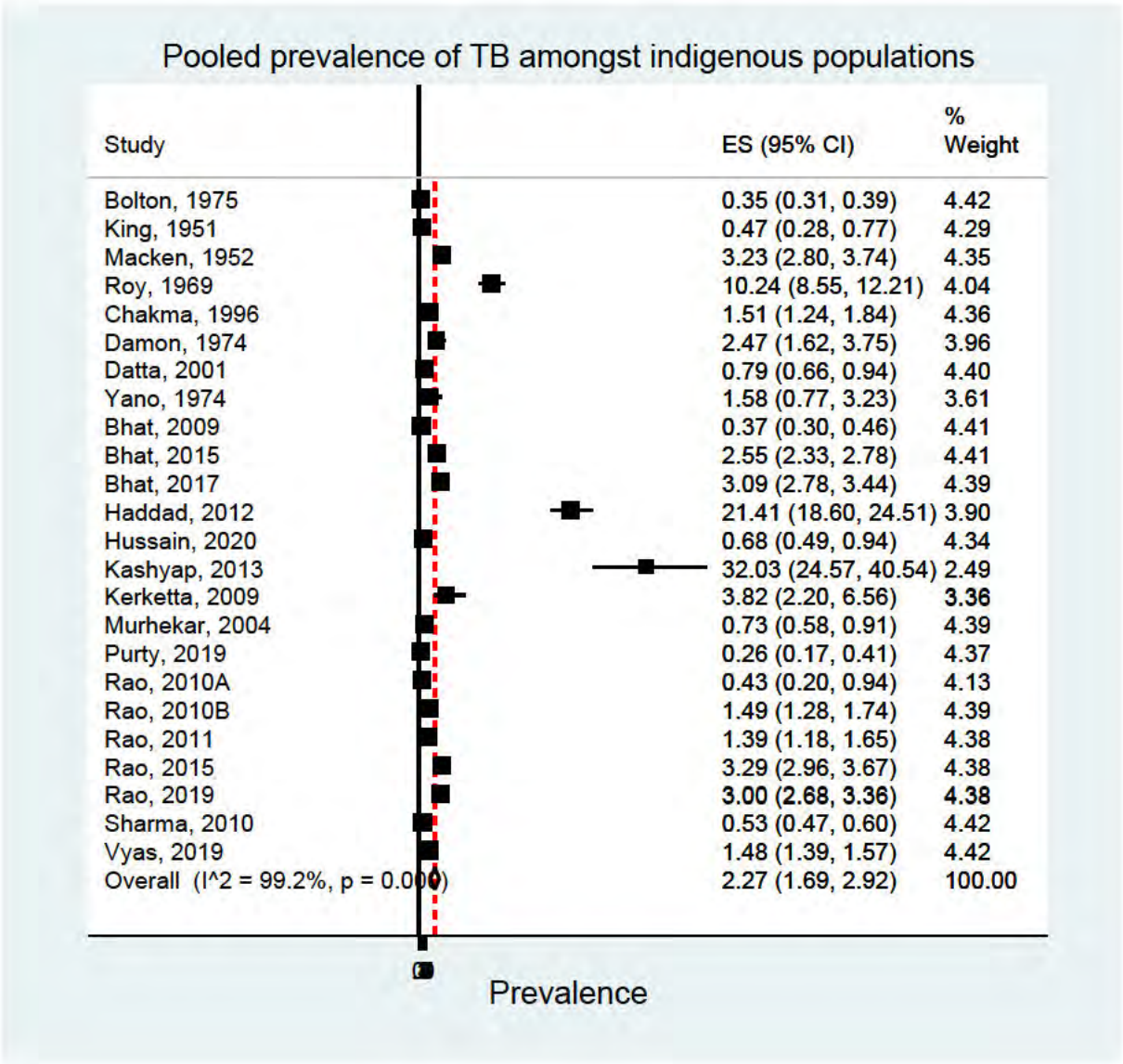


FIG 4: Pooled prevalence of TB within minority indigenous study populations. The forest plot shows overall effect sizes (ES) and their 95% confidence intervals (CI). I^2 statistic describes the percentage of variation due to heterogeneity.

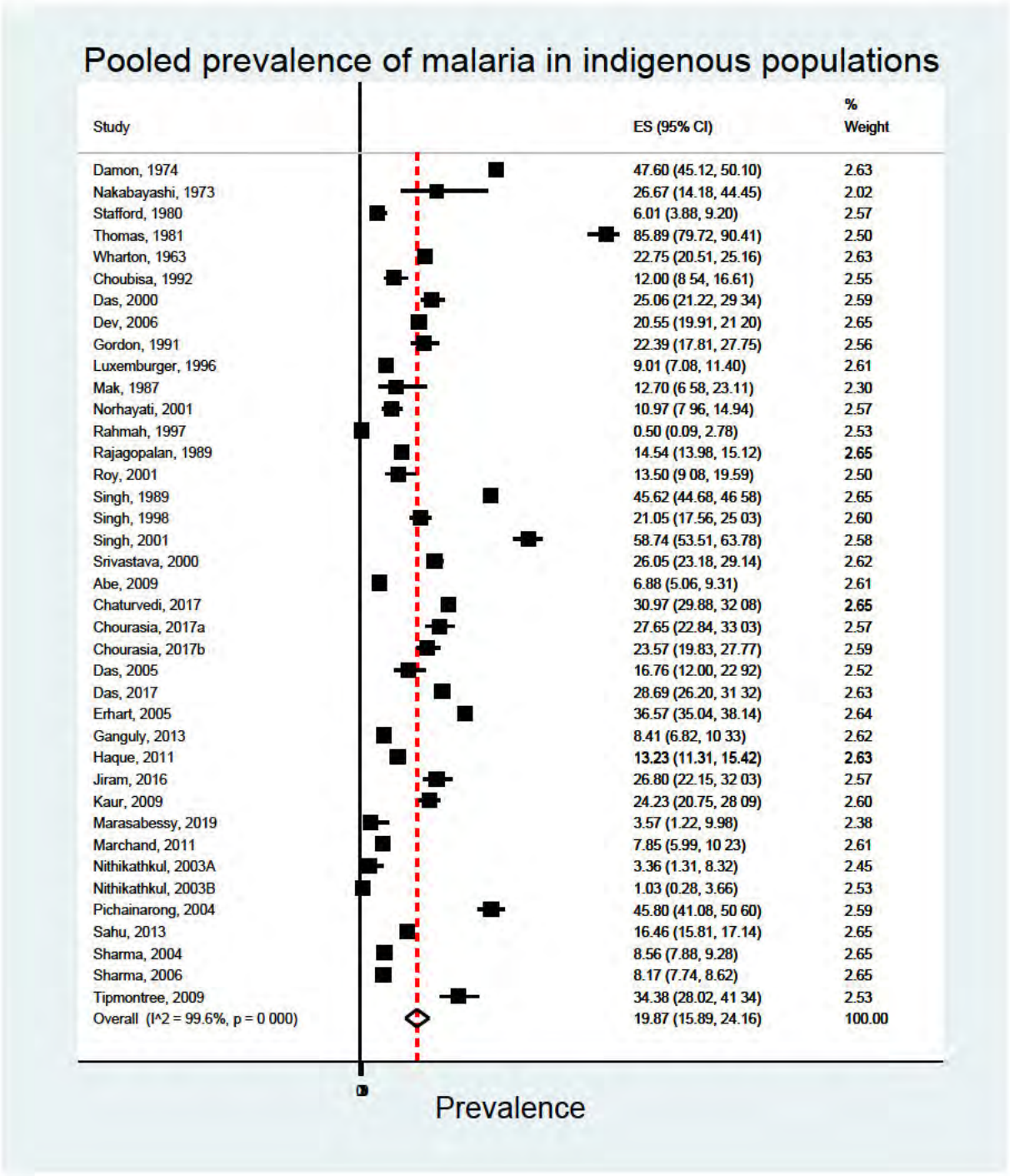


FIG 5: Pooled prevalence of malaria within minority indigenous study populations. The forest plot shows overall effect sizes (ES) and their 95% confidence intervals (CI). I^2 statistic describes the percentage of variation due to heterogeneity.

Appendix 1: Summary of systematic review search terms

Descriptor	Search Terms
TB terms	*Tuberculosis* OR *TB* OR "*Mycobacterium tuberculosis*" **OR**
Malaria terms	malaria* OR plasmodi* **AND**
[Δ] Countries of SEAR and WPR	*Indonesia* OR "*Sri Lanka*" OR *Ceylon* OR *Thailand* OR *Timor** OR *Bangladesh* OR *Bhutan* OR "*Democratic People's Republic of Korea*" OR *India* OR *Maldives* OR *Myanmar* OR *Burma* OR *Nepal* OR *Australia* OR *Brunei* OR *Japan* OR "New Zealand" OR Cambodia OR China OR "*Cook Islands*" OR *Fiji* OR *Kiribati* OR *Lao** OR *Malaysia* OR "*Marshall Islands*" OR *Micronesia* OR Mongolia OR Nauru OR Niue OR Palau OR "*Papua New Guinea*" OR *Philippines* OR "*Republic of Korea*" OR *Samoa* OR "*Solomon Islands*" OR *Tonga* OR *Tuvalu* OR *Vanuatu* OR *Vietnam* **AND**
[α] Indigenous terms	*Indigenous* OR *aborigin** OR *native* OR *"first nation*"* OR *"ethnic group"* OR *tribal* OR *tribe* OR *autochthonous*

[Δ] Countries within the SEAR and WPR were defined according to the WHO Global Burden of Disease (GBD) regional classification system[53]. Singapore was excluded from the search as it does not have any minority indigenous populations according to the definition used in this review.

[α] In addition to these indigenous terms, those relevant to each country as derived from the World Directory Listing of Minorities and Indigenous People[113]; Native Planet- Indigenous Mapping[114] and International Working Group on Indigenous Affairs[24], were included. Studies were included if populations were not on the search criteria list, but the author identified them as minority indigenous groups.

Appendix 2: Quality Assessment (QA) based on modified Newcastle-Ottawa QA Scale

#	References	Study Population 1= The study population is clearly defined 0=The study population is not clearly defined	Representativeness of the sample 2= Study sample is representative of the study population (all subjects or random sampling) 1= Study sample comprises a select group of the study population (non-random sampling) 0=No description of the sampling strategy.	Ascertainment of specimen collection methods 1= The study clearly defines specimen collection methodologies 0= The study does not detail specimen collection methodologies	Sample size 1= Justified and satisfactory (sample size and power calculation included) 0= Not justified	Non-respondents 1= Comparability between respondents and non-respondents characteristics are established. 0= No description of the response rate or the characteristics of the responders and the non-responders.	Impact of Bias (selection bias, measurement bias, participant reporting, confounders) 1= Where relevant, the study acknowledges and mitigates for potential bias. When comparisons are made between different study populations results are adjusted for confounders 0= Where appropriate, the study does not acknowledge or mitigate for potential bias. When comparisons are made between different study populations results are not adjusted for confounders	Assessment of the outcome (TB or Malaria infection) 1= Objective diagnostic methodology with units of measurement and /or definitions 0= No definitive diagnosis or self report	Statistical analysis 1= The statistical method used is clearly described and appropriate for the analysis undertaken. Where comparisons are made between population groups, the measurement of the association is presented, including confidence intervals and the probability level (p value) 0= The statistical test is inappropriate/not described/incomplete	Total Score
	MALARIA STUDIES									
1	Abe, 2009	1	1	1	0	1	0	1	1	6
2	Chaturvedi, 2017	1	1	1	0	0	1	1	1	6
3	Choubisa, 1992	1	1	1	0	0	0	1	0	4
4	Chourasia, 2017a	1	1	1	0	1	1	1	1	7
5	Chourasia, 2017b	1	1	1	0	0	1	1	1	6
6	Damon, 1974	1	1	1	0	1	0	1	0	5
7	Das, 2000	1	0	1	0	0	0	1	0	3
8	Das, 2005	1	1	1	0	1	1	1	0	6
9	Das, 2017	1	1	1	0	1	0	1	1	6

10	Dev, 2006	1	1	1	0	0	0	1	1	5
11	Erhart, 2005	1	1	1	1	1	0	1	1	7
12	Ganguly, 2013	1	1	1	0	1	0	1	1	6
13	Gordon, 1991	1	1	1	0	0	0	1	1	5
14	Haque, 2011	1	1	1	0	1	1	1	1	7
15	Jiram, 2016	1	1	1	0	0	0	1	0	4
16	Kaur, 2009	1	1	1	1	1	1	1	1	8
17	Luxemburger, 1996	1	1	1	0	1	0	1	1	6
18	Mak, 1987	1	1	1	0	0	0	1	1	5
19	Marasabessy, 2019	1	1	1	0	0	0	1	1	5
20	Marchand, 2011	1	1	1	0	0	0	1	1	5
21	Nakabayashi, 1973	1	1	1	0	1	0	1	1	6
22	Nithikathkul, 2003A	1	1	1	0	0	0	1	0	4
23	Nithikathkul, 2003B	1	1	1	0	1	1	1	0	6
24	Norhayati, 2001	1	1	1	0	0	0	1	1	5
25	Pichainarong, 2004	1	1	1	1	0	1	1	1	7
26	Rahmah, 1997	1	1	1	0	0	0	1	0	4
27	Rajagopalan, 1989	1	1	1	0	1	1	1	1	7
28	Roy, 2001	1	1	1	0	0	0	1	1	5
29	Sahu, 2013	1	1	1	1	1	0	1	1	7
30	Sharma, 2004	1	1	1	0	1	0	1	0	5
31	Sharma, 2006	1	1	1	0	1	0	1	1	6
32	Singh, 1989	1	1	1	0	1	0	1	0	5
33	Singh, 1998	1	1	1	0	1	1	1	1	7
34	Singh, 2001	1	1	1	0	0	1	1	1	6
35	Srivastava, 2000	1	1	1	0	0	0	1	1	5
36	Stafford, 1980	1	1	1	0	0	0	1	0	4
37	Thomas, 1981	1	1	1	0	1	0	1	0	5
38	Tipmontree, 2009	1	1	1	1	0	0	0	1	5
39	Wharton, 1963	1	1	1	0	0	0	1	0	4

	TB STUDIES									
1	Bhat, 2009	1	1	1	1	1	0	1	1	7
2	Bhat, 2015	1	1	1	1	1	1	1	0	7
3	Bhat, 2017	1	1	1	1	1	1	1	1	8
4	Bolton, 1975	1	1	1	0	0	0	1	0	4
5	Chakma, 1996	1	1	1	0	1	0	1	1	6
6	Damon, 1974	1	1	1	0	1	0	1	0	5
7	Datta, 2001	1	1	1	0	1	1	1	1	7
8	Haddad, 2012	1	1	1	0	1	1	1	1	7
9	Hussain, 2020	1	1	1	1	1	1	1	0	7
10	Kashyap, 2013	1	1	1	0	0	0	1	1	5
11	Kerketta, 2009	1	1	0	0	0	0	0	0	2
12	King, 1951	1	1	1	0	0	0	1	0	4
13	Macken, 1952	1	1	1	0	1	0	1	0	5
14	Murhekar, 2004	1	1	1	0	1	1	1	1	7
15	Purty, 2019	1	1	1	1	1	1	1	0	7
16	Rao, 2010A	1	1	1	0	1	1	1	1	7
17	Rao, 2010B	1	1	1	1	1	0	1	1	7
18	Rao, 2011	1	1	1	0	0	1	1	1	6
19	Rao, 2015	1	1	1	1	1	1	1	1	8
20	Rao, 2019	1	1	1	1	1	1	1	1	8
21	Roy, 1969	1	1	1	0	1	0	1	0	5
22	Sharma, 2010	1	1	1	0	0	1	1	1	6
23	Vyas, 2019	1	1	1	0	0	1	1	0	5
24	Yano, 1974	1	1	1	0	1	0	1	0	5

The average QA total score across the malaria studies was 5.5 and 6.0 across the TB studies out of a total possible score of 9

Chapter V: The prevalence of STH infections in indigenous ethnic minority populations of the SEAR and WPR

Chapter V addresses STH - the final infectious agent under consideration in Part II of the thesis. STH prevalence was evaluated as STH infection overall and according to each species: *A .lumbricoides*, *T. trichiura*, *S. stercoralis* and Hookworm spp. collectively.

Within indigenous ethnic minority populations, STH infection prevalence was consistently higher in the WPR than the SEAR, with studies from Malaysia contributing the majority of WPR data. For all species, prevalence was high and static with an increasing trend of *S. stercorlais* and *T. trichiura* infection over time. The increasing prevalence of *T. trichiura* was significant and warrants further investigation.

The review found there to be no significant difference in overall STH prevalence between the indigenous ethnic minorities of Australia and India. The considerable difference in socio-economic status between these two countries, shows that STH infection within this vulnerable population group is not a problem limited to developing regions.

Sub-group analyses showed there to be no significant difference in STH infection prevalence between indigenous ethnic minorities and other population groups. Full details of the review can be found in the following paper:

Gilmour B, Alene KA, Clements ACA. The prevalence of STH infections in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis. *PLOS Neglected Tropical* Diseases November 10, 2021 https://doi.org/10.1371/journal.pntd.0009890

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

The prevalence of soil transmitted helminth infections in minority indigenous populations of South-East Asia and the Western Pacific Region: A systematic review and meta-analysis

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Abstract

Introduction

Soil transmitted helminth (STH) infections cause one of the most prevalent diseases in man. STHs disproportionately impact socio-economically disadvantaged communities including minority indigenous populations. This systematic review aimed to quantify the prevalence of STH infection within minority indigenous populations of the South-East Asia and Western Pacific Regions.

Methods

The systematic review was conducted in accordance with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines following a published protocol. A random effects meta-analysis was used to estimate the pooled prevalence of STH infection, and meta-regression analysis was used to quantify associations with study characteristics. Where comparative data were available, sub-group analysis was conducted to evaluate the risk of STH infection in minority indigenous people relative to other population groups. The heterogeneity between studies was evaluated visually using Forest plots and was assessed quantitatively by the index of heterogeneity (I^2) and Cochran Q-statistics.

Results

From 1,366 unique studies that were identified, 81 were included in the final analysis. The pooled prevalence of infection within minority indigenous populations was 61.4% (95% CI 50.8, 71.4) for overall STH infection; 32.3% (95% CI 25.7, 39.3) for *Ascaris.lumbricoides*; 43.6% (95% CI 32.6, 54.8) for *Trichuris.trichiura*; 19.9% (95% CI 15.7, 24.5) for hookworm and 6.3% (95% CI 3.2, 10.2) for *Strongyloides.stercoralis*. A significant increase in *T. trichiura* prevalence was observed over time. The stratified analysis showed that the

in study design, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

prevalence of infection for STH overall and for each STH species were not significantly different in minority indigenous participants compared to other populations groups.

Conclusion

The prevalence of STH infection is high within minority indigenous populations across countries at very different levels of socio-economic development. The increasing prevalence of *T*. *trichiura* calls for the implementation of more effective therapies and control strategies.

Author summary

Neglected Tropical Diseases (NTD) are caused by a range of infectious pathogens and have their greatest impact on poor and vulnerable populations. One such population group, is indigenous people, who are disproportionately impacted by poverty and social disadvantage. Among the World Health Organization (WHO) list of 20 NTD, soil transmitted helminth (STH; *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm) infections are the most prevalent and burdensome. This systematic review and meta-analysis evaluated the prevalence of STH infection in minority indigenous populations of the South-East Asia (SEAR) and Western Pacific Regions (WPR). The results showed a high prevalence of infection for all STH species in minority indigenous populations of both developing and highly industrialized nations. Of concern was the increasing prevalence of *T*. *trichiura* infection over time, which calls for the identification and implementation of more effective therapies and control strategies. Where comparative data were available, the review showed infection prevalence of all STH species not to be significantly different in minority indigenous people compared to those of other population groups. To help break the health burden and poverty cycle created by these infections, accurate, relevant data will be required to inform effective and appropriate interventions.

Introduction

Soil transmitted helminthiasis is a Neglected Tropical Disease (NTD)[1] estimated to impact 1.5 billion people,[2] a figure which equates to 19% of the world's population. The four species of gastro-intestinal nematode commonly included in soil transmitted helminths (STH) are *Ascaris lumbricoides* (roundworms), *Trichuris trichiura* (whipworms), *Necator americanus* and *Ancylostoma duodenale* (hookworms). *Ancylostoma ceylanicum* is also an increasingly recognized hookworm species of public health importance. These parasites prevail in the tropics and subtropics and have their greatest impact on populations affected by poverty and disadvantage.[2–5]

The impact STH infection creates a significant global health burden. In 2016, the WHO estimated a loss of 3.4 million disability adjusted life-years (DALY) worldwide, of which 42% was attributed to *A*. *lumbricoides*, 10% to *T*. *trichiura* and 48% to hookworm infection.[6] A significant proportion of the total disease burden is attributed to Years Lost due to Disability (YLD) which is estimated at 2.9 million.[6]

The quantum of the YLD estimate is reflective of the chronic and debilitating morbidity associated with STH infections. The symptoms of morbidity are often difficult to quantify due to the effects of poverty, malnutrition and co-infection, which are common amongst those worst affected.[7] However, a number of morbidities have been well documented and include

impaired growth and physical development, intestinal obstruction, anaemia, vitamin A deficiency, and poor intellectual and cognitive development.[4,8]

Although not as well represented in the literature, *Strongyloides stercoralis* is another pathogenic STH of significance to human health. While the prevalence of *Strongyloidiasis* is difficult to quantify due to many cases being asymptomatic and traditional diagnostic methods lacking sensitivity,[9] global estimates project between 100 and 370 million infections.[9,10] *S. stercoralis* is differentiated from other STH species by an auto-infective capability within the lifecycle [11] and by its prevalence in both tropical and temperate climates.[12] Statistics for *S. stercoralis* are not included within DALY figures and although hyper-infection syndrome for this parasite is rare, it is often fatal in immunocompromised patients among whom mortality rates of 86% are reported.[13]

The successful control of STH infections will be dependent upon a multi-faceted approach. Economic development is proven to be a significant factor in eradicating STH infections[14] and it is acknowledged that WASH (water, sanitation and hygiene) and education initiatives are fundamental to reducing disease transmission.[15] These approaches are combined with the primary focus of the WHO endorsed control strategy for *A. lumbricoides*, *T. trichiura* and hookworm infection which is the periodic administration of anthelmintic drugs to at-risk populations living in endemic areas.[16] Although well-developed treatment strategies have been developed for *A. lumbricoides*, *T. trichiura* and hookworm,[15] systematic action plans to address *Strongyloidiasis* are lacking.[10] There is a fundamental lack of epidemiological data for *Strongyloides* infection, a knowledge gap not limited to developing regions as evidenced by the call for its inclusion on the Australian Notifiable Disease List.[17]

Although significant reductions in STH prevalence have been achieved over recent times, [18] infections continue to impose a significant global health burden and impact those most vulnerable within society. One population group that has been shown to be disproportionately affected by poverty and social disadvantage is indigenous people.[19]

Although there are published studies on the impact of STH infections within discrete ethnic groups, there is nothing in the literature that quantifies STH infection risk in minority indigenous people as a collective. If the goals of the 2030 Agenda for Sustainable Development are to be achieved, the burden of disease amongst vulnerable populations needs to be evaluated to inform effective interventions.

This systematic review aimed to quantify the prevalence of STH infection amongst minority indigenous populations of the SEAR and WPR. These regions were chosen as WHO data attributes a high proportion of DALYs to be lost as a result of STH infection within these areas.[6]

The SEAR and WPR also include a significant representation of indigenous populations [20] whilst providing an opportunity to compare the prevalence of STH infection across countries of differing socio-economic strata.

Methods

Search strategy

The systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[21] (S1 PRISMA checklist). Specifics on the search criteria and details of the study selection criteria are available in a published protocol.[22]

In summary, four biomedical databases: Scopus, Web of Science, Medline (Ovid) and EMBASE (Ovid), were systematically searched using the criteria detailed in S1 Table, without restriction on the year of publication. In addition to the biomedical database search, reference lists from included publications were hand searched.

Study screening and selection criteria

All studies identified from the systematic search were imported into Endnote X9 (Clarivate Analytics) where duplicates were deleted. Following removal of the duplicates, studies were uploaded to Rayyan Qatar Computing Research Institute (QCRI) [23] and titles and abstracts were independently assessed by two authors (BG and KAA). The full text articles of shortlisted abstracts were independently screened by the same two authors against the inclusion and exclusion criteria.

Any discrepancies relating to the shortlisting of publications were discussed and where consensus could not be achieved, advice was sought from the third author (ACAC). Where further clarification was required, this was requested from the corresponding author of the relevant publication.

Inclusion criteria

Studies were included if they were representative cross-sectional surveys relating to human infection and provided sufficient data to facilitate the calculation of STH prevalence. Studies were required to include minority indigenous population participants within the SEAR or WPR.

In accordance with the protocol,[22] minority indigenous populations were defined when each of the following criteria were met:

- Descendants of the original or earliest known inhabitants of an area; people who have historical continuity with pre-invasion and pre-colonial societies.
- Distinct societies with languages, culture, customs, and social and political frameworks that vary significantly from those of the dominant population.
- Groups of people with strong cultural ties and dependence upon the environment and its resources for their survival.
- People self-identifying as indigenous.
- Groups who face relative disadvantage or discrimination in multiple areas of social existence- success, education, healthcare, employment.
- Numerically non-dominant groups in a country or area.

The WHO Global Burden of Disease (GBD) regional classification system [24] was used to define the countries located within the SEAR and WPR.

Exclusion criteria

Studies were excluded if they were not full text articles and did not publish in English. Publications were excluded if less than 90% of the participants (or, for the comparative studies, the minority indigenous category) met the minority indigenous population criteria. Data from case series with less than 10 participants and case studies; systematic and literature reviews; conference poster or abstracts and scientific correspondence e.g., letters to the editor, were excluded. Singapore was excluded from the search as it does not have any minority indigenous people according to the definitions used by this review.

Outcomes

The primary outcome of the study was prevalence of STH infection amongst minority indigenous populations of the SEAR and WPRs. Prevalence included STH infection overall and

according to species: *A.lumbricoides*, *T.trichiura*, *S.stercoralis* and Hookworm species collectively.

Data extraction and quality assessment

Data were extracted from included studies using Microsoft Excel version 2016 (Microsoft, Redmond, Washington, USA) by BG and independently validated by KAA. Following pilot testing and refinement, a data extraction spreadsheet was used to record the following information: first author and year of publication; year and country in which the study was undertaken; study population classification (minority indigenous or other); species of infectious agent; diagnostic method; sex of study participants; size (n) of the study population and number of disease positive participants. Although the protocol [22] also intended to extract and analyze data by age, this was not undertaken due to the large variation in age classifications across publications.

Where studies evaluated the impact of intervention regimes, only pre-intervention baseline data were extracted. When surveys undertook a comparison of disease prevalence across minority indigenous and other population groups, data were extracted for both to facilitate a comparison.

A modified version of the Newcastle-Ottawa Quality Assessment (QA) Scale[25] was utilized to assess the quality of the studies analysed, the scores for which are detailed in S2 Table. The QA tool has scores ranging from 0 to 9, in accordance with the protocol,[22] scores between 1 and 4 were defined as low quality, scores between 5 and 7 were defined as medium quality, and scores between 8 and 9 defined as high quality.

Study variables

The mortality strata for each country of study was attributed according to the WHO definitions[26], and was evaluated as a study variable. The other study variables used for the sub-group analysis included: WHO region, country of study, year of data collection, study location (community/school), number of samples analysed (singular/multiple), diagnostic method, number of helminth infections, study participant sex, helminth species (for hookworm) and QA grade.

Data analysis

For the studies that identified overall STH infection, and for data extracted by species (*A.lumbricoides*, *T.trichiura*, hookworm and *S.stercoralis*), a random-effects meta-analysis was used to estimate the pooled prevalence of infection. The meta-analysis was undertaken using the Freeman-Tukey double arcsine transformation to address confidence limits outside the 0 to 1 range and variance instability.[27] This was implemented in Stata using the *metaprop* command.[28]

The heterogeneity between studies in minority indigenous populations was assessed using Cochran's Q test and was quantitatively evaluated with the index of heterogeneity squared (I^2) statistic with 95% CI.[29] Heterogeneity between studies was classified low, moderate and high when I^2 values were below 25%, between 25% and 75% and above 75%, respectively.[29]

In an attempt to account for the high heterogeneity that was identified, meta-regression was undertaken using the study characteristics as covariates. The meta- regression was conducted using the robust variance estimation (RVE) method to manage non-independent effect sizes without knowledge of the within-study covariance structure.[30]

Where comparative data were available, sub-group analysis was conducted to evaluate the risk of helminth infection in minority indigenous communities relative to other population

groups. Where differences in infection prevalence were identified across study variables, or between population groups, bivariate meta-regression was used to evaluate their significance (p-value <0.05) when three or more data sets were available for each comparison.

Funnel plots were utilized to evaluate potential publication bias and asymmetry was assessed using Egger's method with a p-value <0.05 denoting significant bias.[31] Analysis was conducted using Stata/MP version 16.1 (StataCorp, College Station, TX).

Results

The search identified 1,366 unique studies from which 157 were shortlisted following title and abstract screening. Following the full text review, 81 studies were included in the final analysis (Fig 1); the characteristics of the studies are provided in Table 1. Publication bias of the included studies was evidenced by the asymmetrical shape of the funnel plot (Fig 2) and a p value = 0.025 calculated with Egger's regression test.

Prevalence of overall STH Infection

Out of the 81 studies, 49 enabled the overall prevalence of STH infection to be calculated. Details on the pooled prevalence of infection and bivariate meta-regression across the study covariates are detailed in Tables 2 and 3, respectively.

The pooled prevalence of STH infection across the 49 studies, which represented 15,238 minority indigenous participants, was 61.4% (95% CI 50.8, 71.4), with high (I^2 = 99.4%) and significant (p = 0.000) heterogeneity shown between studies (Fig 3). Eighty-six percent of the studies were undertaken in the WPR and 61% of the studies that reported overall STH prevalence, had been undertaken within Malaysia. The prevalence of infection was found to be significantly higher in the WPR at 66.3% (95% CI 55.2, 76.6) compared to the SEAR at 30.3% (95% CI 15.6, 47.3; p = 0.010). The only other study covariate found to have a significant effect on overall STH prevalence, was the use of serology as a diagnostic method relative to microscopy (p = 0.000). Where studies detailed the number of infections, the prevalence of single and multiple species infections were found to be comparable.

Five studies provided data that could be used to compare STH infection prevalence between minority indigenous and other population groups. Although the prevalence of infection was higher in minority indigenous populations (41.9%, 95% CI 15.6, 70.9) relative to other groups (37.5%, 95% CI 10.6, 69.5) this was not found to be significant (p = 0.870).

Prevalence of *Ascaris lumbricoides* infection

Out of the 81 studies, 64 reported on the prevalence of *A*. *lumbricoides* infection. Details on the pooled prevalence of infection and bivariate meta-regression across the study covariates are detailed in Tables 4 and 5, respectively.

The pooled prevalence of *A*. *lumbricoides* infection across the 64 studies, representing 21,495 minority indigenous participants, was 32.3% (95% CI 25.7, 39.3- Fig 4). Although there was significant heterogeneity between publications, the only study covariates of significance were WHO region and country. The WPR, where 70% of the studies were undertaken, had a significantly higher prevalence of infection at 39.8% (95% CI 31.9, 47.9) than the SEAR at 16.5% (95% CI 8.22, 26.8; p = 0.002). Where sufficient data were available to allow the country of study to be analyzed as a covariate, prevalence was found to be significantly higher in China (67.8%, 95% CI 39.0, 90.7; p = 0.002) and Malaysia (38.3%, 95% CI 31.8, 44.9; p = 0.022) than elsewhere.

Eight studies provided data that facilitated a comparison of *A.lumbricoides* infection prevalence between minority indigenous and other population groups. Although not significant

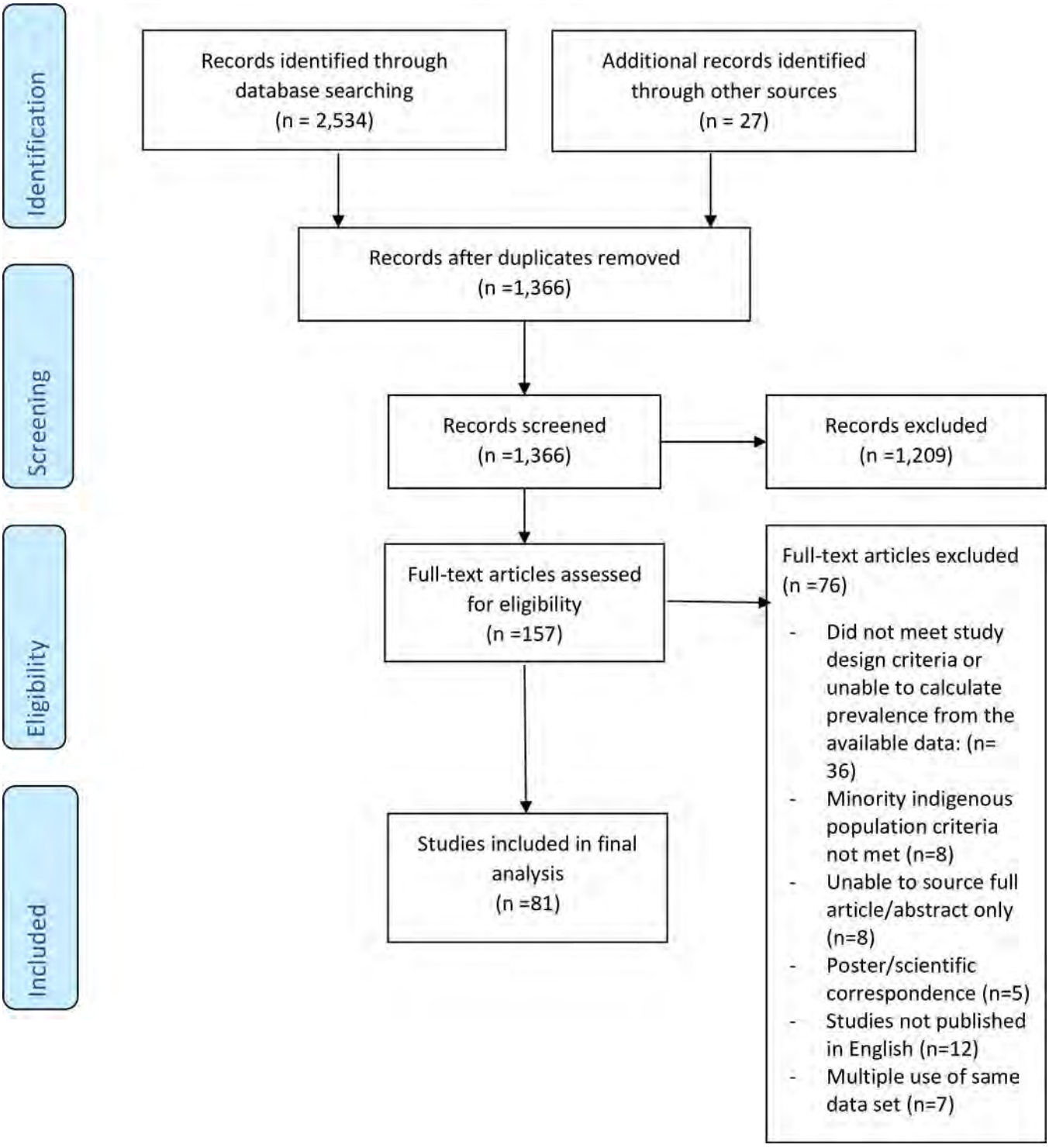

Fig 1. Summary of PRISMA systematic review publication selection process.

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($p = 0.860$), the prevalence of infection was found to be higher in minority indigenous participants (41.0%, 95% CI 25.7, 57.2) compared to those from other population groups (25.2%, 95% CI 8.4, 47.2).

Table 1. Summary of STH studies within minority indigenous populations in South East Asia and the Western Pacific Region.

Study ID	First Author Year of Publication	Year of Data Collection [Δ]	WHO Region	WHO Mortality Strata	Country	STH species	Study Population size (n)	Number Positive ^	% Male	Median Age or *Mean Age
1	Adli, 2019	<2019	WPR	B	Malaysia	Hookworm	71	10		
2	Adli, 2020	2017	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	92	70		
3	Ahmad, 2013	<2013	WPR	B	Malaysia	*S.stercoralis*	54	3		
4	Ahmed, 2011	2010	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	254	238	48.8	9.5
5	Al Delaimy, 2014A	<2014	WPR	B	Malaysia	*Trichuriasis/Ascariasis*/ Hookworm	317	315	48.9	9
6	Al Delaimy, 2014B	2012	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	498	490	50.6	9
7	Al Mekhlafi, 2005	<2005	WPR	B	Malaysia	*Trichuriasis/Ascariasis*/ Hookworm	368		48.7	* 7.1
8	Al Mekhlafi, 2006	<2006	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	281	281	50.9	
9	Al Mekhlafi, 2007	2006	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	292	288	49.7	9.6
10	Al Mekhlafi, 2019	2017	WPR	B	Malaysia	*S.stercoralis*	1142	180	49.4	*10.19
11	Anuar, 2014	<2014	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	500		43.8	
12	Ash, 2017	2013	WPR	B	Laos	*A.lumbricoides/T. trichiura*	100	90		
13	Bangs, 1996	1990	SEAR	B	Indonesia	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	478			
14	Belizario, 2011	2009	WPR	B	Philippines	*A.lumbricoides/T. trichiura*/Hookworm	264	103	43.9	*10.08
15	Brandon Mong, 2017	2013 2014	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	235	192	50.2	26
16	Chakma, 2000	<2000	SEAR	D	India	*A.lumbricoides*/ hookworm	409			
17	Chin, 2016	2014	WPR	B	Malaysia	*A.lumbricoides/T. trichiura/A.ceylancum/ A.americanus*	186	114	42.5	26
18	Choubisa, 1992	<1992	SEAR	D	India	*A.lumbricoides/N. americanus/A. doudenale/T.trichiura*	250			
19	Choubisa, 2012	2010 2011	SEAR	D	India	*A.lumbricoides/A. duodenale/S.stercoralis/ T.trichiura*	224		51.3	
20	Damon, 1974	1966 + 1968	WPR	B	Solomon Isl	*A.lumbricoides/T. trichiura*/Hookworm	105			
21	DeGuia, 2019	<2019	WPR	B	Philippines	*Ascaris/Trichuris*/ Hookworm	223	159		
22	Elyana, 2016	2014 2015	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	165		53.3	
23	Farook, 2002	2001	SEAR	D	India	Roundworm/ Hookworm/ *Strongyloides*/ Whipworm	258	60	44.6	
24	Fryar, 1997	1996	WPR	A	Australia	*T.trichiura*/ *Strongyloides*/ Hookworm	28	9		

(*Continued*)

Table 1. (Continued)

Study ID	First Author Year of Publication	Year of Data Collection Δ	WHO Region	WHO Mortality Strata	Country	STH species	Study Population size (n)	Number Positive ^	% Male	Median Age or *Mean Age
25	Geik, 2015	2014	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	256	161	51.2	* 3.2
26	Ghani, 2013	<2012	WPR	B	Malaysia	*A.lumbricoides*	272	124	47.4	
27	Hall, 1994	<1994	SEAR	D	Bangladesh	*S.stercoralis*	656	89		
28	Hanapian, 2014	2005 2006	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	175	131	49.7	15.11
29	Hartini, 2013	<2013	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	111			
30	Holt, 2017	2010 2011	WPR	A	Australia	*T.trichiura*/ Hookworm/*S. stercoralis*	85			3.7
31	Hung, 2016	2015	WPR	B	Vietnam	*A.lumbricoides/T. trichiura*/Hookworm	1206	301		
32	Kaliappan, 2013	2011 2012	SEAR	D	India	*A.lumbricoides/T. trichiura*/Hookworm	680	265		
33	Kalra, 1982	1979	SEAR	D	India	*A.lumbricoides/T. trichiura*/Hookworm	115			
34	Kearns, 2017	2010	WPR	A	Australia	*S.stercoralis*	818	185	49	21
35	Lee, 2014	2010 2012	WPR	B	Malaysia	*Ascaris spp/T.trichiura*/ Hookworm	269	149		
36	Lili, 2000	1998	WPR	B	China	*Ascaris spp/Trichuris*/ Hookworm	304	219		
37	Lyndem, 2002	1996 1999	SEAR	D	India	*N.americanus/Ascaris/ Trichuris*	2087		51.6	
38	Meloni, 1993	1987 1991	WPR	A	Australia	*A.duodenale/T. trichiura/S.stercoralis*	385			
39	Miller, 2018	2004 2005	WPR	A	Australia	*S.stercoralis*	867	144	46	
40	Mohd Shadaruddin, 2018	2014 2015	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	411	299	48.8	4
41	Muslim, 2019	2016 2017	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	416	358	50	10
42	Nasr, 2013	2011	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	484	378	51.4	7
43	Neo, 1987	<1987	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	142	92		
44	Ng, 2014	2011	WPR	B	Philippines	*A.lumbricoides/T. trichiura*/Hookworm	195	190	42	
45	Ngui, 2015	2009 2011	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	634	380	43.5	11
46	Ngui, 2016	<2016	WPR	B	Malaysia	*S.stercoralis*	236	26	53	44
47	Nithikathkul, 2003	2002	SEAR	B	Thailand	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	70		48.6	
48	Nithikathkul, 2007	2002	SEAR	B	Thailand	*T.trichiura*/Hookworm	133	15	45.9	
49	Nor Aini, 2007	2003 2004	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	281	281		
50	Norhayati, 1995	<1995	WPR	B	Malaysia	Hookworm	193	60	48.2	
51	Norhayati, 1997	<1997	WPR	B	Malaysia	*Ascaris spp/Trichuris*/ Hookworm	123			

(*Continued*)

Table 1. (Continued)

Study ID	First Author Year of Publication	Year of Data Collection [Δ]	WHO Region	WHO Mortality Strata	Country	STH species	Study Population size (n)	Number Positive ^	% Male	Median Age or *Mean Age
52	Norhayati, 1998	<1997	WPR	B	Malaysia	*Ascaris spp/Trichuris*/ Hookworm	205		46.3	
53	Piangjai, 2003	1997 1998	SEAR	B	Thailand	*A.lumbricoides/T. trichiura*/Hookworm	403		48.9	
54	Prownebon, 2013	2008	SEAR	B	Thailand	*A.lumbricoides/T. trichiura*/Hookworm	145		48.3	
55	Rahmah, 1997	1996	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	84	67		
56	Rajeswari, 1994	<1994	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	78			
57	Rajoo, 2017	<2017	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	341	195	45.5	30
58	Ranjitkar, 2014	2011	SEAR	D	Nepal	STH	27	5		
59	Rao, 2002	2000 2001	SEAR	D	India	*Ascaris*/Hookworm	985			
60	Rao, 2006	1997	SEAR	D	India	*A.lumbricoides/T. trichiura*	40	40		
61	Reynoldson, 1997	1996	WPR	A	Australia	*A.duodenale/T. trichiura/S.stercoralis*	108			
62	Ribas, 2017	<2017	WPR	B	Laos	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	305	210		
63	Ritchie, 1954	1949	WPR	A	Japan	*A.lumbricoides/T. trichiura*/Hookworm	195			
64	Sagin, 2002	<2002	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	355			
65	Saksirisampant, 2004	2002 2003	SEAR	B	Thailand	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	542		40.6	
66	Shield, 2015	1994 1996	WPR	A	Australia	*T.trichiura*/ Hookworm/*S. stercoralis*	314	276		
67	Singh, 1993	<1993	SEAR	D	India	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	28			
68	Sinniah, 2012	2011	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	77	36	31	
69	Sinniah, 2014	<2014	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	106			
70	Stafford, 1980	<1980	SEAR	B	Indonesia	*A.lumbricoides/T. trichiura*/Hookworm	287			
71	Steinmann, 2008	2006	WPR	B	China	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	215		47.4	* 29
72	Sugunan, 1996	<1996	SEAR	D	India	*A.lumbricoides/T. trichiura*/Hookworm	46			
73	Tienboon, 2007	<2007	SEAR	B	Thailand	*A.lumbricoides/T. trichiura*/Hookworm/ *S.stercoralis*	158		52.5	
74	Verle, 2003	1999	WPR	B	Vietnam	*A.lumbricoides/T. trichiura*/Hookworm	2103			

(*Continued*)

Table 1. (Continued)

Study ID	First Author Year of Publication	Year of Data Collection [Δ]	WHO Region	WHO Mortality Strata	Country	STH species	Study Population size (n)	Number Positive ^	% Male	Median Age or *Mean Age
75	Wong, 2016	<2016	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	33	32	58	
76	Yanola, 2018	2015 2016	SEAR	B	Thailand	*A.lumbricoides/T. trichiura*	375	33	37	
77	Yap, 2012	2011	WPR	B	China	*A.lumbricoides/T. trichiura*/Hookworm	69	59	42	11
78	Yoshida, 1968	1966	WPR	B	Taiwan	*Ascaris spp/Trichuris*/ Hookworm	233			
79	Zulkifli, 1999A	<1999	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	268	127	49.6	
80	Zulkifli, 1999 B	<1999	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	259	145		
81	Zulkifli, 2000	<2000	WPR	B	Malaysia	*A.lumbricoides/T. trichiura*/Hookworm	123	86		

Notes

^ Where the number of participants positive for STH is not detailed, the study details data by species

[Δ] Where the study does not detail the year of data collection, it is assumed < year of publication

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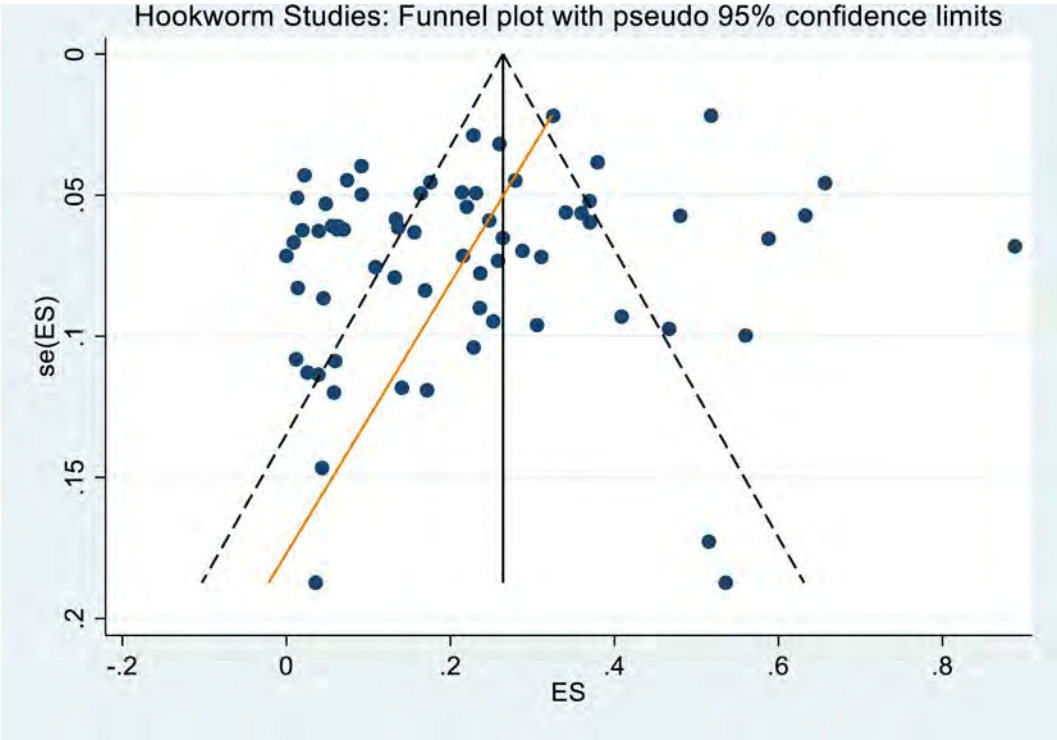

Fig 2. Funnel plot of hookworm* studies with pseudo 95% confidence intervals. *The hookworm data set was used to assess publication bias as this contains the largest number of studies (68 of the 81). Egger's test produced a bias coefficient of 2.09 (95% CI 3.90, 0.28) p value 0.025 indicating publication bias.

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Table 2. Pooled prevalence of STH infections analysed by study covariates.

Categories	Pooled prevalence of STH$^{\Delta}$ Infection	
	Studies (n)	Pooled Prevalence (95% CI)
Population group		
Minority indigenous populations	49	61.38 (50.82, 71.42)
Comparative Studies		
Non minority indigenous populations	5	37.46 (10.57, 69.45)
Minority indigenous populations	5	41.93 (15.63, 70.94)
	Analysis on minority indigenous populations only	
WHO regions		
SEAR	7	30.27 (15.62, 47.28)
WPR	42	66.31 (55.24, 76.55)
WHO Mortality Strata		
A	4	39.98 (10.89, 73.59)
B	40	65.82 (54.36, 76.43)
D	5	40.78 (20.33, 63.02)
Countries		
Australia	4	39.98 (10.89, 73.59)
Bangladesh	1	NA
China	2	74.82 (70.25, 79.14)
India	3	59.22 (27.71, 87.07)
Laos	2	74.84 (70.48, 78.98)
Malaysia	30	68.36 (55.38, 80.04)
Nepal	1	NA
Philippines	3	73.34 (33.34, 98.45)
Thailand	2	9.37 (6.96, 12.09)
Vietnam	1	NA
Year of data collection		
1981 2000	11	61.59 (41.78, 79.60)
2001 2020	38	61.30 (48.92, 73.00)
Study Location		
Community	35	56.57 (45.39, 67.42)
School	14	72.90 (48.59, 91.59)
Number of samples analysed		
Singular	47	62.95 (52.10, 73.18)
Multiple	2	25.42 (23.12, 27.79)
Diagnostic method *		
Microscopy	44	65.97 (55.08, 76.08)
PCR	2	46.72 (40.39, 53.10)
Serology	3	16.78 (11.43, 22.92)
QA Grade		
Low	5	60.24 (31.92, 85.37)
Medium	40	59.24 (48.32, 69.72)
High	4	81.81 (27.17, 100.00)

Notes

$^{\Delta}$ STH prevalence: Overall prevalence is only available for 49 of the 81 studies, the balance of publications present data at species level. For the calculation of overall STH prevalence, 49 studies detailed the summary level of infection when multiple species were investigated, or the studies were based on a single helminth species.

*Diagnostic method: PCR and microscopy classified as PCR; ELISA classified as serology

https://doi.org/10.1371/journal.pntd.0009890.t002

Table 3. Bivariate meta regression of STH infections analysed by study covariates.

Categories	Pooled prevalence of STH Infection		
	95% CI	*p* value	$I^{2\,\alpha}$ (%)
Comparative Studies			95.93
Non Minority indigenous populations	1.00		99.26
Minority indigenous populations	1.03 (0.67, 1.59)	0.870	99.03
Analysis on minority indigenous populations only			
WHO regions			96.24
SEAR	1.00		99.41
WPR	1.39 (1.09, 1.77)	0.010	98.29
WHO Mortality Strata			96.74
A	1.00		99.51
B	1.26 (0.92, 1.72)	0.147	99.38
D	0.99 (0.65, 1.50)	0.147	98.50
Countries			96.41
Australia	1.00		99.51
India	1.15 (0.67, 1.96)	0.611	$^{\Delta}$
Malaysia	1.28 (0.91, 1.81)	0.152	99.34
Philippines	1.34 (0.85, 2.10)	0.196	$^{\Delta}$
Year of data collection			96.74
1981 2000	1.00		98.91
2001 2020	0.98 (0.82, 1.19)	0.891	99.50
Study Location			96.73
Community	1.00		99.21
School	1.14 (0.93, 1.40)	0.213	99.68
Diagnostic method			96.74
Microscopy	1.00		99.39
Serology	0.63 (0.57, 0.70)	0.000	$^{\Delta}$
Number of Infections			93.88
Single	1.00		98.65
Multiple	1.01 (0.90, 1.14)	0.808	98.95
QA Grade			96.73
Low	1.00		97.01
Medium	0.99 (0.73, 1.33)	0.920	99.33
High	1.18 (0.75, 1.86)	0.470	99.87

Note: Bivariate meta regression analysis was only undertaken where there were 3 or more data sets

$^{\alpha}$ the variation in effect size attributable to heterogeneity

$^{\Delta}$ I^2 not calculated where degrees of freedom ≤ 3

https://doi.org/10.1371/journal.pntd.0009890.t003

Heterogeneity was found to be high (I^2 >75%) for *A.lumbricoides* prevalence within all covariates, with the exception of QA grade. Studies classified with a medium QA score (5–7) showed moderate heterogeneity (I^2 25–75%).

Prevalence of *Trichuris trichiura* infection

Sixty -five of the 81 studies reported on the prevalence of *T. trichiura* infection, representing a cumulative study population of 20,466 minority indigenous participants. The pooled prevalence of infection across the study covariates and the subsequent bivariate meta-regression are detailed in Tables 6 and 7, respectively.

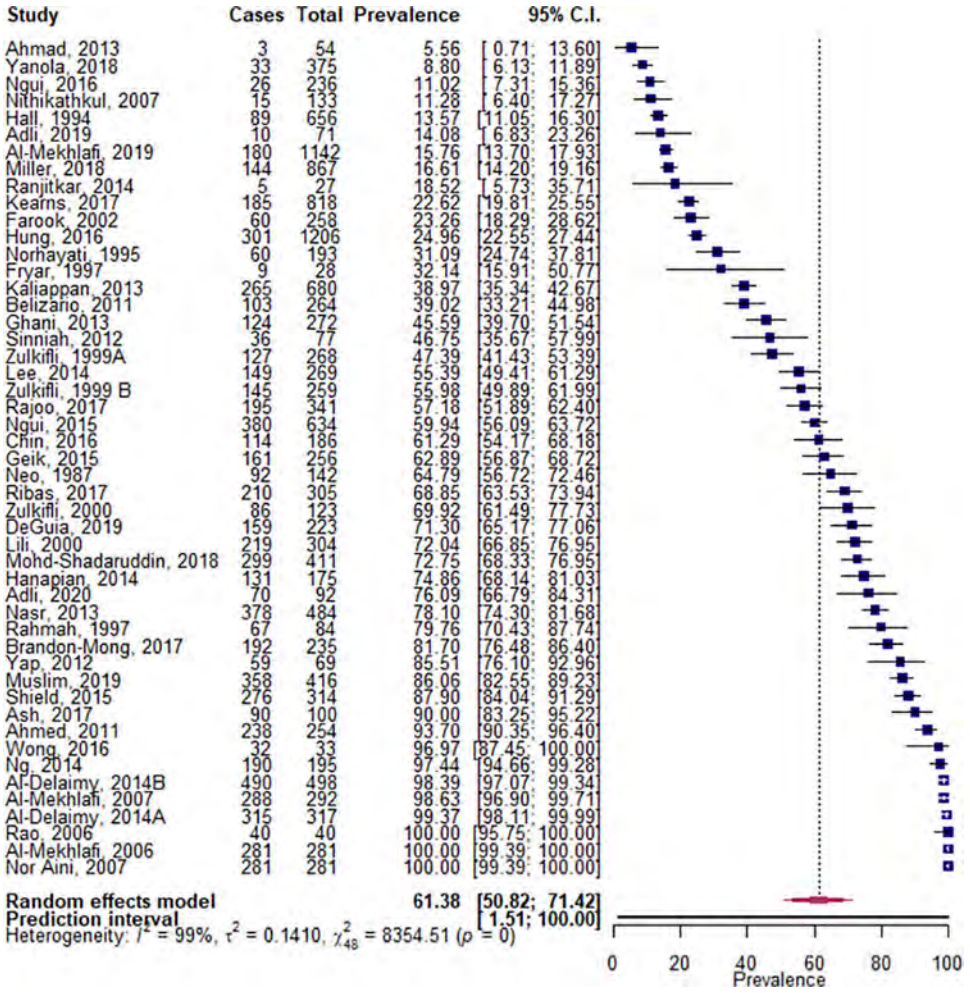

Fig 3. Pooled prevalence of STH infections within minority indigenous study populations. The forest plot shows the pooled prevalence of STH infection with 95% confidence intervals (CI) and the prediction interval. The I^2 statistic is rounded to the nearest integer.

https://doi.org/10.1371/journal.pntd.0009890.g003

The pooled prevalence of *T*. *trichiura* infection within minority indigenous populations was 43.6% (95% CI 32.6, 54.8- Fig 5). There was significant heterogeneity between studies, with WHO region, country of study, period of data collection, and QA grade shown to be significant study co-variates. The prevalence of infection was shown to be significantly higher in the WPR at 55.8% (95% CI 44.2, 67.1) compared to the SEAR at 10.3% (95% CI 5.2, 16.9; $p = 0.000$). Where sufficient data were available to evaluate the country of study as a covariate, infection prevalence was significantly higher in China (51.6%, 95% CI 13.0, 89.1; $p = 0.018$) and Malaysia (67.8%, 95% CI 56.7, 78.0; $p = 0.000$). *T*. *trichiura* infection was found to be significantly higher in 2001–2020 (52.1%, 95% CI 37.0, 67.0) compared to 1949–1980 (17.6%, 95% CI 4.0, 37.9; $p = 0.000$). High QA grade studies were shown to have a significantly higher prevalence of *T*. *trichiura* infection (91.6%, 95% CI 71.62, 99.99) than low QA grade studies (25.1%, 95% CI 11.56, 41.74).

Eight studies reported data that facilitated a comparison of infection prevalence between minority indigenous and other population groups. Although the differential in *T*. *trichiura* prevalence was not significant ($p = 0.115$), it was higher in minority indigenous study participants (42.5%, 95% CI 26.9, 58.9) in comparison to those from other population groups (24.6%, 95% CI 15.5, 35.1).

Table 4. Pooled prevalence of *A.lumbricoides* infections analysed by study covariates.

Categories	Pooled prevalence of *A.lumbricoides*[∝] Infection	
	Studies (n)	Pooled Prevalence (95% CI)
Population group		
Minority indigenous populations	64	32.33 (25.72, 39.30)
Comparative Studies		
Non minority indigenous populations	8	25.22 (8.41, 47.20)
Minority indigenous populations	8	41.01 (25.73, 57.21)
	Analysis on minority indigenous populations only	
WHO regions		
SEAR	19	16.46 (8.22, 26.76)
WPR	45	39.82 (31.98, 47.92)
WHO Mortality Strata		
A	1	NA
B	52	34.39 (27.21, 41.95)
D	11	17.66 (6.50, 32.61)
Countries		
China	4	67.75 (38.95, 90.70)
India	11	17.66 (6.50, 32.61)
Indonesia	2	26.00 (22.95, 29.18)
Japan	1	NA
Laos	2	10.64 (7.78, 13.87)
Malaysia	32	38.26 (31.79, 44.94)
Philippines	3	44.72 (9.67, 83.17)
Solomon Islands	1	NA
Thailand	6	13.61 (3.79, 27.99)
Vietnam	2	27.13 (25.63, 28.66)
Year of data collection		
1949 1980	5	38.96 (2.50, 85.84)
1981 2000	18	29.78 (19.10, 41.69)
2001 2020	41	32.65 (24.45, 41.42)
Study Location		
Community	46	33.11 (25.61, 41.06)
School	18	30.37 (17.77, 44.66)
Sex		
Male	10	33.66 (22.06, 46.32)
Female	10	34.63 (22.60, 47.72)
QA Grade		
Low	8	39.37 (13.21, 69.30)
Medium	53	30.48 (12.51, 37.93)
High	3	47.35 (42.95, 51.77)

Notes

[∝] Where studies report *Ascaris* infection in humans, data is classified as *A.lumbricoides*.

https://doi.org/10.1371/journal.pntd.0009890.t004

Prevalence of hookworm infection

Sixty-eight studies presented data on hookworm infection, representing a cumulative minority indigenous study population of 21,967 participants. The pooled prevalence of infection across the study covariates and the subsequent bivariate meta-regression are detailed in Tables 8 and 9, respectively.

Table 5. Bivariate meta regression of *A.lumbricoides* infections analysed by study covariates.

Categories	Pooled prevalence of *A.lumbricoides* Infection		
	95% CI	*p* value	$I^{2\,\alpha}$ (%)
Comparative Studies			95.77
Non minority indigenous populations	1.00		99.47
Minority indigenous populations	1.13 (0.86, 1.49)	0.86	98.21
Analysis on minority indigenous populations only			
WHO regions			93.59
SEAR	1.00		99.10
WPR	1.23 (1.08, 1.40)	0.002	98.92
WHO Mortality Strata			94.23
B	1.00		98.98
D	0.86 (0.73, 1.02)	0.077	99.23
Countries			94.56
Thailand	1.00		98.06
China	1.63 (1.20, 2.20)	0.002	98.53
India	1.05 (0.84, 1.34)	0.678	99.23
Malaysia	1.26 (1.03, 1.53)	0.022	97.46
Philippines	1.32 (0.88, 1.96)	0.171	$^{\Delta}$
Year of data collection			94.43
1949 1980	1.00		99.59
1981 2000	0.91 (0.63, 1.32)	0.616	99.14
2001 2020	0.92 (0.64, 1.32)	0.651	99.03
Study Location			94.33
School	1.00		99.18
Community	1.03 (0.89, 1.18)	0.712	99.06
Sex			77.10
Male	1.00		94.60
Female	1.01 (0.84, 1.22)	0.898	95.25
QA Grade			94.55
Low	1.00		99.28
Medium	0.93 (0.73, 1.18)	0.532	33.13
High	1.06 (0.84, 1.35)	0.601	$^{\Delta}$

Note: Bivariate meta regression analysis was only undertaken where there were 3 or more data sets

$^{\alpha}$ the variation in effect size attributable to heterogeneity

$^{\Delta}$ I^2 not calculated where degrees of freedom ≤ 3

https://doi.org/10.1371/journal.pntd.0009890.t005

The pooled prevalence of hookworm infection was 19.9% (95% CI 15.7, 24.5) within minority indigenous populations (Fig 6). The heterogeneity between studies was found to be high (I^2 = 98.5%) and significant (p = 0.000). The country of study was found to be the only significant study covariate and although there were insufficient data to evaluate all countries represented, four countries were found to have a significantly higher prevalence of infection than other countries. These countries were: China (49.8%, 95% CI 20.8, 78.9; p = 0.009), India (20.4%, 95% CI 12.7, 29.3; p = 0.010), Malaysia (17.2%, 95% CI 13.3, 21.5; p = 0.001)) and the Philippines (16.0%, 95% CI 11.2, 21.4; p = 0.014).

Eight studies detailed the species of hookworm they identified. Based on these publications, *N. americanus* was more prevalent (44.9%, 95% CI 23.8, 67.0) than *A. duodenale* (11.6%, 95% CI 1.3, 29.7) and *A.ceylanicum* was reported in one study only.[32] In addition to these eight studies,

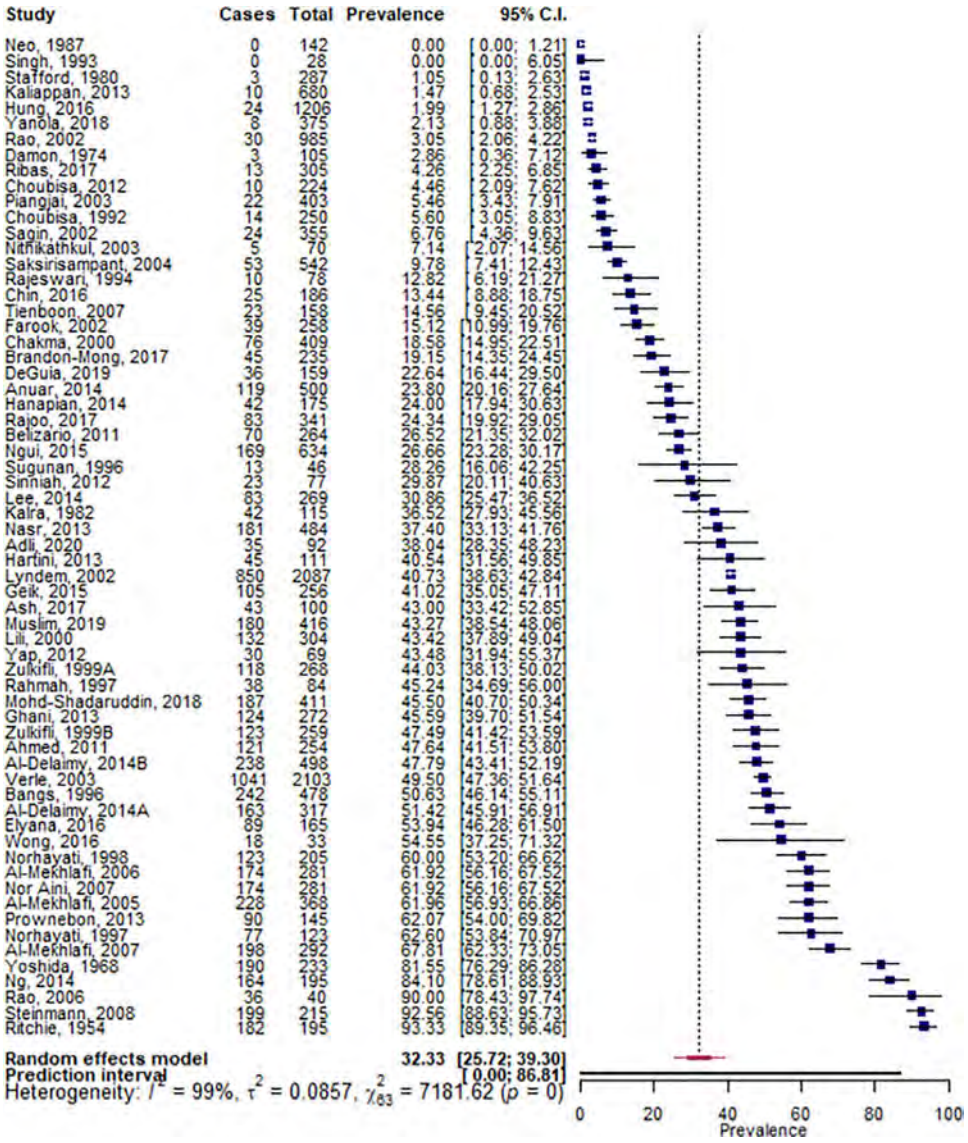

Fig 4. Pooled prevalence of *A.lumbricoides* infections within minority indigenous study populations. The forest plot shows the pooled prevalence of *A.lumbricoides* infection with 95% confidence intervals (CI) and the prediction interval. The I^2 statistic is rounded to the nearest integer.

https://doi.org/10.1371/journal.pntd.0009890.g004

three studies[33–35] undertook further analysis on a subset of their hookworm positive samples and identified *N. americanus*, *A. duodenale*, *A. ceylanicum* and *Anclostoma brazilienze*.

Eight studies presented data that enabled a comparison of hookworm infection prevalence to be evaluated between minority indigenous and other populations. Although the difference between population groups was not found to be significant ($p = 0.597$), it was higher in minority indigenous participants (16.7%, 95% CI 3.9, 35.7) than those from other population groups (10.7%, 95% CI 1.6, 26.3).

Prevalence of *Strongyloides stercoralis* infection

Twenty studies over a cumulative 7,020 minority indigenous participants reported on the prevalence of *S.stercorlais* infection. The prevalence of infection analyzed by study co-variates is detailed in Table 10 and the subsequent meta-analysis in Table 11.

Table 6. Pooled prevalence of *T.trichiura* infections analysed by study covariates.

Categories	Pooled prevalence of *T.trichiura*[∞] Infection	
	Studies (n)	Pooled Prevalence (95% CI)
Population group		
Minority indigenous populations	65	43.55 (32.62, 54.80)
Comparative Studies		
Non minority indigenous populations	8	24.64 (15.49, 35.11)
Minority indigenous populations	8	42.52 (26.93, 58.91)
	Analysis on minority indigenous populations only	
WHO regions		
SEAR	16	10.33 (5.21, 16.85)
WPR	49	55.82 (44.21, 67.12)
WHO Mortality Strata		
A	6	29.36 (1.58, 71.54)
B	51	49.65 (38.13, 61.20)
D	8	16.51 (6.31, 30.10)
Countries		
Australia	5	26.65 (0.00, 78.48)
China	4	51.61 (12.98, 89.12)
India	8	16.51 (6.31, 30.10)
Indonesia	2	10.52 (8.43, 12.80)
Japan	1	NA
Laos	2	30.55 (26.13, 35.15)
Malaysia	31	67.82 (56.71, 77.99)
Philippines	3	40.03 (0.11, 93.81)
Solomon Islands	1	NA
Thailand	6	5.70 (4.23, 7.37)
Vietnam	2	23.92 (22.48, 25.39)
Year of data collection		
1949 1980	5	17.61 (3.98, 37.85)
1981 2000	20	33.78 (18.08, 51.54)
2001 2020	40	52.07 (36.98, 66.96)
Study Location		
Community	48	40.28 (28.72, 52.40)
School	17	52.92 (26.20, 78.79)
Sex		
Male	10	55.15 (31.91, 77.30)
Female	10	53.97 (30.52, 76.54)
QA Grade		
Low	10	25.14 (11.56, 41.74)
Medium	52	43.97 (31.94, 56.36)
High	3	91.61 (71.62, 99.99)

Notes

[∞] Where studies report *Trichuris* infection in humans, data is classified as *T. trichiura*.

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The pooled prevalence of infection within minority indigenous populations was 6.3% (95% CI 3.2, 10.2) with a high and significant degree of heterogeneity between studies (Fig 7). From the study co-variates analyzed, diagnostic method and sex where the only two covariates to

Table 7. Bivariate meta regression of *T. trichiura* infections analysed by study covariates.

Categories	Pooled prevalence of *T.trichiura* Infection		
	95% CI	*p* value	$I^{2\,\alpha}$ (%)
Comparative Studies			90.27
Non minority indigenous populations	1.00		97.85
Minority indigenous populations	1.19 (0.95, 1.48)	0.115	98.25
Analysis on minority indigenous populations only			
WHO regions			95.80
SEAR	1.00		97.85
WPR	1.48 (1.28, 1.72)	0.000	99.49
WHO Mortality Strata			96.97
A	1.00		99.49
B	1.17 (0.89, 1.52)	0.253	99.54
D	0.90 (0.65, 1.26)	0.540	98.32
Countries			97.33
Thailand	1.00		39.85
Australia	1.31 (0.95, 1.79)	0.097	99.58
China	1.57 (1.08, 2.29)	0.018	99.33
India	1.20 (0.95, 1.52)	0.120	98.32
Malaysia	1.80 (1.62, 2.00)	0.000	99.09
Philippines	1.41 (0.86, 2.30)	0.169	$^{\Delta}$
Year of data collection			97.13
1949 1980	1.00		97.95
1981 2000	1.18 (0.97, 1.43)	0.092	99.55
2001 2020	1.38 (1.17, 1.63)	0.000	99.64
Study Location			97.38
Community	1.00		99.56
School	1.11 (0.90, 1.37)	0.303	99.74
Sex			91.30
Male	1.00		98.48
Female	1.00 (0.73, 1.37)	0.991	98.56
QA Grade			97.03
Low	1.00		98.28
Medium	1.18 (0.97, 1.43)	0.094	99.62
High	1.81 (1.46, 2.25)	0.000	$^{\Delta}$

Note: Bivariate meta regression analysis was only undertaken where there were 3 or more data sets

$^{\alpha}$ the variation in effect size attributable to heterogeneity

$^{\Delta}$ I^2 not calculated where degrees of freedom ≤ 3

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demonstrate a significant association with infection prevalence. Disease prevalence was significantly higher when serology was used as a diagnostic (16.8%, 95% CI 11.4, 22.9) compared to microscopy (4.1%, 95% CI 1.6, 7.7; $p = 0.004$). Females had a significantly lower prevalence of infection (4.1%, 95% CI 0.0, 14.3) compared to males (18.6%, 15.8, 21.6; $p = 0.046$).

There was only one study that provided data enabling a comparison of *S. stercorlais* prevalence between minority indigenous and other population participants. Although it was not possible to evaluate the significance of the results, it is noted that prevalence was higher in minority indigenous participants (13.6%, 95% CI 11.2, 16.4) compared to those in other population groups (5.1%, 95% CI 2.8, 9.1).

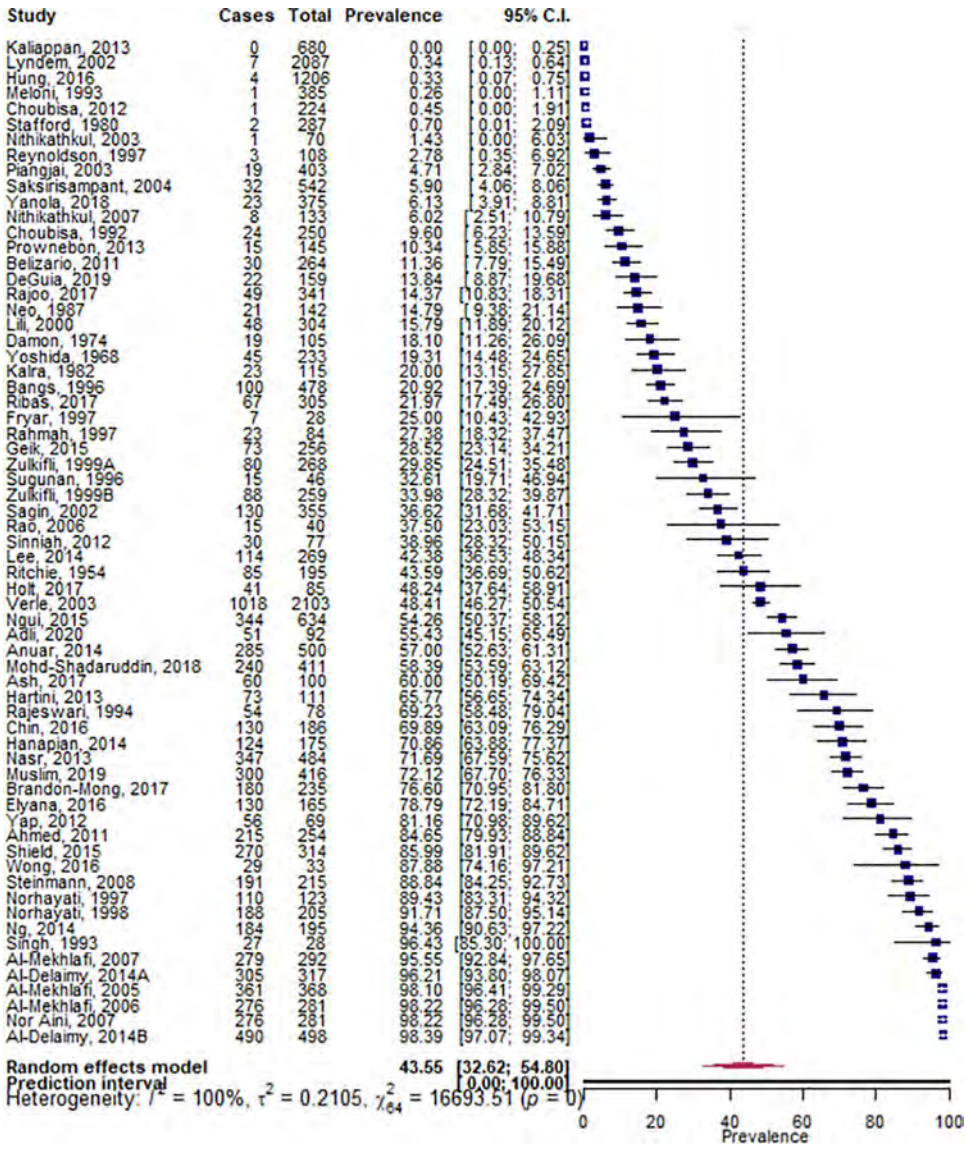

Fig 5. Pooled prevalence of *T.trichiura* infections within minority indigenous study populations. The forest plot shows the pooled prevalence of *T.trichiura* infection with 95% confidence intervals (CI) and the prediction interval. The I^2 statistic is rounded to the nearest integer.

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Discussion

The systematic review shows a high prevalence of STH infection amongst minority indigenous populations. It is likely that the true prevalence of infection is higher due to the low sensitivity of diagnostic methods used.[36] This potential under-estimation of infection is particularly likely in minority indigenous communities, for whom the provision of faecal samples presents a significant obstacle due to cultural beliefs, thereby creating a challenge to the recommended serial sampling over multiple days.[37,38]

The results from our review show the prevalence of infection to be consistently higher in the WPR than the SEAR, although WHO figures show the DALYs to be higher overall within the SEAR.[6] Although there are many potential confounders, the higher prevalence of

Table 8. Pooled prevalence of Hookworm infections analysed by study covariates.

Categories	Pooled prevalence of Hookworm [∞] Infection	
	Studies (n)	Pooled Prevalence (95% CI)
Population group		
Minority indigenous populations	68	19.92 (15.68, 24.53)
Comparative Studies		
Non minority indigenous populations	8	10.69 (1.56, 26.27)
Minority indigenous populations	8	16.73 (3.93, 35.67)
	Analysis on minority indigenous populations only	
WHO regions		
SEAR	17	17.75 (10.20, 26.80)
WPR	51	20.66 (15.55, 26.28)
WHO Mortality Strata		
A	6	7.80 (0.00, 25.42)
B	52	21.42 (16.21, 27.14)
D	10	20.35 (12.68, 29.26)
Countries		
Australia	5	10.87 (0.12, 32.75)
China	4	49.84 (20.84, 78.90)
India	10	20.35 (12.68, 29.26)
Indonesia	2	50.05 (46.50, 53.59)
Japan	1	NA
Laos	2	61.53 (56.71, 66.23)
Malaysia	33	17.18 (13.25, 21.51)
Philippines	3	15.95 (11.18, 21.37)
Solomon Islands	1	NA
Thailand	5	5.53 (1.91, 10.72)
Vietnam	2	40.71 (39.04, 42.39)
Year of data collection		
1949 1980	5	29.45 (7.27, 58.68)
1981 2000	22	20.86 (13.65, 29.11)
2001 2020	41	18.38 (13.44, 23.89)
Study Location		
Community	52	21.17 (15.95, 26.90)
School	16	15.90 (10.77, 21.79)
Sex		
Male	13	19.06 (13.67, 25.08)
Female	13	16.58 (11.57, 22.27)
Hookworm Species		
A.duodenale	5	11.56 (1.27, 29.68)
N.americanus	4	44.93 (23.83, 67.04)
A.ceylanicum	1	NA
QA Grade		
Low	11	17.29 (5.61, 33.36)
Medium	54	20.06 (15.37, 25.18)
High	3	27.56 (20.98, 34.66)

Notes

[∞] Where studies reported by species, figures were aggregated to give overall hookworm prevalence which was evaluated against the study co variates with the exception of the covariate 'hookworm species'

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Table 9. Bivariate meta regression of Hookworm infections analysed by study covariates.

Categories	Pooled prevalence of Hookworm Infection		
	95% CI	*p* value	$I^{2\,\alpha}$ (%)
Comparative Studies			94.43
Non minority indigenous populations	1.00		99.33
Minority indigenous populations	1.06 (0.85, 1.32)	0.597	99.01
Analysis on minority indigenous populations only			
WHO regions			90.85
SEAR	1.00		98.72
WPR	1.02 (0.92, 1.14)	0.659	98.45
WHO Mortality Strata			90.78
A	1.00		98.33
B	1.12 (0.98, 1.29)	0.100	98.57
D	1.12 (0.95, 1.32)	0.188	97.77
Countries			88.13
Thailand	1.00		90.08
Australia	1.08 (0.92, 1.28)	0.329	98.28
China	1.55 (1.12, 2.15)	0.009	98.68
India	1.18 (1.04, 1.33)	0.010	97.77
Malaysia	1.13 (1.05, 1.21)	0.001	96.04
Philippines	1.10 (1.02, 1.18)	0.014	$^{\Delta}$
Year of data collection			90.01
1949 1980	1.00		98.80
1981 2000	0.90 (0.73, 1.10)	0.301	98.70
2001 2020	0.88 (0.72, 1.07)	0.186	98.13
Study Location			90.14
Community	1.00		98.66
School	0.94 (0.86, 1.02)	0.127	96.27
Sex			28.46
Male	1.00		89.38
Female	0.98 (0.90, 1.06)	0.580	89.75
QA Grade			90.78
Low	1.00		98.51
Medium	1.01 (0.88, 1.16)	0.856	98.56
High	1.06 (0.93, 1.22)	0.377	$^{\Delta}$

Note: Bivariate meta regression analysis was only undertaken where there were 3 or more data sets

$^{\alpha}$ the variation in effect size attributable to heterogeneity

$^{\Delta}$ I^2 not calculated where degrees of freedom ≤ 3

https://doi.org/10.1371/journal.pntd.0009890.t009

infection within the WPR identified by this review may reflect a higher burden of disease within indigenous minority populations in this region.

Although research shows the prevalence and intensity of STH infection to be related to socioeconomic status and hygiene conditions,[39–43] it is interesting to note that the review found no significant difference in disease prevalence for some STH between countries that have very different socio-economic profiles. For example, the review shows there to be no significant difference in overall STH infection in minority indigenous populations between Australia, which in 2020 ranked eighth on the Human Development Index (HDI), and India which ranked 131st. [44] This re-enforces the fact that vulnerable population groups within otherwise highly developed countries continue to be at risk of NTDs such as STH infection.

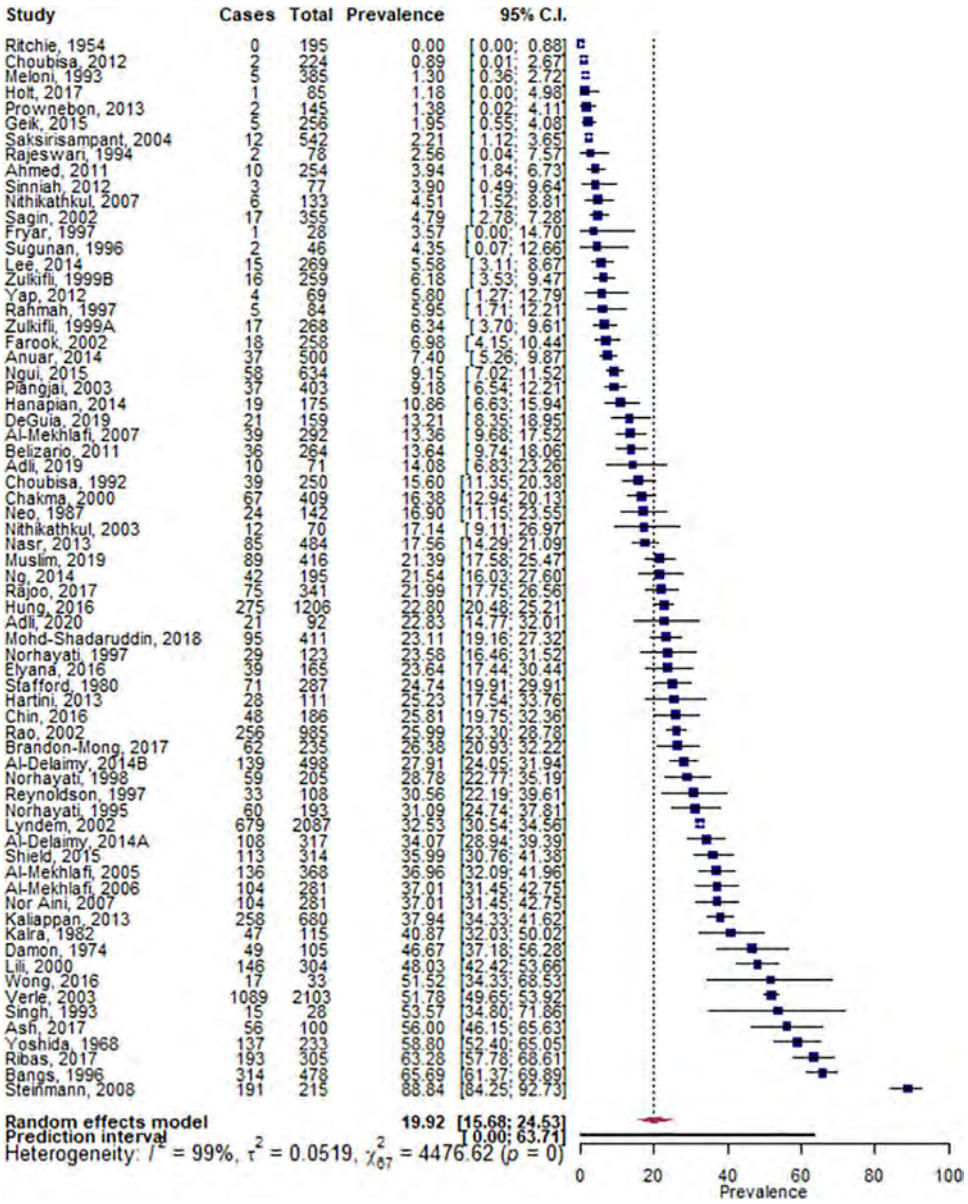

Fig 6. Pooled prevalence of hookworm infections within minority indigenous study populations. The forest plot shows the pooled prevalence of hookworm infection with 95% confidence intervals (CI) and the prediction interval. The I^2 statistic is rounded to the nearest integer.

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Although it is hoped that economic development and preventative chemotherapy programs have led to a reduction in the global burden of STH infection over time,[18] results from the systematic review show the prevalence of overall STH infections within minority indigenous populations to have remained static. When the review analyzes the prevalence of infection by species, some interesting trends are observed. In particular, the prevalence. of *S. stercorlais* and *T. trichiura* infections within minority indigenous populations have increased over time, with the increasing prevalence of *T. trichiura* being significant. The increasing trend in *S. stercoralis* prevalence may in part be due to developments in diagnostic capabilities as the parasite is very difficult to detect by microscopy;[45] but may also reflect the treatment challenges presented by its autoinfection capability.[46] The significant increase in *T.trichiura* infection within this

Table 10. Pooled prevalence of *S. stercoralis* infections analysed by study covariates.

Categories	Pooled prevalence of *S. stercoralis* [∞] Infection	
	Studies (n)	Pooled Prevalence (95% CI)
Population group		
Minority indigenous populations	20	6.26 (3.16, 10.24)
Comparative Studies		
Non minority indigenous populations	1	NA
Minority indigenous populations	1	NA
	Analysis on minority indigenous populations only	
WHO regions		
SEAR	6	4.00 (0.35, 10.55)
WPR	14	7.35 (3.64, 12.14)
WHO Mortality Strata		
A	7	8.10 (2.17, 17.03)
B	10	4.98 (1.61, 9.92)
D	3	6.79 (0.01, 21.40)
Countries		
Australia	7	8.10 (2.17, 17.03)
Bangladesh	1	NA
China	1	NA
India	2	0.93 (0.00, 2.88)
Indonesia	1	NA
Laos	1	NA
Malaysia	5	6.11 (1.08, 14.42)
Thailand	2	1.11 (0.33, 2.21)
Year of data collection		
1981 2000	8	4.63 (0.55, 11.65)
2001 2020	12	7.39 (3.41, 12.66)
Study Location		
Community	18	6.25 (2.95, 10.58)
School	2	9.22 (7.88, 10.66)
Diagnostic method *		
Microscopy	15	4.14 (1.58, 7.68)
PCR	2	14.95 (12.95, 17.06)
Serology	3	16.78 (11.43, 22.92)
Sex		
Male	3	18.61 (15.77, 21.61)
Female	3	4.07 (0.00, 14.29)
QA Grade		
Low	3	2.45 (0.00, 10.73)
Medium	15	6.94 (3.25, 11.79)
High	2	10.77 (9.27, 12.36)

Notes

[∞] Human *strongyloides* infection classified as *S stercoralis*

*Diagnostic method: PCR and microscopy classified as PCR; ELISA classified as serology

https://doi.org/10.1371/journal.pntd.0009890.t010

Table 11. Bivariate meta regression of *S. stercoralis* infections analysed by study covariates.

Categories	Pooled prevalence of *S.stercoralis* [∞] Infection		
	CI 95%	*p* value	$I^{2\,\alpha}$ (%)
Analysis on minority indigenous populations only			
WHO regions			49.02
SEAR	1.00		96.37
WPR	1.03 (0.97, 1.10)	0.287	96.62
WHO Mortality Strata			53.54
A	1.00		97.56
B	0.96 (0.88, 1.04)	0.316	96.43
D	0.98 (0.88, 1.09)	0.706	[Δ]
Countries			47.25
Malaysia	1.00		96.24
Australia	1.03 (0.91, 1.16)	0.590	97.56
Year of data collection			55.70
1981 2000	1.00		96.58
2001 2020	1.02 (0.95, 1.10)	0.507	97.18
Diagnostic method *			55.28
Microscopy	1.00		94.90
Serology	1.12 (1.04, 1.20)	0.004	[Δ]
Sex			0.000
Male	1.00		[Δ]
Female	0.88 (0.78, 0.99)	0.046	[Δ]
QA Grade			56.30
Low	1.00		[Δ]
Medium	1.05 (0.99, 1.11)	0.091	96.89

Note: Bivariate meta regression analysis was only undertaken where there were 3 or more data sets

[∞] Human *strongyloides* infection classified as *S stercoralis*

[α] the variation in effect size attributable to heterogeneity

[Δ] I^2 not calculated where degrees of freedom ≤ 3

https://doi.org/10.1371/journal.pntd.0009890.t011

vulnerable population group however warrants further investigation. Although the WHO recommend the administration of albendazole or mebendazole as part of their STH control strategy,[2] these drugs are shown to have limited efficacy against *T. trichiura*. [47,48]

Although the review provides an indication of STH prevalence within indigenous minority populations as a collective, research showing the significant heterogeneity in infection prevalence and intensity between individuals within a population is noted. [36] There is an argument that infection intensity would be a more useful metric than prevalence, as morbidity severity is relative to infection intensity and heavily infected individuals present a major source of infection for their community.[36]

If the 2021–2030 NTD road map targets[49] are to be achieved, countries need to address the impact of STH infections within their vulnerable indigenous populations. By impacting productivity and human development, STH infections re-enforce poverty,[50] which already disproportionately affects these communities[19]. To be effective, interventions need to be culturally appropriate[51] and as a result of disruptions to public health programmes caused by the Coronavirus Disease 2019 (COVID 19) pandemic, they will need to be increasingly innovative if 2021–2030 targets are to be achieved.[52]

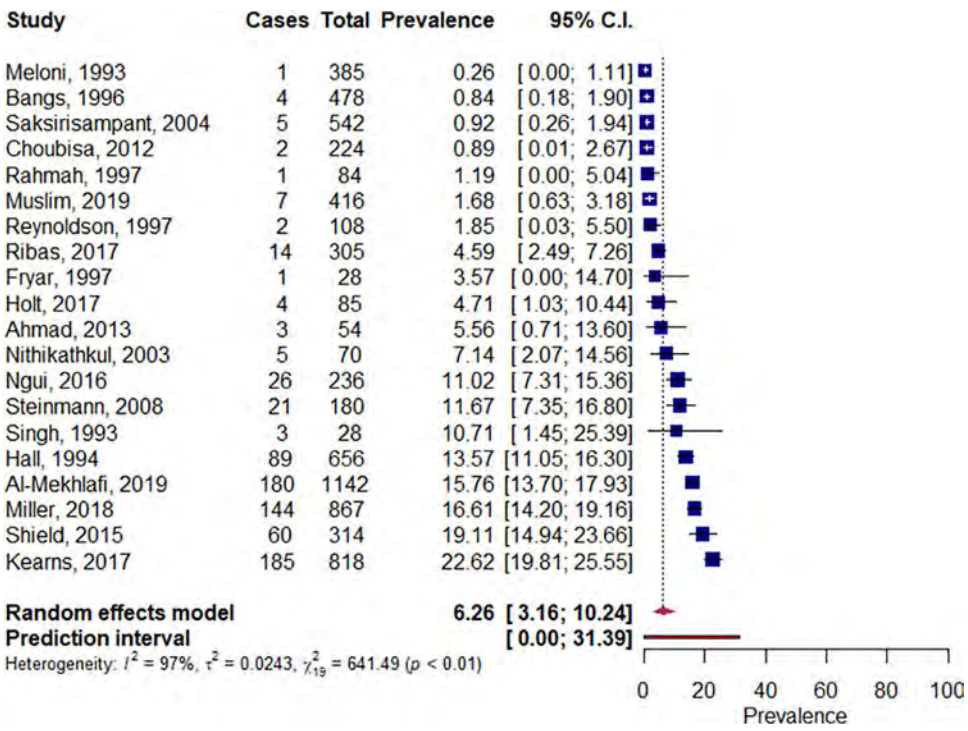

Fig 7. Pooled prevalence of *S.stercoralis* infections within minority indigenous study populations. The forest plot shows the pooled prevalence of *S.stercoralis* infection with 95% confidence intervals (CI) and the prediction interval. The I^2 statistic is rounded to the nearest integer.

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This systematic review provided information on STH prevalence amongst minority indigenous populations of the SEAR and WPRs and showed where further data and research are required. However, the limitations of systematic reviews and the scope of data need to be taken into consideration when results of the systematic review are used to inform public health policy. The following limitations of the review are noted. Publication bias is an inherent potential limitation of the systematic review process. As a result of resource constraints data extraction was limited to articles published in English. The accuracy of estimating disease prevalence may be impacted by the inclusion of small study populations. The review did not take into consideration the effect of treatment and intervention regimes which may impact infection prevalence over time. The definition of a minority indigenous population is not based upon a universal classification.

Conclusion

STH infections continue to create a significant global health burden within vulnerable communities. Soil transmitted helminthiasis is prevalent within indigenous communities who reside in countries across the spectrum of WHO mortality strata. To stop the ongoing impacts of STH infection upon the poverty cycle, accurate relevant prevalence and infection intensity data are required to inform innovative and culturally appropriate interventions.

Supporting information

S1 PRISMA Checklist.
(DOCX)

S1 Table. Systematic review search terms summary.
(DOCX)

S2 Table. QA assessment of STH studies based on modified Newcastle-Ottawa Quality Assessment Scale.
(DOCX)

S3 Table. Key to modified Newcastle-Ottawa Quality Assessment Scale scoring.
(DOCX)

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Part III : Identification of touch points on the TB health-care continuum where indigenous ethnic minority status is a risk factor.

The WHO has a classification system that facilitates the prioritization of resources to countries that carry the greatest burden of TB.[125] There are three WHO lists, comprising the top 30 countries in terms of TB burden, TB-and HIV coinfection (TB/HIV) and multidrug/rifampicin-resistant TB (MDR/RR-TB) burden. For each list, the top 30 countries are defined as the top 20 countries in terms of case numbers and an additional 10 countries that have the greatest burden of disease in terms of incidence per capita that do not already feature in the top 20 country listing. China falls within each of the three lists and in 2020, had the second-highest burden of TB globally.[64 125] Although progress has been made in reducing TB incidence and mortality over recent years, the disease continues to present a significant health concern.[126]

Hunan province located in the central-south, is a high burden TB region with an incident rate of 76.9 per 100,000 population recorded in 2018.[127] The province, occupies 2.2% of China and is the ninth most populous region with a population of 66.4 million recorded in 2020.[128] The 2000 population census showed indigenous ethnic minorities to represent 10.1% of Hunan's population.[128]

Although China does not officially recognize indigenous status, data are systematically collected according to a 56 ethnic group population structure, comprising the Han majority and 55 minority groups.[10] Understanding China's unique socio-cultural environment within the context of TB management could be of value in combating the disease.[129] Effective TB management is dependent upon early case detection and timely and appropriate treatment.[130]

Part III of this thesis evaluates the impact of indigenous ethnic minority status on TB management in Hunan Province, China. Chapter six appraises diagnosis and treatment delays, and chapter seven evaluates risk factors associated with poor treatment outcomes.

Chapter VI: The impact of indigenous ethnic minority status on TB diagnosis and treatment delays in Hunan, China

Although a number of factors have been associated with TB diagnosis and treatment delay in China,[129] to our knowledge ethnicity has not been evaluated as a risk factor. To assess this risk factor, data on patients diagnosed with TB in Hunan province between 2013 and 2018 were evaluated.

TB diagnosis delay was defined as the time interval between symptom onset and diagnosis, with the median (21 days) used to define delay. TB treatment delay was defined as the time interval between diagnosis and treatment commencement, with the upper quartile (15 days) used to specify a delay.

The odds of experiencing a diagnostic delay were significantly higher for five of the seven indigenous ethnic minority groups compared to the Han majority. Conversely, the odds of experiencing a treatment delay were significantly lower in five of the seven indigenous ethnic minority populations compared to the Han majority.

The findings of this study show there are opportunities to reduce TB diagnosis delays within indigenous ethnic minority groups and that there is a need to research why the majority population is at greater risk of treatment delay. Full details of the analysis can be found in the following paper:

Gilmour B, Xu Z, Bai L, Alene KA, Clements ACA. The impact of ethnic minority status on tuberculosis diagnosis & treatment delays in Hunan Province, China *BMC Infectious Diseases* (2022) 22:90 https://doi.org/10.1186/s12879-022-07072-4

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The impact of ethnic minority status on tuberculosis diagnosis and treatment delays in Hunan Province, China

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Abstract

Background: Tuberculosis (TB) continues to be a major public health challenge in China. Understanding TB management delays within the context of China's unique ethnic diversity may be of value in tackling the disease. This study sought to evaluate the impact of ethnic minority status on TB diagnosis and treatment delays.

Methods: This retrospective cohort study was conducted on patients diagnosed with TB in Hunan Province, China between 2013 and 2018. Diagnosis delay was defined as the time interval between the onset of symptoms and the date of diagnosis. Treatment delay was defined as the time interval between diagnosis and treatment commencement. Univariable and multivariable logistic regression models were used to identify factors associated with TB diagnosis and treatment delay, including ethnic minority status. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were calculated to assess the strength of association between the dependant and independent variables.

Results: A total of 318,792 TB patients were included in the study with a mean age of 51.7 years (SD 17.7). The majority of patients were male (72.6%) and Han ethnicity (90.6%). The odds of experiencing diagnosis delay (> 21 days) were significantly higher for Tujia (AOR: 1.46, 95% CI: 1.41, 1.51), Miao (AOR: 1.31, 95% CI: 1.26, 1.37), Dong (AOR: 1.97, 95% CI: 1.85, 2.11), Yao (AOR: 1.27, 95% CI: 1.17, 1.37), and Bai (AOR: 1.45, 95% CI: 1.22, 1.74) ethnic minorities compared to the Han majority. The odds of experiencing treatment delay (> 15 days) were significantly lower for five of the seven ethnic minority groups relative to the Han majority: Tujia (AOR 0.92, 95% CI 0.88, 0.96), Miao (AOR 0.74, 95% CI 0.70, 0.79), Dong (AOR 0.87, 95% CI 0.81, 0.95), Yao (AOR 0.20, 95% CI 0.17, 0.24) and 'other' (ethnic minorities that individually represented < 0.1% of the patient population) (AOR 0.70, 955 CI 0.51, 0.97).

Conclusions: This study shows ethnic minority status to be a significant risk factor in diagnosis delay, but for it to reduce the odds of treatment delay. Further research is required to determine the underlying causes of diagnosis delay within ethnic minority populations.

Keywords: Tuberculosis, Ethnic minority, Diagnosis delay, Treatment delay, China

Background

Tuberculosis (TB) is currently second to Coronavirus Disease 2019 (COVID -19) as a leading cause of death from a single infectious agent [1], claiming a life every 22 s [2]. Prior to the COVID-19 pandemic, TB was the leading cause of death [3] and throughout history is thought to have claimed more lives than any other microorganism [4]. TB is caused by *Mycobacterium*

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tuberculosis (MTB), an airborne pathogen that most commonly affects the lungs (pulmonary TB) albeit the pathogen can affect all organs (extrapulmonary TB). Although the disease can be cured, escalating drug resistance presents a global health security threat [3].

In 2019, China ranked third for the greatest number of new TB cases globally [3] with 833,000 people falling ill to the disease [5]. To address the burden of disease, China is in the process of comprehensive public health system reforms, including setting the goal of universal health coverage and transformation of the TB service delivery model [6–8]. In 1991, China launched its National Tuberculosis Control Programme (NTP) based on the World Health Organization (WHO) recommended Directly Observed Treatment Short-course (DOTS) strategy. The NTP aims to provide TB diagnosis and treatment services free of charge, with a focus on the poor, ethnic minorities and other vulnerable population groups. [9, 10].

Fundamental to the success of national TB control programs, is early detection and prompt and appropriate treatment [11]. Delays in timely diagnosis and treatment lead to disease progression, poor treatment outcomes, increased risk of transmission and an exacerbation of the socioeconomic consequences of the disease. [12].

A systematic review and meta-analysis of patient and diagnosis delays in China, found an array of contributing factors [13]. Factors included indicators of low socio-economic status (e.g., low level of education, low disposable income, lack of health insurance); rural residence; female sex; initial consultation with traditional healers and resource constraints within the health care service [13]. However, to our knowledge, the impact of ethnic minority status upon diagnosis and treatment delays within China's TB patient population has not been investigated.

China has a unique socio-cultural environment, and understanding this within the context of delays in TB management could be of value in combating the disease [13]. Hunan Province, located in south-central China, is one of the most populous divisions of the country where ethnic minority groups represent 10.1 percent of the population [14]. Despite significant investments in TB control and treatment strategies by the Hunan government [14], which have reduced the burden of disease [15], Hunan remains a high TB burden province. [16, 17].

This study aimed to evaluate the impact of ethnic minority status on the time to diagnosis and the time to treatment among patients registered in Hunan Province between 2013 and 2018.

Methods

Study design and data sources

Operating under the provincial health committee, the Hunan Tuberculosis Control Institute is responsible for the province's TB control and prevention, and research and development [18]. This is a retrospective cohort study conducted on patients diagnosed with pulmonary and extrapulmonary TB in Hunan Province between 2013 and 2018 inclusive. Data were obtained from the internet-based TB management system administered by the TB Control Institute of Hunan Province (TBCIHP).

The date of symptom onset and the date of any previous diagnosis (if any) were recorded in the system on the basis of information provided by the patient. The date of TB diagnosis and date of treatment commencement were recorded by health professionals at the designated TB institutions. Demographic data e.g., ethnic group, sex, age, occupation, year of registration at the designated TB institution and residential address were also available.

Definitions

Total delay is defined as the timeframe between the onset of disease and the start of treatment [19]. The total delay can be classified in two ways- as the sum of the diagnosis delay (time between the onset of symptoms and diagnosis) and the treatment delay (time between diagnosis and treatment commencement) or as the patient delay (time between onset of symptoms and consultation with a health care provider) and the health system delay (time between patient consultation and start of treatment, Fig. 1) [19]. This study evaluated diagnostic and treatment delays.

Hunan's TB institutions follow a TB diagnosis based on WHO recommended methods, e.g., clinical assessment based on symptoms, sputum smear microscopy, chest x-ray, sputum culture and molecular detection [20].

China's ethnic classification system recognizes 55 minority groups in addition to the Han majority [21]. For this study, associations between diagnosis delay and treatment delay with Tujia, Miao, Dong, Yao, Bai, Mongolian and 'other' ethnic minority group status were estimated relative to the Han majority. The 'other' ethnic minority group comprised the summation of all other ethnic minority groups, who constitute < 0.1% of the patient population. The 'other' group included Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic minorities.

Definitions pertaining to the other clinical descriptors/variables analyzed are detailed in Table 1.

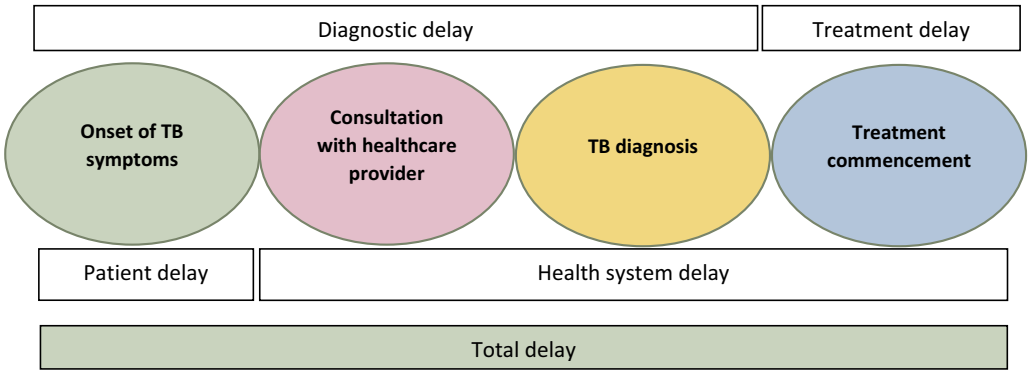

Fig. 1 Conceptual framework for TB diagnosis and treatment delay [19]. Total delay = time between the onset of symptoms and the commencement of treatment. Diagnosis delay = time between onset of symptoms and diagnosis. Treatment delay = time between diagnosis and treatment commencement. Patient delay = time between onset of symptoms and consultation with healthcare provider. Health care system delay = time between consultation and treatment commencement

Statistical analysis

Data were translated from Mandarin to English, checked for completeness, cleaned, and entered into STATA version 16.1 (StataCorp, College Station, TX) for analysis. Frequency and cross-tabulation were used to cross check data completeness.

Descriptive statistics were used to summarize data and define characteristics of the patient population. Treatment and diagnosis delays were calculated in days and summarized, using the median and interquartile range (IQR) because the data showed a non-normal distribution.

To dichotomize data, the median (21 days) was used to define diagnosis delay and the upper quartile (15 days) was used to define treatment delay. Categorical variables were described by counts and percentages, and continuous and normally distributed variables were summarized by means and standard deviations (SD). Univariable logistic regression models were fitted and Crude Odds Ratios (COR) with 95% Confidence Intervals (CI) reported. Multicollinearity between independent variables was assessed using variance inflation factors (VIF) and variables with VIF > 5 were excluded from the final multivariable analysis.

All variables assessed in the univariable models were fitted into multivariable logistic regression models. Adjusted odds ratios and 95% confidence intervals (CI) were computed to measure the association between the dependent (i.e., diagnosis and treatment delays) and independent variables (i.e., ethnic minority status, sex, occupation year of patient registration, residential address, patient enrolment classification, diagnosis institution and whether a patient was severely ill). Variables with a p-value < 0.05 in the multivariable analysis were considered as having a statistically significant association with the outcome (diagnosis or treatment delay). Additional models were created for sensitivity analyses to evaluate a 14 day delay used by some studies [13, 22], compared a 21 day diagnosis delay used by others [23–27]. An analysis was also conducted using the median (> 1 day) to define treatment delay.

To evaluate the outcome variables (i.e., diagnosis and treatment delay) in their continuous form sensitivity analyses were undertaken using a negative binomial regression model.

An additional model was constructed to determine treatment delay for patients with two TB diagnosis dates. 'New patient' treatment delay was defined as the time period (days) between the date of the second diagnosis and treatment commencement. This analysis was undertaken to mitigate the risk of treatment being administered between a patients first diagnosis and a subsequent diagnosis, a timeframe for which we had no data.

Ethics statement

Ethical clearance was obtained from Curtin University (HRE2019-0581) and written permission to access the data granted from TBCIHP. Medical records of the patient population were de-identified to preserve privacy. Because this study used secondary, de-identified data, informed patient consent was not required.

Results

Socio-demographic and clinical characteristics of the patients

A total of 318,792 TB patients registered in Hunan Province between 2013 and 2018 were included in this study. The sociodemographic characteristics of the patients are presented in Table 2. The majority of patients were male (72.6%) and the study population

Table 1 Definitions of clinical variables included in the study

Variable/Demographic descriptor	Definition
Residential address	
Local	Patients who reside in local counties
Intra-provincial	Patients who reside in other counties within the province
Inter-provincial	Patients who reside in provinces other than Hunan
Foreign nationality	Patients who reside in other countries
Patient enrolment classification	
Consultation due to symptoms	Patients who consult the TB institution due to symptoms
Referral	Patients who are referred to the TB institution due to symptoms
Contact tracing	TB patients identified by contact tracing
Health check	TB patients who are identified as a result of a health check
TB diagnosis results	
Etiological examine negative	TB cases identified on the basis of symptoms
Smear positive	Positive Acid-Fast Bacillus test
Extrapulmonary TB	TB identified in organs other than the lungs
Culture positive	TB positive sputum culture
Severely ill	Patients with miliary TB, cavities, TB empyema or serious damage to one or more organ caused by TB disease
Drug resistance pattern	
Drug susceptible TB	*M.tuberculosis* that is susceptible to first line antibiotics (isoniazid, rifampin, ethambutol, and pyrazinamide)
MDR-TB	*M.tuberculosis* that is resistant to isoniazid and rifampicin
Mono-resistant TB	*M.tuberculosis* resistant to a single first line antibiotic
Diagnosis institution	
CDC	Centre for disease control and prevention that has a TB clinic
Hospital	General hospital
TB dispensary	Specialized TB hospital (TB patients only)
Other	Other health institution or hospital not covered by above classifications
Registration category	
New patient	TB patients who have never taken anti-TB drugs, or who have been receiving irregular treatment for less than one month
Relapse	TB patients with a history of disease, who complete a full course of chemotherapy and appear cured according to symptoms, but who return a smear positive sputum sample
Return after default	TB patients who receive chemotherapy for $\geq$ 1 month but discontinue therapy for $\geq$ 2 months and then return for treatment
Initial treatment failed	New sputum smear positive TB patients with positive sputum smear microscopy results at the end of the 5th month or after completion of therapy; and sputum smear negative TB patients with a positive smear result for any sputum sample
Chronic patient	Positive sputum examination results after several episodes of irregular therapy
Treatment category	
Initial treatment	TB patients who have never taken anti-TB drugs
Retreatment	Patient who has history of TB treatment
TB treatment	
Accept treatment	Patient who accepts the recommended treatment regime
Reject treatment	Patient who rejects the recommended treatment regime

had a mean age of 51.75 years (SD 17.67). Patients of Han ethnicity formed the majority (90.6%) with the remainder of the patient population represented by 28 ethnic minority groups (ethnicity data were not available for 4 patients). Seventy-eight percent of patients were employed in the agricultural sector. Most patients were new (95.7%), with the majority not severely ill (96.2%) and in receipt of a drug susceptible TB diagnosis (87.2%).

Median time to diagnosis and treatment by ethnic minority status

Table 3 illustrates median time to diagnosis and treatment by study characteristics. Across all patients, the

Table 2 Sociodemographic and clinical characteristics of TB patients registered in Hunan Province, China, 2013–2018

Variable	Number	Percent
Sex		
Male	231,495	72.62
Female	87,297	27.38
Age (years)		
Mean = 51.75; SD 17.67		
0–10	346	0.11
11–20	15,767	4.95
21–30	37,135	11.65
31–40	30,470	9.56
41–50	56,269	17.65
51–60	62,606	19.64
61–70	69,209	21.71
71–80	38,807	12.17
81–101	8183	2.57
Occupation		
Agriculture[~]	249,093	78.14
Housekeeping[$]	30,802	9.66
Education[Δ]	10,679	3.35
Commercial services/civil servant	7818	2.45
Migrant worker	2601	0.82
Healthcare	1009	0.32
Hospitality	612	0.19
Other	16,178	5.07
Ethnicity		
Han	288,802	90.59
Tujia	13,680	4.29
Miao	8460	2.65
Dong	4033	1.27
Yao	2662	0.84
Bai	509	0.16
Mongolian	349	0.11
Other*	293	0.09
Residential address		
Local	310,343	97.35
Intra-provincial	6215	1.95
Inter-provincial	2182	0.68
Foreign nationality	52	0.02
Patient enrolment classification		
Consultation due to symptoms	117,834	36.96
Referral	103,261	32.39
Contact tracing	93,183	29.23
Health check	3179	1.00
Other	1335	0.42
TB diagnosis results		
Etiological examination negative	189,129	59.32
Smear positive	122,006	38.27
Extrapulmonary TB	5609	1.76
Culture positive	1355	0.43
Molecular diagnosis positive	693	0.22
Severely ill		
No	306,534	96.15
Yes	12,258	3.85
Drug resistance pattern		
Drug susceptible TB	15,555	87.23
MDR-TB	1248	7.00
Mono-resistant TB	1030	5.78
Diagnosis institution		
Centre for Disease Control & Prevention (CDC)	278,707	88.15
Hospital	33,104	10.47
TB dispensary	4276	1.35
Other	69	0.02
Registration category		
New patient	305,218	95.74
Relapse	12,179	3.82
Return after default	350	0.11
Initial treatment failed	279	0.09
Chronic patient	122	0.04
Other	644	0.20
Treatment category		
Initial treatment	305,306	95.77
Retreatment	13,486	4.23
TB treatment		
Accept treatment	318,324	99.86
Reject treatment	462	0.17

[~] Agriculture includes famer, herdsman, fisherman

[$] Housekeeping includes housekeeping, childcare, retired and unemployed

[Δ] Education includes students and teachers

[*] Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups

median time to diagnosis was 21 days (IQR 7–50 days), and the median time to treatment was 1 day (IQR 0–15 days).

Results show differences in median time to diagnosis and treatment across different ethnic groups. The median time to diagnosis for the Han majority population was 20 days (IQR 6–49 days); 30 days (IQR 7–65 days) for Tujia; 27 days (IQR 10–61 days) for Miao; 35 days (IQR 10–75 days) for Dong; 24 days (IQR 7–58 days) for Yao; 28 days (IQR 7–51 days) for Bai; 23 days (IQR 7–52 days) for Mongolian and 16 days (IQR 3–46 days) for 'other' ethnic minority groups. For each of the ethnic groups, the median time to diagnosis by year of patient registration is represented graphically in Fig. 1 of the Additional file 1. The median time to treatment was 1 day (IQR 0–16 days) for Han; 1 day (IQR 0–9 days) for Tujia; 1 day (IQR 0–9 days) for Miao; 1 day (IQR 0–9 days) for Dong; 0 days (IQR 0–2 days) for Yao; 2 days (IQR 0–9 days) for

Table 3 Median time from symptom onset to diagnosis and from diagnosis to treatment commencement for TB patients registered in Hunan Province, China 2013–2018, by demographic and clinical characteristics

	Number of patients (%)	Median time to diagnosis (days)	Median time to treatment (days)
All patients	318,792	21 (IQR 7–50)	1 (IQR 0–15)
Ethnicity			
Han	288,802 (90.59)	20 (IQR 6–49)	1 (IQR 0–16)
Tujia	13,680 (4.29)	30 (IQR 7– 65)	1 (IQR 0–9)
Miao	8460 (2.65)	27 (IQR 10–61)	1 (IQR 0–9)
Dong	4033 (1.27)	35 (IQR 10–75)	1 (IQR 0–9)
Yao	2662 (0.84)	24 (IQR 7–58)	0 (IQR 0–2)
Bai	509 (0.16)	28 (IQR 7–51)	2 (IQR 0–9)
Mongolian	349 (0.11)	23 (IQR 7–52)	1 (IQR 0–12)
Other*	293 (0.09)	16 (IQR 3–46)	1 (IQR 0–9)
Sex			
Male	231,495(72.62)	21 (IQR 7–50)	1 (IQR 0–14)
Female	87,297 (27.38)	21 (IQR 7–51)	1 (IQR 0–17)
Age			
< 18 years	7155 (2.24)	14 (IQR 3–36)	2 (IQR 0–17)
≥ 18 years	311,637 (97.76)	21 (IQR 7–51)	1 (IQR 0–15)
Occupation			
Agriculture~	249,093 (78.14)	22 (IQR 7–54)	1 (IQR 0–12)
Housekeeping$	30,802 (9.66)	19 (IQR 5–46)	4 (IQR 0–27)
Education$^{\Delta}$	10,679 (3.35)	13 (IQR 3–33)	2 (IQR 0–20)
Commercial services/civil servant	7818 (2.45)	16 (IQR 4–39)	7 (IQR 0–30)
Migrant worker	2601 (0.82)	19 (IQR 7–46)	1 (IQR 0–10)
Healthcare	1009 (0.32)	15 (IQR 4–36)	4 (IQR 0–25)
Hospitality	612 (0.19)	14 (IQR 3–32)	6 (IRQ 0–27)
Other	16,178 (5.07)	16 (IQR 4–40)	2 (IQR 0–23)
Year			
2013	56,198 (17.63)	21 (IQR 6–55)	1 (IRQ 0–14)
2014	55,815 (17.51)	21 (IQR 7–51)	1 (IQR 0–14)
2015	55,196 (17.31)	21 (IQR 7–50)	1 (IQR 0–14)
2016	49,996 (15.68)	22 (IQR 7–52)	1 (IQR 0–13)
2017	49,843 (15.63)	21 (IQR 6–48)	1 (IQR 0–16)
2018	51,744 (16.23)	19 (IQR 6–48)	1 (IQR 0–18)
Residential address			
Local	310,343 (97.35)	21 (IQR 7–50)	1 (IQR 0–14)
Intra-provincial (within province)	6215 (1.95)	27 (IQR 6–59)	2 (IQR 0–30)
Inter-provincial (between provinces)	2182 (0.68)	18 (IQR 4–44)	5 (IQR 0–28)
Foreign nationality	52 (0.02)	29.5 (IQR 7.5–65)	0 (IQR 0–4)
Patient enrolment classification			
Consultation due to symptoms	117,834 (36.96)	26 (IQR 11–60)	0 (IQR 0–1)
Referral	103,261 (32.39)	17 (IQR 5–45)	1 (IQR 0–12)
Contact tracing	93,183 (29.23)	19 (IQR 4–48)	17 (IQR 0–38)
Health check	3179 (1.00)	3 (IQR 0–14)	0 (IQR 0–3)
Other	1335 (0.42)	15 (IQR 4–34)	8 (IQR 1–28)
Diagnosis institution			
CDC	278,707 (88.15)	21 (IQR 7–51)	1 (IQR 0–15)
Hospital	33,104 (10.47)	20 (IQR 6–45)	0 (IQR 0–9)
TB dispensary	4276 (1.35)	19 (IQR 10–35)	11 (IQR 2–18)

Table 3 (continued)

	Number of patients (%)	Median time to diagnosis (days)	Median time to treatment (days)
Other	69 (0.02)	16 (IQR 5–38)	1 (IQR 0–7)
Severely ill			
No	306,534 (96.15)	21 (IQR 7–50)	1 (IQR 0–15)
Yes	12,258 (3.85)	28 (IQR 9–62)	1 (IQR 0–13)

~ Agriculture includes famer, herdsman, fisherman

$ Housekeeping includes housekeeping, childcare, retired and unemployed

Δ Education includes students and teachers

* Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups

Bai; 1 day (IQR 0–12 days) for Mongolian and 1 day (IQR 0–9 days) for 'other' ethnic minority groups.

The median time to diagnosis (21 days) was used to define delay in subsequent analyses. For clinical relevance, the upper quartile (15 days) was used to define treatment delay, with a sensitivity analysis conducted at the median (1 day).

Factors associated with tuberculosis diagnosis delays

Results of univariable and multivariable logistic regression models to identify factors associated with diagnosis delay are detailed in Table 4. Univariable analysis shows five of the seven ethnic minority groups (i.e., Tujia, Miao, Dong, Yao, and Bai) to have significantly longer diagnosis delays than the reference Han majority. The same five ethnic minority groups had significant greater odds of experiencing diagnosis delays in the multivariable models. The odds of experiencing diagnosis delays relative to the Han majority were significantly higher for Tujia (adjusted odds ratio (AOR): 1.46, 95% CI: 1.41, 1.51), Miao (AOR: 1.31, 95% CI: 1.26, 1.37), Dong (AOR: 1.97, 95% CI: 1.85, 2.11), Yao (AOR: 1.27, 95% CI: 1.17, 1.37), and Bai (AOR: 1.45, 95% CI: 1.22, 1.74) ethnic minorities. Differences in diagnosis delay for the Mongolian ethnic group (AOR 1.20, 95% CI 0.97, 1.48) and the 'other' ethnic minorities (AOR 0.92 95% CI 0.73, 1.17) relative to the Han majority were not significant.

The results of the sensitivity analysis using > 14 days to define a diagnosis delay are presented in the Additional file (Additional file 1: Table S1). The analysis shows there to be no difference (14 day vs. 21 day) in the ethnic minority groups that are associated with a significant diagnosis delay relative to the Han majority.

Other variables found to be associated with a > 21 day diagnosis delay in the multivariable analysis include female sex (AOR: 1.04; 95% CI 1.03,1.06); increasing age (AOR 1.004 per one year increase; 95% CI 1.003, 1.004); agriculture (AOR 1.25; 95% CI 1.19, 1.31) and housekeeping (AOR 1.17; 95% CI 1.11, 1.23) occupations relative to the commercial services/civil servants; patient registrations in 2016 (AOR 1.06, 95% CI 1.03, 1.09) relative to 2013; residing within the province (AOR 1.48; 95% CI 1.41, 1.56) relative to being local; and being severely ill (AOR 1.35; 95% CI 1.31, 1.41).

The negative binomial regression assessment of factors associated with time to diagnosis is detailed in the Additional file (Additional file 1: Table S2).

Factors associated with tuberculosis treatment delays

Results of univariable and multivariable regression models to identify factors associated with treatment delay > 15 days are detailed in Table 5. The multivariable analysis shows that five of the seven ethnic minority groups have significantly lower odds of treatment delay than the Han majority: Tujia (AOR 0.92, 95% CI 0.88, 0.96), Miao (AOR 0.74, 95% CI 0.70, 0.79), Dong (AOR 0.87, 95% CI 0.81, 0.95), Yao (AOR 0.20, 95% CI 0.17, 0.24) and 'other' (AOR 0.70, 95% CI 0.51, 0.97).

A sensitivity analysis using the median (> 1 day) to define treatment delay is presented in the Additional file (Additional file 1: Table S3). This analysis shows a variety of treatment delays across the different ethnic groups, with no clear trend detectable.

The other variables associated with > 15 day treatment delay in the multivariable model include female sex (AOR 1.07; 95% CI 1.05, 1.09); increasing age (AOR 1.001 per one year increase; 95% CI 1.0004, 1.002); 2018 as the year of registration relative to 2013 (AOR 1.08; 95% CI 1.05, 1.12); residing inter-provincially relative to being local (AOR 1.14; 95% CI 1.04, 1.26); being enrolled due to referral (AOR 3.62, 95% CI 3.52, 3.72), contact tracing (AOR 14.45, 95% CI 14.06, 14.84) and for other reasons (AOR 7.78, 95% CI 6.94, 8.72) relative to consultation due to symptoms and being diagnosed at a TB dispensary (AOR 3.32; 95% CI 3.09, 3.56) relative to a CDC.

Table 4 Univariable and multivariable regression assessment of factors associated with 21 day diagnosis delay in TB patients registered in Hunan Province, 2013–2018

	Number of patients (%)	Univariable odds ratio (95% CI)	Univariable *p* value	Multivariable odds ratio (95% CI)	Multivariable *p* value
Ethnicity					
Han	288,802 (90.59)	1.00		1.00	
Tujia	13,680 (4.29)	1.38 (1.33, 1.43)	0.000	1.46 (1.41, 1.51)	0.000
Miao	8460 (2.65)	1.29 (1.77, 2.02)	0.000	1.31 (1.26, 1.37)	0.000
Dong	4033 (1.27)	1.89 (1.77, 2.02)	0.000	1.97 (1.85, 2.11)	0.000
Yao	2662 (0.84)	1.18 (1.10, 1.28)	0.000	1.27 (1.17, 1.37)	0.000
Bai	509 (0.16)	1.30 (1.09, 1.55)	0.004	1.45 (1.22, 1.74)	0.000
Mongolian	349 (0.11)	1.21 (0.98, 1.49)	0.078	1.20 (0.97, 1.48)	0.099
Other*	293 (0.09)	0.81 (0.64, 1.02)	0.067	0.92 (0.73, 1.17)	0.494
Sex					
Male	231,495 (72.62)	1.00		1.00	
Female	87,297 (27.38)	1.02 (1.00, 1.03)	0.021	1.04 (1.03, 1.06)	0.000
Age	318,792 (100)	1.01 (1.01, 1.01)	0.000	1.004 (1.003, 1.004)	0.000
Occupation					
Commercial services/civil servant	7818 (2.45)	1.00		1.00	
Agriculture ~	249,093 (78.14)	1.42 (1.36, 1.49)	0.000	1.25 (1.19, 1.31)	0.000
Housekeeping[$]	30,802 (9.66)	1.23 (1.17, 1.30)	0.000	1.17 (1.11, 1.23)	0.000
Education[Δ]	10,679 (3.35)	0.80 (0.75, 0.85)	0.000	0.84 (0.79, 0.90)	0.000
Migrant worker	2601 (0.82)	1.17 (1.07, 1.28)	0.000	1.06 (0.97, 1.16)	0.196
Healthcare	1009 (0.32)	0.96 (0.84, 1.10)	0.556	0.94 (0.82, 1.07)	0.332
Hospitality	612 (0.19)	0.80 (0.67, 0.94)	0.009	0.82 (0.69, 0.97)	0.022
Other	16,178 (5.07)	1.06 (1.01, 1.12)	0.027	0.98 (0.93, 1.04)	0.508
Year					
2013	56,198 (17.63)	1.00		1.00	
2014	55,815 (17.51)	1.01 (0.99, 1.04)	0.278	0.99 (0.97, 1.02)	0.648
2015	55,196 (17.31)	1.01 (0.99, 1.03)	0.428	0.99 (0.97, 1.02)	0.603
2016	49,996 (15.68)	1.07 (1.04, 1.10)	0.000	1.06 (1.03, 1.09)	0.000
2017	49,843 (15.63)	1.00 (0.97, 1.02)	0.798	1.01 (0.98, 1.03)	0.550
2018	51,744 (16.23)	0.93 (0.91, 0.96)	0.000	1.01 (0.98, 1.03)	0.656
Residential address					
Local	310,343 (97.35)	1.00		1.00	
Intra-provincial (within province)	6215 (1.95)	1.23 (1.17, 1.30)	0.000	1.48 (1.41, 1.56)	0.000
Inter-provincial (between provinces)	2182 (0.68)	0.86 (0.79, 0.94)	0.001	1.06 (0.98, 1.16)	0.153
Foreign nationality	52 (0.02)	1.45 (0.83, 2.53)	0.186	1.58 (0.90, 2.79)	0.111
Patient enrolment classification					
Consultation due to symptoms	117,834 (36.96)	1.00		1.00	
Referral	103,261 (32.39)	0.66 (0.65, 0.67)	0.000	0.65 (0.63, 0.66)	0.000
Contact tracing	93,183 (29.23)	0.73 (0.72, 0.74)	0.000	0.74 (0.72, 0.75)	0.000
Health check	3179 (1.00)	0.18 (0.17, 0.20)	0.000	0.20 (0.18, 0.22)	0.000
Other	1335 (0.42)	0.53 (0.47, 0.59)	0.000	0.55 (0.49, 0.61)	0.000
Diagnosis Institution					
CDC	278,707 (88.15)	1.00		1.00	
Hospital	33,104 (10.47)	0.92 (0.90, 0.95)	0.000	0.93 (0.91, 0.96)	0.000
TB dispensary	4276 (1.35)	0.74 (0.69, 0.78)	0.000	0.72 (0.67, 0.76)	0.000
Other	69 (0.02)	0.75 (0.46, 1.20)	0.226	0.85 (0.52, 1.39)	0.521
Severely Ill					
No	306,534 (96.15)	1.00		1.00	
Yes	12,258 (3.85)	1.31 (1.00, 1.02)	0.000	1.35 (1.31, 1.41)	0.000

Table 4 (continued)

~ Agriculture includes famer, herdsman, fisherman

$ Housekeeping includes housekeeping, childcare, retired and unemployed

Δ Education includes students and teachers

* Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups

The negative binomial regression assessment of factors associated time from diagnosis to treatment commencement is detailed in the Additional file (Additional file 1: Table S4).

New patients represented 95.74% of the total study population and the results of the sensitivity analysis showed that there were no differences in treatment delays across the study variables between the two population groups (i.e., all TB patients vs. new patients only) (S1 Tables 5 and 6).

Discussion

Within Hunan Province, this study shows consistent and significant diagnosis delays for ethnic minority TB patients compared to the Han majority. However ethnic minority groups have lower odds of treatment delay relative to the Han majority.

Variables associated with TB diagnosis and treatment delay in previous studies include poverty, socio-economic disadvantage, knowledge, cultural beliefs, literacy, language, and distance and cultural barriers to health care provision [28–31]. The significant difference in the odds of TB diagnosis delay observed between Han majority and ethnic minority patients, and the differences observed between ethnic minority groups, may in part reflect socio-economic and cultural differences that have been reported to be associated with delay by previous studies. [28–31].

The ethnic minorities that inhabit Hunan occupy 28% of the province's land area [14], with approximately 96% occupying six cities and prefectures located within the 'Great Western Hunan' region [32], a region that is rural and less developed. In many rural and remote areas of China there is a lack of infrastructure and resources and a disparity in accessibility to services and facilities. [33, 34].

Although the disparity between urban and rural incomes in China is reducing, in 2019 the respective ratio was 2.59:1 in Hunan Province [35]. Disposable income is an important metric as TB patients face a myriad of direct (e.g., out of pocket medical expenses and health insurance exclusions/co-payments) and indirect costs (e.g., loss of income, cost of transport, food and accommodation) [7, 36–38]. Despite China successfully progressing its goal of universal public health insurance, catastrophic health expenditure (CHE) continues to be a significant confounder in effective TB diagnosis and treatment outcomes [9, 36, 39, 40]. 2016 figures estimate 15.11% of Chinese households experience CHE, with the rate 1.36 times higher in rural compared to urban households [41].

One of the most important confounders in the Chinese urban–rural income gap is education [42]. Improving ethnic minority educational attainment has been a high priority for China since 1949, prior to which it is estimated that up to 80% of its minority population were illiterate [43]. Despite the implementation of preferential policies however, lagging educational attainment continues to contribute to the Han-minority opportunity gap [44]. In addition to the differential between minority and majority populations, there is significant variation in educational attainment between minority groups [45].

The findings of this study show there are opportunities to reduce diagnosis delay within ethnic minority populations. The data supports integration of TB screening within routine health checks, a process that has been shown to be cost effective at improving case detection [46]. As evidenced by other studies, opportunities to improve patient seeking behaviour may relate to the socio-economic and cultural disadvantage experienced by ethnic minorities [13]. Health literacy is a key component of health seeking behaviour thereby reducing diagnosis delay. Population surveys in China show rural location and illiteracy to be significant risk factors in understanding TB and its symptoms [47]. Health seeking behaviour is also impacted by awareness of the NTP and distance to the nearest hospital [48]. Due to structural and economic constraints, patients in rural locations usually seek initial care within their own communities which often adds to the time delay in receiving a correct diagnosis [49].TB health seeking behaviour is also impacted by stigma of the disease, which in itself it impacted by social and cultural context [49, 50]. Due to the significant diversity between and within different Chinese ethnic groups [44], detailed socioeconomic and cultural information is required to inform appropriate interventions.

When evaluating treatment delay, this study found all ethnic minority groups had lower odds of delay than the Han majority, with the finding significant in five of the seven ethnic minority groups. Further research is required to elucidate why the majority population is at greater risk of a treatment delay, and whether these findings are attributable to success of the NTP which

Table 5 Univariable and multivariable regression of factors associated with 15 day treatment delay in TB patients registered in Hunan Province, 2013–2018

	Univariable odds ratio (95% CI)	Univariable *p* value	Multivariable odds ratio (95% CI)	Multivariable *p* value
Ethnicity				
Han	1.00		1.00	
Tujia	0.75 (0.71, 0.78)	0.000	0.92 (0.88, 0.96)	0.000
Miao	0.61 (0.58, 0.65)	0.000	0.74 (0.70, 0.79)	0.000
Dong	0.77 (0.72, 0.84)	0.000	0.87 (0.81, 0.95)	0.001
Yao	0.20 (0.17, 0.24)	0.000	0.20 (0.17, 0.24)	0.000
Bai	0.67 (0.54, 0.84)	0.000	0.83 (0.65, 1.05)	0.126
Mongolian	0.85 (0.66, 1.09)	0.205	0.78 (0.59, 1.03)	0.082
Other*	0.69 (0.52, 0.93)	0.014	0.70 (0.51, 0.97)	0.030
Sex				
Male	1.00		1.00	
Female	1.11 (1.09, 1.13)	0.000	1.07 (1.05, 1.09)	0.000
Age	0.998 (0.998, 0.999)	0.000	1.001 (1.0004, 1.002)	0.000
Occupation				
Commercial services/civil servant	1.00		1.00	
Agriculture ~	0.45 (0.43, 0.47)	0.000	0.58 (0.55, 0.61)	0.000
Housekeeping[$]	0.85 (0.81, 0.90)	0.000	0.81 (0.76, 0.86)	0.000
Education[Δ]	0.64 (0.60, 0.68)	0.000	0.67 (0.63, 0.72)	0.000
Migrant worker	0.41 (0.37, 0.46)	0.000	0.64 (0.57, 0.72)	0.000
Healthcare	0.80 (0.70, 0.92)	0.002	0.81 (0.70, 0.95)	0.009
Hospitality	0.87 (0.73, 1.03)	0.115	0.91 (0.75, 1.10)	0.320
Other	0.68 (0.64, 0.72)	0.000	0.82 (0.77, 0.87)	0.000
Year				
2013	1.00		1.00	
2014	0.98 (0.96, 1.01)	0.266	0.94 (0.91, 0.97)	0.000
2015	0.97 (0.94, 0.99)	0.026	0.93 (0.90, 0.96)	0.000
2016	0.94 (0.91, 0.96)	0.000	0.89 (0.87, 0.93)	0.000
2017	1.06 (1.03, 1.09)	0.000	0.98 (0.95, 1.02)	0.309
2018	1.17 (1.14, 1.20)	0.000	1.08 (1.05, 1.12)	0.000
Residential address				
Local	1.00		1.00	
Intra-provincial	1.74 (1.65, 1.84)	0.000	0.97 (0.91, 1.02)	0.233
Inter-provincial	1.74 (1.60, 1.90)	0.000	1.14 (1.04, 1.26)	0.008
Foreign nationality	0.75 (0.38, 1.50)	0.418	1.18 (0.56, 2.51)	0.660
Patient enrolment				
Consult-symptoms	1.00		1.00	
Referral	3.62 (3.53, 3.72)	0.000	3.62 (3.52, 3.72)	0.000
Contact tracing	14.44 (14.07, 14.83)	0.000	14.45 (14.06, 14.84)	0.000
Health check	1.15 (1.00, 1.31)	0.042	1.10 (0.96, 1.25)	0.181
Other	8.38 (7.49, 9.39)	0.000	7.78 (6.94, 8.72)	0.000
Diagnosis institution				
CDC	1.00		1.00	
Hospital	0.74 (0.72, 0.76)	0.000	0.72 (0.69, 0.74)	0.000
TB dispensary	1.40 (1.31, 1.49)	0.000	3.32 (3.09, 3.56)	0.000
Other	0.64 (0.34, 1.19)	0.156	0.78 (0.39, 1.55)	0.477
Severely Ill				
No	1.00		1.00	
Yes	0.86 (0.83, 0.90)	0.000	0.73 (0.69, 0.76)	0.000

Table 5 (continued)

~ Agriculture includes famer, herdsman, fisherman

$ Housekeeping includes housekeeping, childcare, retired and unemployed

Δ Education includes students and teachers

* Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups

prioritizes vulnerable population groups [9, 10]. Another possible explanation is that due to diagnosis delay in ethnic minorities, an increase in disease progression may lead to prioritization of treatment, however further research is required to test this hypothesis.

A significant strength of this study is the large, detailed data set on a well described cohort of patients. However, a lack of information on variables that may relate to the underlying causes of delay e.g., income and level of education, is a limitation of this study. The study is reliant upon the patient for the date of symptom onset from which diagnosis and treatment delay are calculated. Recall bias on the date of symptom onset therefore has the potential to impact subsequent findings. Only patients presenting for treatment at designated institutions are included in the analysis and so the data may not be representative of the variables across all TB patients within the province.

Conclusions

Reducing the time between TB onset and treatment is important in reducing morbidity and mortality and preventing further disease transmission This study shows ethnic minority groups experience significant TB diagnosis delay compared to the Han majority. Ethnicity is a complex variable that is often associated with a multitude of socio-economic disparities. These disparities are likely to be the underlying root cause of TB delay differentials observed between and within different population groups, which highlights the need for further research. It is also recommended that further studies evaluate the impact of ethnicity on TB treatment outcomes, as treatment outcomes are also key to effective TB control.

Abbreviations

AOR: Adjusted odds ratio; CDC: Centre for disease control and prevention; CHE: Catastrophic health expenditure; CI: Confidence interval; COVID-19: Coronavirus disease 2019; DOTS: Directly observed treatment short-course; HIV: Human immunodeficiency virus; IQR: Interquartile range; IQR: Multi-drug resistant; NTP: National Tuberculosis Control Programme; p-value: Probability value; SD: Standard deviation; TB: Tuberculosis; TBCIHP: TB Control Institute of Hunan Province; VIF: Variance inflation factor; WHO: World Health Organization.

Supplementary Information

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Additional file 1: **Fig S1.** Median time to diagnosis by ethnicity for TB patients registered in Hunan Province 2013-2018. **Table S1**. Sensitivity Analysis: Univariable and multivariable regression of factors associated with 14 day diagnosis delay in TB patients registered in Hunan Province, 2013-2018. **Table S2.** Univariable and multivariable negative binomial regression assessment of factors associated with time to diagnosis in TB patients registered in Hunan Province, 2013-2018. **Table S3**. Sensitivity Analysis: Univariable and multivariable regression assessment of factors associated with 1 day treatment delay in TB patients registered in Hunan Province, 2013-2018. **Table S4.** Univariable and multivariable negative binomial regression assessment of factors associated with time from diagnosis to treatment commencement in TB patients registered in Hunan Province, 2013-2018. **Table S5**. Median time from diagnosis to treatment commencement for new TB patients registered in Hunan Province, 2013-2018, by demographic characteristics. **Table S6.** Univariable and multivariable regression of factors associated with >15 day treatment delay in new TB patients registered in Hunan Province, 2013-2018.

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Authors' contributions

BG, KAA, and ACAC conceived the study. ZX and LB collected the data. BG undertook the analysis and prepared the draft manuscript. ACAC and KAA advised on the data analysis and the development of the manuscript. ZX and LB revised the drafted manuscript. All authors critically revised the manuscript for methodological and intellectual content and have read and approved the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from Curtin University Human Research Ethics Committee (protocol number HRE2019-0581), and Hunan Chest Hospital provided written permission to access the data. All methods were performed in accordance with the relevant guidelines and regulations. As this study used secondary data, the need to obtain informed consent was waived by the Curtin University Human Research Ethics Committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Chapter VII: Risk factors associated with poor tuberculosis treatment outcomes in Hunan, China

To maximize the efficacy of TB control programs and prevent escalating drug resistance, risk factors associated with unsuccessful treatment outcomes need to be identified and addressed. Of the studies that have been conducted on risk factors associated with unsuccessful TB outcomes, few have been conducted in China. To our knowledge, only one study has been conducted in Hunan Province which evaluated treatment default and mortality in TB patients registered between 2005 and 2006.[131]

To address the research question in chapter seven, a retrospective study was undertaken on TB patients that underwent treatment in Hunan Province between 2013 and 2018. An unsuccessful treatment outcome was defined as the sum of treatment failure, death, and loss to follow-up. Although the study found a number of risk factors to be associated with an unsuccessful TB treatment outcome, indigenous ethnic minority status was not one of them. The risk factors that were identified, included male sex, increasing age, being severely ill, having a history of TB treatment, patients not under systematic management and treatment regimens that differed from full course management. The odds of an unsuccessful treatment outcome increased in more recent years of registration. Within the variables that contribute to an unsuccessful treatment outcome, the study identified an increasing trend in mortality rate. These increasing trends warrant further research and the analysis of data subsequent to 2018.

Full details of the study are included in the following paper:

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RESEARCH ARTICLE

Risk factors associated with unsuccessful tuberculosis treatment outcomes in Hunan Province, China

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Abstract

Objectives: Globally, China has the third highest number of tuberculosis (TB) cases despite high rates (85.6%) of effective treatment coverage. Identifying risk factors associated with unsuccessful treatment outcomes is an important component of maximising the efficacy of TB control programmes.

Methods: Retrospective cohort study to evaluate the outcomes of 306,860 drug-susceptible TB patients who underwent treatment in Hunan Province, China between 2013 and 2018. Univariable and multivariable logistic regression models were used to identify factors associated with unsuccessful TB treatment outcomes.

Results: A successful treatment outcome was recorded for 98.6% of patients, defined as the sum of patients who were cured (36.2%) and completed treatment (62.4%). An unsuccessful treatment outcome was recorded for 1.8% of patients, defined as the sum of treatment failure (1.1%), deaths (0.5%) and lost to follow up (0.2%). The odds of an unsuccessful treatment outcome showed an increasing trend in more recent years of registration (2018 adjusted odds ratio (AOR): 1.43; 95% Confidence Interval (CI) 1.31, 1.57 relative to 2013). Other significant risk factors were male sex (AOR: 1.17; 95% CI 1.10, 1.25); increasing age (AOR:1.02 per year increase; 95% CI 1.02,1.02); being severely ill (AOR: 1.50; 95% CI 1.33, 1.70); having a history of TB treatment (AOR: 2.93; 95% CI 2.69, 3.20); not being under systematic management (AOR: 16.10 (14.49, 17.88) and treatment regimens that differed from full course management.

Conclusions: The increasing likelihood of an unsuccessful treatment outcome over time necessitates the need for further research.

KEYWORDS
China, risk factors, treatment outcome, tuberculosis

Sustainable Development Goals: Good health and well-being, Reduced inequalities

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INTRODUCTION

Throughout history *Mycobacterium tuberculosis* (MTB), the pathogen responsible for tuberculosis (TB), is thought to have claimed more lives than any other microorganism [1]. With an estimated 1.4 million lives lost to the disease in 2019, TB continues to be one of the leading infectious causes of death globally [2]. Tuberculosis is associated with poverty and it fuels the cycle of deprivation and vulnerability [3].

Tuberculosis can be cured, but if left untreated the mortality rate is high, with 10-year case fatality rates ranging between 54 and 86% in human immunodeficiency virus (HIV) negative patients [4]. For drug-susceptible TB, a 6-month treatment regime containing four first-line antibiotics (i.e. isoniazid, rifampicin, ethambutol and pyrazinamide) is recommended, which has an 85% success rate [3]. Successful treatment is key to curing the disease, preventing transmission of infection and preventing the development of drug resistance [3]. Drug-resistant TB is an escalating global health security threat [2], projected to cost the world US$ 16.7 trillion by 2050 [5].

Previous studies have found a number of factors to be associated with unsuccessful TB treatment outcomes, including positive HIV status, male sex, ethnicity, low body mass index (BMI), substance abuse, other co-morbidities, previous treatment, drug resistance, low level of education, lack of knowledge on treatment duration and the importance of treatment completion, household income, the requirement for hospitalisation during treatment, side effects of medication, improved symptoms resulting in the cessation of therapy, lack of family support and unsupervised treatment administration [6–13]. The factors relating to unsuccessful treatment outcomes need to be understood and addressed to maximise the efficacy of TB control programmes and prevent escalating drug resistance.

In 2014, the World Health Assembly adopted the *End TB Strategy*, which is integral to Sustainable Development Goal 3.3 that aims to end the TB epidemic by 2030 [14,15]. By 2030, the End TB Strategy aims to reduce TB deaths by 90%, reduce TB incidence by 80% and eliminate catastrophic costs faced by TB households [15].

In terms of 2019 TB cases numbers, China ranks third with 8.4% of the global total [3], despite effective treatment coverage being estimated at >85.6% [16]. In 2019, China had the second-greatest burden (14%) of multidrug-resistant TB (MDR-TB), which was estimated to occur in 7.1% of new and 23% of previously treated cases [3]. To address the burden of disease, China has initiated a National Tuberculosis Control Programme (NTP) based on the Directly Observed Treatment Short-course (DOTS) strategy recommended by WHO [17]. Although the NTP aims to provide TB diagnosis and treatment services free of charge, patients often face significant out of pocket expenses and financial hardship [18].

Hunan province, located in south-central China, carries a high burden of TB despite significant investments that have been made by the Hunan government to combat the disease [19–21]. An understanding of the risk factors associated with unsuccessful treatment outcomes in province-specific TB patient populations could help reduce the burden of disease by informing targeted interventions, for example, systematic drug supervision, sex-specific TB education/messaging. Few of the studies on risk factors associated with unsuccessful TB outcomes have been conducted in China. To our knowledge, only one study has evaluated treatment default and mortality in TB patients that were registered in Hunan between 2005 and 2006 [22]. Our study aimed to evaluate the rate of treatment success and the risk factors associated with unsuccessful treatment outcomes among drug-susceptible TB (DS-TB) patients in Hunan Province who were undergoing treatment between 2013 and 2018.

METHODS

Study design and data sources

This is a retrospective cohort study conducted on patients undergoing treatment for pulmonary and extrapulmonary DS-TB in Hunan Province, China between 2013 and 2018 inclusive. Within China, TB is a category II notifiable disease and health professionals are responsible for the collection and entry of data from notified patients into an Internet-based TB management information system [23]. Within Hunan, the TB management information system is managed by the Tuberculosis Control Institute of Hunan Province (TBCIH), which provided access to the data for this study. Clinical data relating to the date of treatment commencement, date of treatment completion, treatment outcome and type of treatment management were available, as were demographic data such as ethnicity, age, sex, occupation and residential address.

Definitions

We used the WHO definitions of treatment outcomes: [24]

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month five or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.

Outcome	Definition
Lost to follow up	A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed

To dichotomise data into successful and unsuccessful treatment outcomes, treatment success was classified as 'cured' plus 'treatment completed' and an unsuccessful outcome as the sum of 'treatment failed', 'died' and 'lost to follow-up'. Definitions pertaining to the other demographic descriptors/variables analysed are detailed in Table 1.

Statistical analysis

Data were translated from Mandarin to English, cleaned, checked for completeness and entered into STATA version 16.1 (StataCorp, College Station, TX) for analysis. Cross-tabulation was used to verify data completeness. The following data were excluded from the original data set prior to analysis: patients who were still on treatment and those who were transferred out, for example, diagnosis changed, HIV +ve, MDR-TB. The treatment outcomes of patients transferred out were not recorded in the TBCIH database.

Descriptive statistics were used to summarise data and illustrate characteristics of the study population. Univariable logistic regression models were performed and crude odds ratios (COR) with 95% confidence intervals (CI) were reported. Multicollinearity between independent variables was assessed by variance inflation factors (VIF) and variables with a high degree of association with other independent variables (i.e. VIF >5) were excluded from the final models.

All independent variables with a VIF <5 were included in multivariable logistic regression models and adjusted odds ratios with 95% CIs used to determine the strength of association between the dependent and independent variables. In the multivariable regression analysis, variables with a p-value <0.05 were considered significantly associated with an unsuccessful treatment outcome.

Ethical approval

Ethics approval was obtained from Curtin University (HRE2019-0581) and permission to access the data was obtained from TBCIH. As this study used secondary and routinely collected clinical data, informed consent was not obtained from the study participants. Medical records were anonymised by TBCIH to maintain patient confidentiality.

RESULTS

Figure 1 details the patient record selection process: 318,792 records were available after translation and data cleaning. The data set included patients on treatment between 2013 and 2018; we were in receipt of this in 2018 and so some patients were yet to complete their course of treatment and were excluded (n = 10,679). Of the patients that had completed treatment (n = 308,113), records for those transferred out (n = 1,253) were excluded, as their treatment outcomes were not recorded on the TBCIH database.

Socio-demographic and clinical characteristics of the TB patients

The sociodemographic characteristics of the final patient cohort (n = 306,860) are detailed in Table 2. The mean age of the patient population was 51.6 years (SD 17.6), the majority was male (72.6%), employed in agriculture (78.3%) and new patients (95.9%).

Unsuccessful TB treatment outcomes

A successful treatment outcome was recorded for 98.24% of the patient population (treatment completed 62.04% and cured 36.20%). An unsuccessful treatment outcome was recorded for 1.76% of the patient population (treatment failure 1.08%, death 0.46% and lost to follow up 0.21%).

Risk factors associated with an unsuccessful TB treatment outcome

Table 3 shows results of univariable and multivariable logistic regression models and factors associated with an unsuccessful treatment outcome. In the univariable analysis, demographic factors such as male sex, increasing age, occupation (i.e. agriculture housekeeping, childcare, retired and un-employed) and year of enrolment; and clinical factors such as severe illness, non-systematic management and supervision process were significantly associated with unsuccessful TB treatment outcomes.

In the final multivariable analysis, male sex (AOR:1.17; 95% CI 1.10, 1.25), increasing age (AOR:1.02 per year increase; 95% CI 1.02, 1.02) and being severely ill (AOR: 1.50; 95% CI 1.33, 1.70) were significant risk factors for unsuccessful treatment outcomes. The odds of an unsuccessful treatment outcome were greater where a patient was not systematically managed (AOR: 16.10; 95% CI 14.49, 17.88) and when they were under full process supervision (AOR: 1.51 (95% CI 1.37, 1.66); intensive phase supervision (AOR: 1.39; 95% CI 1.26, 1.55) or self -administered medication (AOR: 1.98; 95% CI 1.53, 2.55) relative to full course management. Registration in the years 2016–2018 was also associated with an unsuccessful treatment outcome relative to 2013 (2016

TABLE 1 Definitions of the variables included and relating to our study

Variable	Definition
Residential address	
Local	Patients who reside in local counties
Intra-provincial	Patients who reside in other counties within the province
Inter-provincial	Patients who reside in provinces other than Hunan
Foreign nationality	Patients who reside in other countries
Registration category	
New patient	PTB patients who have never taken anti-TB drugs, or who have been receiving irregular treatment for less than one month
Relapse	PTB patients with a history of disease, who complete a full course of chemotherapy and appear cured according to symptoms, but who return a smear positive sputum sample
Return after default	PTB patients who receive chemotherapy for ≥1 month but discontinue therapy for ≥2 months and then return for treatment
Initial treatment failed	New sputum smear positive PTB patients with positive sputum smear microscopy results at the end of the 5th month or after completion of therapy; and sputum smear negative PTB patients with a positive smear result for any sputum sample
Chronic patient	Positive sputum examination results after several episodes of irregular therapy
TB diagnosis results	
Etiological examination negative	TB cases confirmed on basis of symptoms
Smear positive	Positive Acid-Fast Bacillus test
Extrapulmonary TB	TB identified in organs other than the lungs
Culture positive	Positive sputum culture
Molecular biology positive	TB confirmed on basis of molecular diagnosis
Severely ill	Patients with miliary TB, cavities, TB empyema or serious damage to one or more organs caused by TB infection.
Drug resistance pattern	
Drug susceptible TB	*M. tuberculosis* that is susceptible to first line antibiotics (isoniazid, rifampin, ethambutol, and pyrazinamide)
MDR-TB	*M. tuberculosis* resistant to isoniazid and rifampicin
Mono-resistant TB	*M. tuberculosis* resistant to a single first line antibiotic
History of TB treatment	
No (Initial treatment)	• a patient who has never taken anti-TB drugs; or • a patient receiving standardized TB treatment but who has not completed the full course of treatment; or • a patient receiving irregular TB treatment for less than one month.
Yes (Retreatment)	• a patient receiving irregular anti-TB drugs for one month or longer; or • initial treatment failure and relapse
TB treatment outcomes [50]	
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment failure	A TB patient whose sputum smear or culture is positive at month five or later during treatment.
Death	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more
Successful treatment outcome	The sum of cured and treatment completed
Unsuccessful treatment outcome	The sum of treatment failure, death and lost to follow up

TABLE 1 (Continued)

Variable	Definition
Treatment management	
Full process supervision	Patients take all TB medications under the direct observation of a medication supervisor during the full course of treatment.
Intensive phase supervision	Patients take all TB medications under the direct observation of a medication supervisor during the intensive phase. Full-course management is conducted during the continuation phase.
Full course management	Comprehensive management is conducted during the full course of TB treatment to ensure medications are taken regularly. This includes health education; regular drug collection; cross checking, tracing, and patient visits in the event of failure to collect drugs/visit the clinic.
Self-administered medication	Health education is provided on standardized chemotherapy and patients self-medicate
Systematic management	A registered PTB patient who has accepted timely sputum examinations, medication supervision and regular treatment
China recognizes 56 ethnic classifications comprising the Han majority and 55 minority groups [51]. For this study, data were analysed for Han majority and Tujia, Miao, Dong, Yao, Bai, Mongolian and 'other' ethnic minority groups. The 'other' ethnic minority grouping comprises the summation of ethnic minority groups which constitute <0.1% of the patient population. The 'other' group was represented by Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic minorities.	

Note: Effective treatment coverage = 'an indicator that combines treatment coverage and the treatment success rate to estimate the proportion of TB cases that are detected and successfully treated' [52].

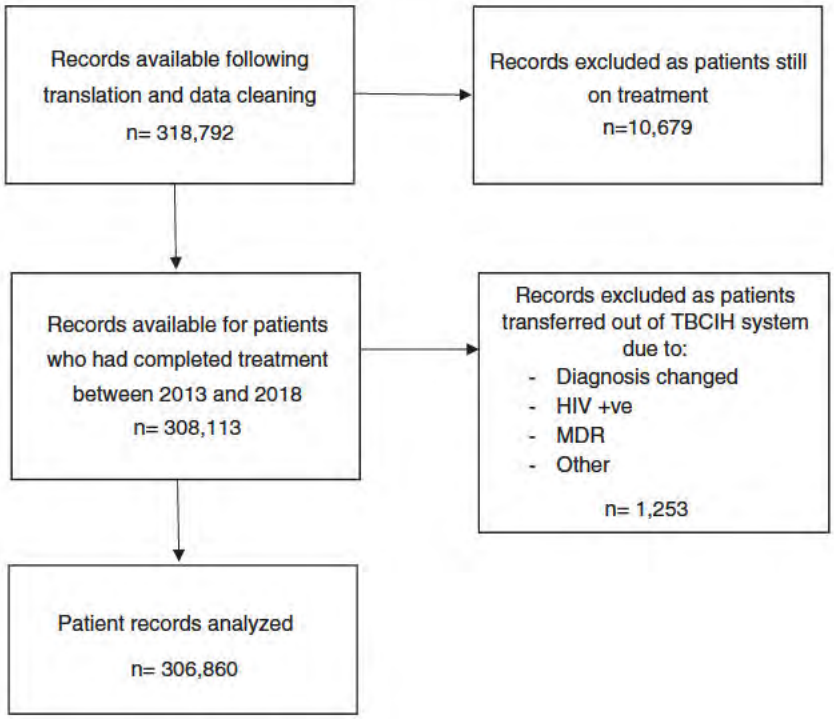

FIGURE 1 Flowchart of patient record selection process

AOR: 1.12; 95% CI 1.02, 1.23; 2017 AOR:1.12; 95% CI 1.02, 1.23 and 2018 AOR:1.43; 95% CI 1.31, 1.57). An evaluation of the factors contributing to unsuccessful treatment outcome over time shows an increasing mortality rate in the later years of patient registration (Figure 2).

DISCUSSION

This study found a treatment success rate of 98.24% amongst DS-TB patients undergoing therapy between 2013 and 2018 in Hunan Province, China. This figure is higher than the 94% success rate reported for new cases across China in 2018 [25], and the WHO target of 85% [26]. It is noted, however, that the exclusion of patients who were transferred out, may have increased the reported success rate.

Our study found the likelihood of unsuccessful treatment outcome to be higher in the last three years of patient enrolment, with an increasing trend over time. Within the variables that contribute to an unsuccessful treatment outcome, there is an increasing trend in the mortality rate over recent years. Modelling studies have suggested that an increasing

TABLE 2 Sociodemographic characteristics of TB patients registered for treatment in Hunan Province, China, 2013–2018

Variable	Number	Percent
Sex		
Male	222,783	72.60
Female	84,077	27.40
Mean age 51.6 years (SD 17.6)		
Occupation		
Agriculture	240,235	78.29
Housekeeping, childcare, retired, un-employed	29,144	9.50
Education[a]	10,341	3.37
Commercial services/civil servant	7,479	2.44
Migrant worker	2,531	0.82
Healthcare	962	0.31
Hospitality	586	0.19
Other	15,582	5.08
Ethnicity		
Han	277,813	90.54
Tujia	13,254	4.32
Miao	8,168	2.66
Dong	3,888	1.27
Yao	2,621	0.85
Bai	496	0.16
Mongolian	337	0.11
Other[b]	279	0.09
Residential address		
Local	298,844	97.39
Intra-provincial	5,896	1.92
Inter-provincial	2,071	0.67
Foreign nationality	49	0.02
Registration category[c]		
New patient	294,355	95.92
Relapse	11,210	3.65
Return after default	328	0.11
Initial treatment failed	246	0.08
Chronic patient	120	0.04
TB diagnosis results		
Etiological examination negative	182,343	59.42
Smear positive	117,491	38.29
Extrapulmonary TB	5,031	1.64
Only culture positive	1,154	0.38
Only molecular biology positive	637	0.21
No etiological results	180	0.06
Only pathologically positive	24	0.01
Severely ill		
No	295,172	96.19
Yes	11,688	3.81
Mean age 51.6 years (SD 17.6)		
History of TB treatment		
No	294,439	95.95
Yes	12,421	4.05
Median treatment time 184 days (IQR 182, 188)		
TB treatment outcomes		
Treatment completed	190,372	62.04
Cured	111,089	36.20
Treatment failure	3,317	1.08
Death	1,426	0.46
Lost to follow-up	656	0.21
Treatment management		
Full process supervision	178,325	58.24
Intensive phase supervision	83,506	27.27
Full course management	41,381	13.52
Self-administered medication	2,954	0.96
Successful TB treatment outcome	301,461	98.24
Unsuccessful TB treatment outcome	5,399	1.76
Systematic management		
Yes	303,924	99.04
No	2,936	0.96

[a]Education includes both teachers and students.

[b]Other are represented by 21 separately defined ethnic groups. NB ethnicity data are not available for four patients.

[c]Patient registration category not available for 601 patients.

trend of unsuccessful TB treatment outcomes may be related to the increasing prevalence of MDR-TB and the relatively low rate of MDR detection and treatment in China [3,27,28]. Further research is required to elucidate whether the increasing trend in mortality is related to an increasing prevalence of MDR-TB or whether it relates to other factors such as disease severity, age or co-morbidities. Among the causes for TB treatment default, economic hardship is cited as one of the most common reasons [7,9,18,27] with 2019 global figures estimating that 44% of people with DS-TB and 80% of people with MDR-TB face catastrophic costs [3]. Although the Chinese Action Plan to Stop TB (2019–2022) aims to provide drug susceptibility testing (DST) to 90% of bacteriologically confirmed cases by 2022 [27], the cost implications of the additional resources required to detect and treat MDR are not fully covered by Chinese health insurance schemes [18,27,29]. Interventions that identify and help patients facing catastrophic costs maybe an effective way of improving the efficacy of TB programme outcomes.

Within the Hunan study population, male sex and increasing age were associated with increased odds of unsuccessful treatment outcome. The finding supports sex specific TB education and messaging. Gender differences in TB treatment outcomes remain inconsistent, although a number of studies support our finding [30–33]. Possible explanations for sex disparities in TB treatment outcomes

TABLE 3 Univariable and multivariable logistic regression model results assessing factors associated with an unsuccessful TB treatment outcome

	TB treatment outcome					
Risk factor for n TB treatment outcome	**No Successful (%)**	**No. Unsuccessful (%)**	**Univariable estimate**	**Univariable *p* value**	**Multivariable estimate**	**Multivariable *p* value**
Ethnicity						
Han	272,912 (98.24)	4,91 (1.76)	1.00		1.00	
Tujia	13,031 (98.32)	223 (1.68)	0.95 (0.83, 1.09)	0.485	0.93 (0.81, 1.07)	0.337
Miao	8,018 (98.16)	150 (1.84)	1.04 (0.88, 1.23)	0.625	1.08 (0.92, 1.28)	0.334
Dong	3,816 (98.15)	72 (1.85)	1.05 (0.83, 1.33)	0.680	1.20 (0.95, 1.53)	0.130
Yao	2,583 (98.55)	38 (1.45)	0.82 (0.59, 1.13)	0.224	0.69 (0.49, 0.97)	0.033
Bai	492 (99.19)	4 (0.81)	0.45 (0.17, 1.21)	0.115	0.42 (0.16, 1.13)	0.083
Mongolian	331 (98.22)	6 (1.78)	1.01 (0.45, 2.26)	0.982	1.11 (0.49, 2.49)	0.803
Other*	274 (98.21)	5 (1.79)	1.02 (0.42, 2.46)	0.972	1.22 (0.50, 2.98)	0.660
Sex						
Female	82,847 (98.54)	1,230 (1.46)	1.00		1.00	
Male	218,614 (98.13)	4,169 (1.87)	1.28 (1.20, 1.37)	<0.0001	1.17 (1.10, 1.25)	<0.0001
Age (mean, years)	51.4	58.4	1.02 (1.02, 1.03)	<0.0001	1.02 (1.02, 1.02)	<0.0001
Occupation						
Comm services/civil servant	7,384 (98.73)	95 (1.27)	1.00		1.00	
Agriculture	235,774 (98.14)	4,461 (1.86)	1.47 (1.20, 1.80)	<0.0001	1.04 (0.84, 1.29)	0.707
At home[a]	28,618 (98.20)	526 (1.80)	1.43 (1.15, 1.78)	0.001	0.99 (0.79, 1.24)	0.917
Education	10,263 (99.25)	78 (0.75)	0.59 (0.44, 0.80)	0.001	0.98 (0.72, 1.33)	0.878
Migrant worker	2,506 (99.01)	25 (0.99)	0.78 (0.50, 1.21)	0.260	0.74 (0.48, 1.17)	0.196
Healthcare	956 (99.38)	6 (0.62)	0.49 (0.21, 1.12)	0.089	0.57 (0.25, 1.31)	0.186
Hospitality	575 (98.12)	11 (1.88)	1.49 (0.79, 2.79)	0.217	1.74 (0.91, 3.31)	0.093
Other	15,385 (98.74)	197 (1.26)	1.00 (0.78, 1.27)	0.970	0.91 (0.71, 1.17)	0.473
Year						
2013	53,660 (98.38)	886 (1.62)	1.00		1.00	
2014	53,501 (98.37)	886 (1.63)	1.00 (0.91, 1.10)	0.951	1.01 (0.92, 1.12)	0.768
2015	53,051 (98.47)	824 (1.53)	0.94 (0.85, 1.04)	0.210	0.97 (0.88, 1.07)	0.526
2016	47,634 (98.26)	842 (1.74)	1.07 (0.97, 1.18)	0.160	1.12 (1.02, 1.23)	0.022
2017	47,407 (98.20)	869 (1.80)	1.11 (1.01, 1.22)	0.030	1.12 (1.02, 1.23)	0.022
2018	46,208 (97.69)	1,092 (2.31)	1.43 (1.31, 1.57)	<0.0001	1.43 (1.31, 1.57)	<0.0001
Residential address						
Local	293,564 (98.23)	5,280 (1.77)	1.00		1.00	
Intra-provincial	5,808 (98.51)	88 (1.49)	0.84 (0.68, 1.04)	0.113	0.92 (0.74, 1.15)	0.467
Inter-provincial	2,040 (98.50)	31 (1.5)	0.84 (0.59, 1.21)	0.353	1.16 (0.80, 1.66)	0.434
Foreign nationality	49 (100)	–	–	–	–	–
Severely ill						
No	290, 085 (98.28)	5,087 (1.72)	1.00		1.00	
Yes	11,376 (97.33)	312 (2.67)	1.56 (1.39, 1.76)	<0.0001	1.50 (1.33, 1.70)	<0.0001
History of TB treatment						
No	289,756 (98.41)	4,683 (1.59)	1.00		1.00	
Yes	11,705 (94.24)	716 (5.76)	3.78 (3.49, 4.10)	<0.0001	2.93 (2.69, 3.20)	<0.0001
Treatment management						
Full course management	40,860 (98.74)	521 (1.26)	1.00		1.00	

(Continues)

TABLE 3 (Continued)

Risk factor for n TB treatment outcome	TB treatment outcome: No Successful (%)	TB treatment outcome: No. Unsuccessful (%)	Univariable estimate	Univariable *p* value	Multivariable estimate	Multivariable *p* value
Full process supervision	174,865 (98.06)	3,460 (1.94)	1.55 (1.41, 1.70)	<0.0001	1.51 (1.37, 1.66)	<0.0001
Intensive phase supervision	82,194 (98.43)	1,312 (1.57)	1.25 (1.13, 1.39)	<0.0001	1.39 (1.26, 1.55)	<0.0001
Self-administered medication	2,882 (97.56)	72 (2.44)	1.96 (1.53, 2.51)	<0.0001	1.98 (1.53, 2.55)	<0.0001
Systematic management						
Yes	299,075 (98.40)	4,849 (1.60)	1.00		1.00	
No	2,386 (81.27)	550 (18.73)	14.21 (12.90, 15.66)	<0.0001	16.10 (14.49, 17.88)	<0.0001

Note: 'Registration category' has been excluded from the regression analysis due to multicollinearity with the variable 'History of TB treatment'.

Patients with a residential address of 'foreign nationality' have been excluded from the regression analysis as no patients within this category had an unsuccessful treatment outcome.

*Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu,Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups.

[a]At home = housekeeping, childcare, retired, un-employed.

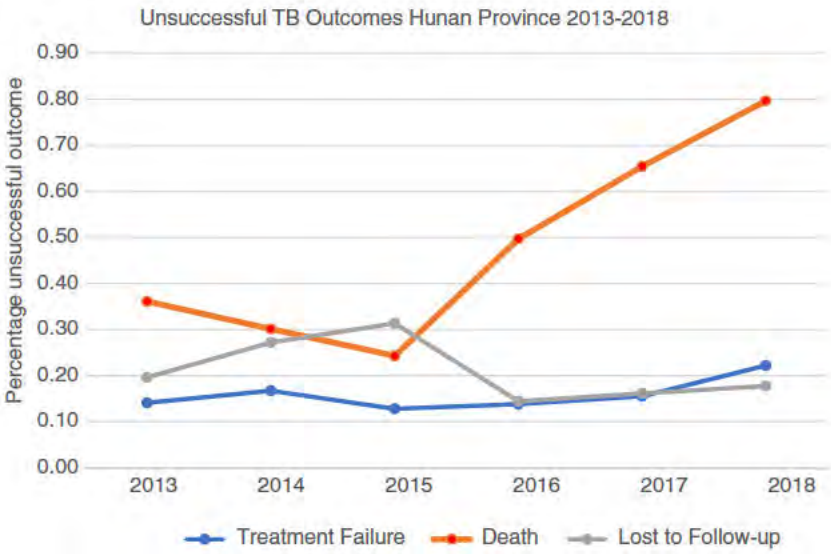

FIGURE 2 Unsuccessful TB treatment outcomes Hunan Province 2013–2018

include immunological, socio-cultural and clinical factors [30,34–36]. Socio-cultural factors are complex and varied, and clinical factors are patient-specific, highlighting the need for detailed data to determine and address the underlying causes. Patient specific data on clinical factors, for example, co-morbidities may also be of value in identifying the underlying causes of age as a risk factor [37,38]. As a result of China's aging demographic, diabetes, which is associated with unsuccessful TB treatment outcomes, is becoming significantly more prevalent [39,40]. Although China has a policy of treating HIV patients at separate institutions, screening for and clinical management of confounders such as diabetes may be of benefit in improving TB treatment outcomes [40,41].

For the patient population in this study, systematic and full process treatment management were associated with more favourable treatment outcomes and as such these treatment regimens are recommended where resources allow. Directly Observed Treatment, Short-course (DOTS) continues to be key to the WHOs Stop TB Strategy [42], a component of which includes the direct observation of drug intake [43]. The significant reduction in TB prevalence that has been achieved in China is primarily attributed to the implementation of DOTS [44,45]. There is, however, debate in the literature on how much credit should be attributed to DOTS and to what extent other factors are responsible [46,47]. This raises the question of which strategies and interventions are really achieving the most resource-effective outcomes [47].

The same is true of the conclusions drawn from this study. Are the risk factors themselves responsible for unsuccessful treatment outcomes or are confounders such as comorbidities, malnutrition, substance abuse, underlying causes of unsuccessful treatment outcomes? This ambiguity highlights the need for access to detailed data if TB control programs are going to succeed in reducing the personal and societal burden of this disease.

A limitation of this study is the lack of detailed data that would have allowed potential confounders (e.g. diabetes mellitus, substance abuse) to be interrogated. However, the large size of the patient cohort is a significant strength. Despite the large cohort, it is acknowledged that these data may not be representative of Hunan's total TB patient population. Although TB reporting is mandatory in China, there may be potential under-reporting [48]. Patients may also seek care from traditional healers and therefore not be captured in the database [49].

CONCLUSION

This study found that demographic (e.g. sex, age) and clinical factors (e.g. year of patient registration, illness severity, history of TB treatment and management regime) were significantly associated with unsuccessful TB treatment outcomes. The underlying causes of the demographic and clinical risk factors need to be interrogated so that effective strategies can be implemented to achieve the End TB Strategy. Consideration is required on data requirements to maximise the efficacy of TB control programmes. Both TB programmes and their associated data requirements need to evolve as the disease and confounders change over time.

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Part IV Discussion and conclusion

Chapter VIII Study findings and considerations

HIV, TB, malaria, and STH disease burden and SDG objectives

In 2019, the WHO estimated the global burden of HIV, TB and malaria represented the loss of 139.6 million DALYs.[132] The burden of STH infection is included in diarrhoeal diseases, that collectively, were the fifth-leading cause of DALY loss in 2019.[132] HIV, TB, malaria, and STH infections are endemic in developing countries and have their greatest impact on marginalized and disadvantaged populations.[133] HIV, TB, malaria and STH infection are diseases of poverty, which in addition to income disadvantage is defined by capability and optimization deprivation.[133] These infectious diseases fuel the poverty cycle and exacerbate disadvantage.[134] Although significant improvement has been made in reducing the burden of these diseases in recent times, there are new and emerging threats to progress including multidrug resistance, new pandemics i.e., COVID-19 and climate change.[135-137] These new and emerging threats also have a disproportionate impact on those populations most vulnerable within society.[138-140]

In 2015, the United Nation Member States adopted the 2030 Agenda for Sustainable Development, an ambitious program that seeks to eradicate poverty in all its dimensions.[2] Within the goals and targets of this agenda, SDG 3.3 aims to end the epidemics of AIDS, TB, malaria and NTDs by 2030.[2] To achieve this goal, inequities must be understood and appropriate interventions implemented.[3] Within identified inequalities, it is important to distinguish and understand the differences that are attributable to host and pathogen biology, those that are a function of socio-economic and political factors and those that result from the healthcare system.[3] Minority ethnic indigenous people were chosen as the subjects of this study because they can face a myriad of inequities and a disproportionate burden of numerous diseases.[7 141 142] Although these populations are recognized as vulnerable, they are not typically represented as a collective in infectious disease analyses.

The prevalence of HIV, TB, malaria, and STH infections within different populations of the SEAR and WPR

Through a series of systematic reviews, part II of this study sought to evaluate the prevalence of HIV, TB, malaria, and STH infection within indigenous ethnic minority populations of the SEAR and WPR and undertake parallel analyses where comparative population data were available. Across all diseases of interest, with the exception of TB, the prevalence of infection was higher in indigenous ethnic minorities compared to other populations.

Chapter III evaluates HIV prevalence and shows infection to be higher in indigenous ethnic minorities than comparative populations with the differential significant in the WPR. The observed differential in infection risk is consistent with other studies, with research showing colonization has created marginalization and resulted in behaviours that increase indigenous peoples vulnerabilities to HIV infection.[143 144]

The results of chapter IV show that only a small number of studies undertook TB and malaria prevalence surveys across comparative population groups. On the basis of the studies available within the SEAR and WPR, no difference in TB prevalence was observed between indigenous ethnic minorities and other population groups. Results from another global systematic review of TB prevalence, found indigenous people have a higher burden of infection than comparative populations, but the review found no differential for select indigenous populations in South-East Asia and Africa.[124] These findings align with our results, as three of the four comparative TB studies analyzed were undertaken in the SEAR. Results from the global systematic review show the burden of TB on indigenous people of the SEAR to be variable over time.[124] Other research shows the importance of time, as indigenous people are at an increased risk of TB when transitioning to a more modern lifestyle.[145] The TB surveys eligible for inclusion in our systematic review were dated, highlighting the need for more current information on these populations.

As detailed in chapter IV only a small number of comparative population surveys were available on malaria, with results showing indigenous ethnic minority populations to be at greater risk of infection (although the risk was marginally not

significant). These findings agree with results from other studies,[146] and reflect the increased risk associated with the environments that indigenous people inhabit.[147]

As detailed in Chapter VI, the prevalence of infection across all species of STH was found to be higher in indigenous ethnic minorities than in comparative populations, although the differentials were not statistically significant. While our review identified a high prevalence of STH infections within indigenous ethnic minorities, the results are likely to be an under-estimate due to the low sensitivity of the diagnostic methods used and the cultural barriers within these populations to serial faecal sampling.[148-150]

The limited data available for comparative population analyses identified by the systematic reviews, supports calls for routine data disaggregation by race, ethnicity, indigenous, and minority status.[151-153] Although disaggregated data collection is fraught with difficulties e.g., data privacy, fear of exposing complex issues, definition complexities and perceived intent,[154 155] it is essential to understanding health disparities.[151]

HIV, TB, malaria, and STH prevalence data availability for indigenous ethnic minority populations of the SEAR and WPR

Across all diseases of interest, there was a paucity of data for indigenous ethnic minority populations within the SEAR and WPR, even in countries that are classified as carrying a high burden of disease. Results showed a noticeable variation in the countries that were over or underrepresented in the data, and this varied according to the disease of interest.

In 2015, the WHO attributed 10% of the global HIV burden to the SEAR, with five countries - India, Indonesia, Myanmar, Nepal, and Thailand - estimated to carry 99% of this burden.[156] The WHO estimates that India carries 60% of the SEAR HIV burden,[156] however, our systematic review only identified two studies within India's indigenous ethnic minority populations, highlighting the need for more data within these vulnerable populations.

Although HIV prevalence within the general population of the WPR is low, the WHO note that this is masking a growing epidemic in key populations that face stigma and discrimination and who fail to equitably access prevention and treatment services.[157] Of the 27 countries within the WPR, our systematic review identified studies on indigenous ethnic minority populations from three countries, with China representing 86% of the studies in this region.

In 2020, the SEAR was estimated to carry 43% of the global burden of TB and to include six high TB burden countries - Bangladesh, Democratic People's Republic of Korea, India, Indonesia, Myanmar, and Thailand.[125 158] Despite the high burden of disease in this region, our systematic review only identified TB surveys for indigenous ethnic minority populations from one country - India.

In 2020, there were three countries within the WPR classified as carrying a high burden of TB- China, the Philippines and Vietnam, with China carrying the second highest burden globally.[64 125] For indigenous ethnic minority populations however, our systematic review identified surveys from only 3 countries within the WPR- none of which are currently classified as high burden.

The SEAR carries the second greatest burden of malaria, and in 2020 nine countries in the region were classified as being endemic.[84] Within the systematic review, the majority of studies were undertaken in India which in 2020 accounted for 83% of cases within the region.[84] However, very limited data were available for the other malaria-endemic countries in the region.

In 2020, eight countries within the WPR reported cases of human malaria, with Papua New Guinea accounting for 86% of cases.[84] Although Malaysia was certified as 'malaria free' in 2018, the classification is based on human transmission and does not take into account zoonotic infections, which are increasing.[84 159] Within the systematic review, the prevalence of *P. knowlesi* was high amongst indigenous ethnic minority populations, a finding that supports calls for zoonotic species to be considered in public health policy.[160]

The systematic review on the pooled prevalence of STH infection in indigenous ethnic minority populations of the SEAR and WPR identified data from ten countries, with Malaysia representing 61% of the studies. Comparative cumulative data to quantify the burden of STH infections across countries and regions were not available. The lack of accurate epidemiological data is a reflection of the non-specificity of clinical signs of STH infection, the intermittent shedding of larvae or eggs and the low sensitivity of conventional methods of diagnosis.[161 162]

Although the systematic reviews identified a paucity of data for indigenous ethnic minority populations, where data were available, there was shown to be large and significant heterogeneity between survey results for all diseases of interest. To understand the underlying causes of this heterogeneity, community-specific data will be required and will be key to ensuring that interventions are appropriate and effective.

Trends in HIV, TB, malaria, and STH infections in indigenous ethnic minority populations of the SEAR and WPR

The systematic reviews provided an opportunity to evaluate HIV, TB, malaria, and STH infection prevalence within indigenous ethnic minority populations of the SEAR and WPR over time. Within these populations, no significant reduction in infection prevalence was observed over time for any of the diseases of interest.

Within the HIV review however, a significant reduction in disease prevalence across the years of data collection was observed for comparative populations. The underlying reason for this finding warrants further research - is health education failing minority indigenous ethnic populations?

Contrary to an improvement in infection prevalence, the STH review identified a significant increase in *T. trichiura* prevalence in indigenous ethnic minority populations. The increasing trend in *T. trichiura* prevalence that was identified may correlate with the low and reducing efficacy profile of anthelmintics available against this species of STH and the calls for more effective treatment regimes.[117]

The systematic reviews also provided an opportunity to evaluate HIV, TB, malaria, and STH infection prevalence within indigenous ethnic minority populations that reside in countries across a broad spectrum of economic development. Although research shows that indigenous populations of low-income countries have poorer health outcomes in absolute terms, differences relative to benchmark populations are highly variable across countries of all income classifications.[163] The STH review showed there to be no significant difference in infection prevalence between indigenous ethnic minorities of Australia, India, Malaysia, and the Philippines. The lack of difference in STH infection between countries on a spectrum of economic development supports the call to prioritize neglected populations in the fight to end NTDs and acknowledge that this is a global issue, not one limited to developing nations.[164 165]

Risk factors associated with TB diagnosis and treatment delays and unsuccessful treatment outcomes in Hunan Province, China

Across the myriad of socio-economic and political inequities that contribute to poorer health outcomes, the complexities and interactions are disease, population, and time specific. Part III of this study evaluated indigenous ethnic minority status as a risk factor in time to diagnosis and treatment, and in treatment outcomes in DS-TB patients treated in Hunan Province, China between 2013 and 2018.

Early case detection and prompt and appropriate treatment are fundamental to the success of TB control programs, as delays lead to disease progression, poor treatment outcomes and an increased risk of transmission.[70 75] Chapter VI of this study found indigenous ethnic minority populations to have significantly longer TB diagnosis delays than the reference Han majority. Further research is required to determine the underlying reasons for this finding. Previous research has identified poverty, socio-economic disadvantage, knowledge, cultural beliefs, language, literacy and distance and cultural barriers to health care provision, as risk factors for TB diagnosis and treatment delays. [166-169] Additional socio-economic and cultural patient data are required to elucidate the longer diagnosis delays experienced by indigenous ethnic minorities in Hunan province. The underlying reasons for the variations in diagnosis

delays that were observed between indigenous ethnic minority groups, also need to be understood to ensure that interventions are appropriate and effective.

Chapter VI of this study found indigenous ethnic minorities to have lower odds of treatment delay relative to the Han majority, - a finding that also requires further data and research to explain. These findings suggest there is an opportunity to reduce treatment delay for the majority population. A possible hypothesis linking diagnosis and treatment delay within minority populations, is that the delay in diagnosis results in disease progression thereby leading to prompter treatment. Alternatively, the results may reflect an opportunity to improve patient health-seeking behaviour and reflect the successes of prioritizing vulnerable populations within Hunan's healthcare system.

Key to curing TB, preventing onward transmission and the development of drug resistance, is successful treatment.[46] Part VII of this study evaluated the risk factors associated with unsuccessful outcomes in patients treated for DS-TB in Hunan Province, China between 2013 and 2018. An unsuccessful treatment outcome was defined as the sum of treatment failure, death, and loss to follow-up. Although other studies have shown ethnicity to be an independent risk factor for unsuccessful treatment outcomes,[170] it was not found to be a significant predictor in the Hunan patient population studied. Other variables that were found to be significant in the Hunan population e.g., male sex, previous treatment, unsupervised treatment administration and increasing age, align with the findings of previous studies.[171 172] These findings can be used to guide risk assessment and sub-group patient stratification.

Within the Hunan TB patient population, the odds of an unsuccessful treatment outcome showed an increasing trend in more recent years of registration, with increasing mortality being the underlying metric responsible for these results. Further research is required to elucidate whether this increase in mortality is related to an increasing prevalence of MDR-TB or whether it relates to other factors such as disease severity, age, or co-morbidities. A recent study showed there to be a significant increase in the incidence of DR-TB notifications in Hunan Province, with rates increasing from 0.25 per 100,000 population in 2012 to 0.83 per 100,000

population in 2018.[173] In addition to evaluating the underlying reasons for the observed increase in mortality, is the need to analyze data subsequent to 2018 to determine the trajectory of unsuccessful treatment outcomes.

Study results and the SDGs

To explain and address the underlying causes for the results identified in Parts II and III of this study, further research and detailed linked health, socio-economic and cultural data will be required.

Social determinants of health (SDH), defined as the conditions into which people are born and live and which are shaped by economic and social policy, account for an estimated 30-55% of health outcomes.[174] Vulnerable populations are often disadvantaged across SDH metrics e.g., education, employment, income, food security, housing and sanitation, social inclusion and access to healthcare.[174] Indigenous ethnic minorities as a collective are an example of a vulnerable population disadvantaged across the SDH metrics, but the heterogeneity between and within populations needs to be taken into consideration to effectively address inequality.

The collection of linked, comorbidity and health-related risk factor data, would also help combat HIV and TB.[175] Examples of data that would be of value in combating these diseases include concurrent HIV/TB, diabetes, malnutrition, tobacco and substance abuse, status and information on mental health.[175] [176]

To address the health inequities of minority populations, genuine intercultural solutions will be required.[177] For indigenous people, health and wellbeing is a holistic concept that includes physical, cultural, social, emotional, and spiritual wellbeing and is applicable to both the individual and the community.[178] For these people, physical and spiritual wellbeing are inextricably linked to the land in which they live or from which they have been displaced.[6] If we are going to achieve the SDGs, dominant cultures need to respect and take into consideration the nuances and complexities of indigenous belief systems across socio-economic and political policy. Ironically the West finds itself in a position where it is trying to address the

issues that are a result of its culture and actions. The West has coined terms such as sustainability and equity, but these are values that have been fundamental to indigenous cultures for centuries.[179] Indigenous culture, knowledge, tradition and beliefs will be key to achieving the SDGs.

Strengths and limitations

This PhD thesis comprehensively quantified the burden of major infectious diseases (i.e., HIV, TB, malaria, and STH) in indigenous ethnic minority peoples of the Asia Pacific region. The systematic reviews detailed in Part II of this study provide a summary of the available evidence and provide an opportunity to identify information gaps. The systematic reviews provided an opportunity to evaluate the prevalence of HIV, TB, malaria, and STH infection in indigenous ethnic minorities as a collective. The SEAR and WPRs were chosen, as the majority of the world's indigenous ethnic minority populations occupy these regions. The PRISMA process and pre-defined published protocol that were followed, provides transparency in methods at each stage of the synthesis process.

The inherent limitations of the systematic review process are however noted, including the use of secondary data and publication bias. The accuracy of estimating disease prevalence may be impacted by the inclusion of small study populations and the reviews did not take into consideration the effect of treatment and intervention regimes which may impact infection prevalence over time. Although the reviews specified criteria to describe the population group of interest, there is no universal definition for indigenous and some countries e.g., China do not recognise the term indigenous and classify their population according to ethnicity. The study tried to address this lack of definition by analysing minority populations indigenous to their country of origin and including search terms relative to each country's classification system. The lack of a globally accepted and applied term to differentiate the population group of interest is a limitation. Due to resource constraints, data extraction was limited to articles published in English. A lack of data limited the ability to undertake age-related prevalence analyses that could benefit subsequent intervention designs

Part III of this study evaluated population status as a risk factor across the TB health-care continuum. The large, detailed data set on a well-described cohort of patients that was analyzed within Part III, is considered a significant strength. It is acknowledged however that these data may not be representative of Hunan's total TB patient population, as they only represent patients presenting for treatment at designated institutions. Although TB reporting is mandatory in China, there is potential for under-reporting, in addition to which, patients may seek healthcare from traditional healers and so not be captured in the system.

A limitation of Part III of this study is the lack of detailed data that would have allowed the potential confounders of findings to be interrogated. Examples of such data include income and level of education for the analysis of diagnosis and treatment delay and diabetes mellitus and substance abuse for the analysis of risk factors associated with unsuccessful treatment outcomes. The study on diagnosis and treatment delay was reliant upon the patient for the date of symptom onset from which subsequent delays were calculated. Recall bias on the date of symptom onset therefore has the potential to impact subsequent findings.

Recommendations

Future research recommendations

- Current prevalence data are required for the diseases of interest within ethnic indigenous minority populations, especially in countries that report a high burden of infection.
- The underlying reasons to explain why HIV infection prevalence in indigenous ethnic minority populations has not reduced over time should be identified.
- The underlying reasons to explain the increasing trend in *T. trichuris* infection prevalence in indigenous ethnic minority populations should be identified.
- The underlying reasons to explain the longer TB diagnosis delays experienced by indigenous ethnic minorities in Hunan Province, China should be identified.
- Opportunities to reduce treatment delay in the Han majority population in Hunan Province, China should be identified.
- The reasons for the increasing trend in mortality within unsuccessful TB treatment outcomes in Hunan Province, China, should be identified.
- Analyse diagnosis and treatment delay, and treatment outcome data, for DS-TB patients treated within Hunan province, China post 2018.

Policy recommendations

- That health, socio-economic and cultural data are routinely disaggregated by ethnicity/minority/indigenous status.
- Disease infection records are linked to co-morbidity and health risk factor data.
- Public health policy takes into consideration the impact of zoonotic *Plasmodium* spp.
- All countries, across the spectrum of economic development, need to prioritize indigenous health and address the inequities that are creating a greater burden of disease within these vulnerable populations.

Conclusions

The results of our systematic reviews showed a paucity of data on the prevalence of HIV, TB, malaria, and STH infection in indigenous ethnic minority populations of the SEAR and WPR. For HIV, TB, and malaria there was a lack of data for these populations in countries that are classified as carrying a high burden of infection. Conversely, the classification of a country's malaria status on the basis of human transmission is failing to acknowledge the impact of zoonotic *Plasmodium* spp. on these populations. Across all diseases of interest, where data were available, significant heterogeneity between studies was observed. Although it may be argued that pooled prevalence is not an appropriate measure where heterogeneity is significant, this measure provides an opportunity to evaluate these populations as a collective, which has not previously been undertaken. Although the extent of statistical significance varied, analyses across comparative populations showed the prevalence of HIV, malaria, and STH to be higher in indigenous ethnic minority populations. Results showed that indigenous ethnic minority populations failed to experience a reduction in infection prevalence over time for any of the diseases of interest. Contrary to an improvement, these populations demonstrated an increasing prevalence of *T. trichiura* infection. When comparing STH prevalence between countries, our study found that a country's advanced economic status does not confer its indigenous ethnic minorities any advantage.

Part III of this study evaluated indigenous ethnic minority status as a risk factor along the health-care continuum within a DS-TB patient population registered in Hunan Province, China between 2013 and 2018. Results showed indigenous ethnic minority status to be a significant risk factor for diagnosis delay but for it to confer an advantage relative to the Han majority population for treatment delay. Ethnicity was not found to be an independent risk factor for unsuccessful treatment outcomes in the Hunan patient population. The 2013-2018 Hunan patient population did however show an increasing trend in the odds of an unsuccessful treatment outcome over time.

Additional data and research will be required to identify the underlying causes for the findings within this study. The paucity of data for indigenous ethnic minorities across

the diseases of interest highlights the need for further data. To identify health disparities and implement appropriate interventions, data will need to be accurate, current, detailed, disaggregated, and linked. If the SDGs are to be achieved, focus must be given to vulnerable populations and the concept of equity. If inequities are to be addressed the values inherent to indigenous culture need to be embraced to address the marginalization that has resulted from colonization and global policy.

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Appendix 1: Authorship attribution tables

The following tables summarize the authorship roles within the publications included in this thesis.

Paper I: ***The prevalence of HIV infection in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis.***						
Authors	**Conception & design**	**Acquisition of data & method**	**Data conditioning & manipulation**	**Analysis & statistical method**	**Interpretation & discussion**	**Final approval**
Gilmour B	x	x	x	x	x	x
Co Author 1 Acknowledgement: I acknowledge that these represent my contribution to the above research output. Signed: [redacted]						
Alene KA	x			x	x	x
Co Author 2 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Atalell KA		x				x
Co Author 3 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Clements ACA	x				x	x
Co Author 4 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						

Paper II: The prevalence of TB, malaria & STH infection in minority indigenous people of SEAR and WPR: protocol for a systematic review and meta-analysis						
Authors	**Conception & design**	**Acquisition of data & method**	**Data conditioning & manipulation**	**Analysis & statistical method**	**Interpretation & discussion**	**Final approval**
Gilmour B	x	N.A.	N.A.	N.A.	x	x
Co Author 1 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Alene K.A.	x	N.A.	N.A.	N.A.	x	x
Co Author 2 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Clarke N		N.A.	N.A.	N.A.	x	x
Co Author 3 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Clements ACA	x	N.A.	N.A.	N.A.	x	x
Co Author 4 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						

Paper III: ***The prevalence of TB & malaria in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis.***						
Authors	**Conception & design**	**Acquisition of data & method**	**Data conditioning & manipulation**	**Analysis & statistical method**	**Interpretation & discussion**	**Final approval**
Gilmour B	x	x	x	x	x	x
Co Author 1 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Alene K.A.	x			x	x	x
Co Author 2 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Clements ACA	x				x	x
Co Author 3 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						

Paper IV: ***The prevalence of STH infections in minority indigenous populations of SEAR and WPR- a systematic review and meta-analysis.***						
Authors	**Conception & design**	**Acquisition of data & method**	**Data conditioning & manipulation**	**Analysis & statistical method**	**Interpretation & discussion**	**Final approval**
Gilmour B	x	x	x	x	x	x
Co Author 1 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Alene K.A.	x			x	x	x
Co Author 2 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Clements ACA	x				x	x
Co Author Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						

Paper V: The impact of ethnic minority status on tuberculosis diagnosis & treatment delays in Hunan Province, China						
Authors	**Conception & design**	**Acquisition of data & method**	**Data conditioning & manipulation**	**Analysis & statistical method**	**Interpretation & discussion**	**Final approval**
Gilmour B	x	x	x	x	x	x
Co Author 1 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Xu Z		x			x	x
Co Author 2 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Bai L		x				x
Co Author 3 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Alene K.A.	x	x		x	x	x
Co Author 4 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Clements ACA	x				x	x
Co Author 5 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						

Paper VI: Risk factors associated with poor tuberculosis treatment outcomes in Hunan Province, China						
Authors	**Conception & design**	**Acquisition of data & method**	**Data conditioning & manipulation**	**Analysis & statistical method**	**Interpretation & discussion**	**Final approval**
Gilmour B	x	x	x	x	x	x
Co Author 1 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Xu Z		x			x	x
Co Author 2 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Bai L		x				x
Co Author 3 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Alene K.A.	x	x		x	x	x
Co Author 4 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						
Clements ACA	x				x	x
Co Author 5 Acknowledgement: I acknowledge that these represent my contribution to the above research output Signed: [redacted]						

PRISMA Checklist (1)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary data "search strategy"
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for	8-9

results		each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supplementary Data Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary data: Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figs 1 + 2 Supplementary Data Fig 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2 +5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Data: Fig 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3,4 +5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Supplementary Data: Systematic review search terms

Each search comprised:

A. country **AND**
B. HIV terms **AND**
C. generic and country relevant indigenous terms

A. Countries

The WHO Global Burden of Disease (GBD) regional classification system (2) was used to define the countries located within the SEAR and WPR.

SEAR Category B [#]	SEAR Category D [#]
Indonesia	Bangladesh
Sri Lanka	Bhutan
Thailand	Korea, Democratic People's Republic of
	India
	Maldives
	Myanmar
	Nepal
	Timor-Leste

WPR Category A [#]	WPR Category B [#]
Australia	Cambodia
Brunei	China
Japan	Cook Islands
New Zealand	Fiji
Singapore*	Kiribati
	Korea, Republic of
	Lao
	Malaysia
	Marshall Islands
	Micronesia
	Mongolia
	Nauru
	Niue
	Palau
	Papua New Guinea
	Philippines
	Samoa
	Solomon Islands
	Tonga
	Tuvalu
	Vanuatu
	Vietnam

* Singapore was omitted from the search as there are no minority indigenous populations according to the classification criteria used in this review.

[#] Countries are classified according to mortality strata(3)

Mortality Stratum Category A: very low child, very low adult mortality

Mortality Stratum Category B: low child, low adult mortality

Mortality Stratum Category C: Low child, high adult mortality (there are no Category C countries within the SEAR and WPR)

Mortality Stratum Category D: high child, high adult mortality

Mortality Stratum Category E: High child, very high adult mortality (there are no Category E countries within the SEAR and WPR).

B. HIV Terms

"*human immunodeficiency virus*" OR *HIV* OR "*acquired immunodeficiency syndrome"* OR *AIDS*

C. Country Relevant Indigenous Terms

In addition to generic indigenous search terms, those relevant to each country were included. The country specific search terms were derived from the International Working Group on Indigenous Affairs(4), Native Planet- Indigenous Mapping(5), and the World Directory Listing of Minorities and Indigenous People(6). If indigenous minority study populations were not identified according to the search criteria list, but the author identified them as such, they were included within the analysis.

INDONESIA: SEAR B
Indigenous OR aborigin* OR native OR first nation* OR "ethnic group" OR tribal OR tribe OR autochthonous OR "adat terpencil" OR Acehnese OR Achinese OR Atjeher OR "Orang Aceh" OR Acehnais OR Acehno OR Atjeh OR Atjehnese OR Achehnese OR Achenese OR Adabe OR Ataura OR Atauru OR Atauro OR Raklu-Un OR "Raklu Un" OR Adonara OR "Tusa Tadon" OR Waiwerang OR Vaiverang OR Sagu OR Alorese OR Ampanang OR Andio OR Masama OR Andio'o OR Imbao'o OR Aralle OR Tabulahan OR Asmat OR Asamat OR Asemer OR Asomat OR Bagusa OR "Batak Alas-Kluet" OR "Alas-Kluet Batak" OR "Batak Kluet-Alas" OR "Kluet-Alas Batak" OR "Alas Kluet" OR "Kluet Alas" OR Alas OR Kluet OR "Batak Angkola" OR "Orang Angkola" OR Anakola OR Angkola OR "Batak Dairi" OR Dairi OR "Dairi Batak" OR "Orang Batak Dairi" OR Pakpak OR "Pakpak Dairi" OR Sumut OR "Batak Karo" OR "Karo Batak" OR "Orang Batak Karo" OR Karonese OR "Batak Mandailing" OR "Mandailing Batak" OR Batta OR "Orang Mandailing" OR "Batak Simalungun" OR "Simalungun Batak" OR "Orang Batak Simalungun" OR Simelungun OR Simelungan OR Timur OR "Batak Toba" OR "Toba Batak" OR "Orang Batak Toba" OR "Silindung Batak" OR Bauzi OR Baudi OR Bauri OR Baudji OR Baudzi OR Damal OR Uhunduni OR Amung OR "Amung Kal" OR Amungme OR Amuy OR Enggipiloe OR Hamung OR Oehoendoeni OR Dani OR Gayo OR "Orang Gayo" OR Gayonese OR Ketengban OR Kupel OR Oktengban OR Kombai OR Komboy OR Kubu OR Djambi OR "Orang Darat" OR Mentawai OR Mentawei OR Mentawi OR Minangkabau OR Minang OR Padang OR "Orang Minangkabau" OR Moni OR Migani OR Djonggunu OR Jonggunu OR Moronene OR Maronene OR Nias OR Batu OR Nuaulu OR "Southern Nuaulu" OR "Northern Nuaulu" OR Rejang OR "Keme Tun Djang" OR "Orang Rejang" OR Djang OR "Tun Djang" OR "Redjang Empat Petulai" OR "Djang Lebong" OR "Djang Bele Tebo" OR "Djang Musai" OR "Djang Lai" OR "Djang Bekulau" OR "Djang Abeus" OR "Djang Aweus" OR "Bang

Hadji" OR Semitul OR Sawang OR Selako OR "Selako Dayak" OR Selakau OR Salakau OR Salako OR Silakau OR Tamiang OR Malayu OR Wandamen OR Wandamen-Windesi OR Windesi OR Windessi OR Bintuni OR Bentuni OR Bentoeni OR Wamesa OR Wolio OR Buton OR Butonese OR Walio

"SRI LANKA" OR CEYLON: SEAR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR "Ceylon Tamils" OR "Jaffna Tamils" OR "Indian Tamils" or "Estate Tamils" OR "Sri Lankan Moors" OR Burghers OR "Sri Lankan Chetty" OR Bharatha OR Wanniyala-Aetto OR Veddhas OR Sinhalese OR Tamil OR Wanniya-laeto OR Vedda OR Veddha OR Veddah OR Wanniyala-Aetto

THAILAND: SEAR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Akha OR Hmong OR Karen OR Lahu OR Lisu OR Mein OR Mon OR "Khmer Thai Isan" OR "Thai Lao" OR Khmer OR Kaw OR Bisu OR Mbi OR Mbisu OR Mibisu OR Misu OR "Hmong Daw" OR "White Meo" OR "White Hmong" OR "Hmong Njua" OR "Black Meo" OR "Blue Meo" OR H'tin OR T'in OR Ht'in OR Thin OR Tin OR Khatin OR Isan OR Lao OR Isaan OR Issan OR Esarn OR Karen S'gaw OR Khmu OR Khamu OR Kammu OR Kui OR Kuoy OR Kuy OR Suoy OR Suay OR Suai OR Lahu OR Musser OR Lisu OR Lisaw OR "lu Mien" OR Mien OR Yao OR "Yui Mien" OR Mani OR Manik OR Maniq OR Negrito OR Mannee OR Mlabri OR "Phi Tong Luang" OR Moken OR Salong OR Selung OR Salone OR "Sea Gypsy" OR Moklen OR "Chao Lay" OR Palaung OR "Silver Palaung" OR "Pale Palaung" OR Bulay OR Dlang OR Palay OR Palong OR Pulei OR Shwe OR Ta'ang OR "Tai Lue" OR "Dai Lue" OR "Urak Lawoi*" OR "Chao Lay" OR "Lumoh Lawoi" OR "Sea Gypsies" OR "Thai Mai" OR "Chao thale" OR "Chao khao" OR "Chon phao" OR "Chon phao mueang"

BANGLADESH: SEAR D

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Adivasis OR Jumma OR Chakmas OR Marma OR Tripura OR Mro OR Biharis OR Chakma OR Takam OR Chakama OR Tsakma OR Changma OR "Changma Vaj" OR "Changma Kodha" OR Chin OR Khumi OR Khumi OR Khami OR Kami OR Kumi OR Khweymi OR Khuni OR Darlong OR Dalong OR Zo OR Garo OR A'Chik OR Mande OR Mandi OR Lamdani OR Achchik OR Acchiks OR Achik OR Oraon OR Uraon OR Khurukh

BHUTAN: SEAR D

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Lhotshampas OR Chali OR Dakpa OR Sagtengpa OR Brokpa OR Brokkat OR Layap OR Lepcha OR Rong OR Rongke OR Rongpa OR Lhop OR Doya OR Lhokpu OR Lhops OR Lhopu OR Lhotshampas OR Gurkhali OR Nepali OR Paharia OR "Southern Bhutanese" OR Monpa OR Menba OR Moinba OR Monba OR Menpa OR Mongba OR Ngalop OR Bhote OR Sharchop OR Schachop OR Bhotia OR "Central Monba" OR "Cuona Monba" OR Memba OR Sarchapkkha OR "Southern Moonba" OR Tshalingpa OR "Bhotia Eastern" OR "Cona Monba" OR "Eastern Bhutanese" OR Mompa OR Sangla OR Sharchagpakha OR Tsangla

"DEMOCRATIC PEOPLE'S REPUBLIC OF KOREA": SEAR D

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

INDIA: SEAR D
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Dalits OR Nagas OR Adivasis OR Adaman* OR Onges OR Jarawa OR Sentinelese OR "Adi Padam" OR Padam OR Miri OR Abor OR Arbor OR Abor-Miri OR Aimol OR Angami OR "Southern Angami" OR Japfuphiki OR "Western Angami" OR Jotsoma OR Khonoma OR Mezoma OR Chakhro OR "Northern Angami" OR Ao OR Awan OR "QuTB Shahi Awan" OR Badaga OR Badag OR Badagux OR Badugu OR Vadagu OR Baiga OR Bhumia OR Bhuiya OR Narotia OR Binjwar OR Bharotia OR Raibhaina OR Kathbhaina OR Kondwan OR Gonwaina OR Bangni OR Dafla OR Nishi OR "Nishi Bangni" OR Banjara OR Vanzara OR Lambadi OR Sugali OR Ghor OR Bharia OR Bhar OR Bharat OR Bhumia OR Bhumiya OR Paliha OR "Bhuinha Bhumia" OR Bhumiya OR Pando OR Bhil OR Bhilbari OR Bhilboli OR Bhilla OR Bhili OR Bhilodi OR Vil OR Bhagoria OR Lengotia OR Birhor OR Bihor OR Birhar OR Birhore OR Mankidi OR Mankidia OR Bishnoi OR Marwadi OR Vishnoi OR Bodo OR Boro OR Bodi OR Bara OR Boroni OR Mechi OR Meche OR Mech OR Meci OR Kachari OR Bondo OR "Bondo Poraja" OR Bonda OR Remo OR Chakhesang OR Chang OR Chenchu OR Chenchucoolam OR Chenchwar OR Chenswar OR Choncharu OR Chote OR Chowte OR Chawtes OR Purum OR Dal OR "Dandami Marias" OR "Bison Horn Marias" OR "Kalpati Marias" OR "Singh Marias" OR "TalaguDDa Marias" OR Maria OR Dhodia OR Dhobi OR Dhori OR Dhore OR Dhowari OR Doria OR Didayi OR Gataq OR Getaq OR Geta' OR Gta' OR "Gta Asa" OR Didei OR Dire OR Gata' OR Didayee OR Digaro-Mishmi OR Digaru-Mishmi OR Taraon OR "Dimasa Kachari" OR Dimasa OR Dima-fisa OR Dogra OR Dogri OR Dogri-Kangri OR Dhogaryali OR Dogari OR "Dogri Jammu" OR "Dogri Pahari" OR Dogri-Kangr OR Gaddis OR Gaddies OR Garo OR Achik OR Abeng OR Ambeng OR Awe OR Ruga OR Atong OR Garrow OR Mande OR Gowlan OR Gujjars OR Halbaa OR Halba OR Halbi OR Hmar OR Mhar OR Mar OR Ho OR Lanka Kol OR "Bihar Ho" OR "Idu Mishmi" OR "Yidu Lobha" OR Chulikatas OR Irula OR Jaintias OR Jayantias OR Syntengs OR Pnars OR Hynniewtrep OR Jarawa OR "Jenu Kurumba" OR "Jennu Kurumba" OR "Jenu Kuruba" OR "Kadu Nayikas" OR Juang OR Patuas OR Puttooas OR Patra-Saara OR Patta-Savara OR Juango OR Kabui OR Rongmei OR Zeliangrong OR Puimei OR Inpui OR Kapwi OR Koboi OR Kubai OR "Kabui Naga" OR "Kacha Naga" OR "Kadu Kuruba" OR "Kadu Kurumba" OR Khasi OR Khoibu OR "Khoibu Maring" OR "Khoibu Maring Naga" OR Khond OR Kandhs OR "Raj Khonds" OR Kinnaure OR Kinners OR Kinnauris OR Kisan OR Nagasia OR Nagesia OR Nagesar OR Naksia OR Diharia OR Oraon OR Dhangad OR Dhangar OR Dhanka OR Kuda OR Kurukh OR Kurunkh OR Orao OR Uraon OR Kondh OR Kond OR Kui OR Buda Kondh OR "Bura Kandha" OR "Desia Kandha" OR "Dungaria Kondh" OR "Kutia Kandha" OR "Kandha Gauda" OR "Muli Kondh" OR "Malua Kondh" OR "Pengo Kandha" OR "Raja Kondh" OR "Raj Khond" OR "Desia Kondh" OR "Dongariya Kondh" OR Korku OR Bondhi OR Bopchi OR Kodaku OR Kurku OR Mouasi OR Muwasi OR Koya OR Koi OR "Koi Gondi" OR Kavor OR Koa OR Koitar OR Koyato OR Kaya OR Koyi OR Raj Koya OR Kavor OR Koitor OR Koithur OR Koitur OR Kutchi OR Kacchi OR Kanbis OR Bhanushali OR Rabari OR Ahirs OR Meghwals OR Lahules OR Lahulas OR Lahaulis OR Liangmai OR Kacha OR Liyang OR Lyengmai OR Liangmei OR Lyangmay OR Lohara OR Lohra OR Luhura OR Luhara OR Lotha OR "Naga Lotha" OR Madia OR Madia-Gond OR Maria OR Maria-Gond OR Madiya OR "Hill Madia" OR "Bison Horn Maria" OR Magahi OR Magadhi OR Magaya OR Maghai OR Maghaya OR Maghori OR Magi OR Magodhi OR Bihari OR Megahi OR "Magar Eastern" OR Magari OR Mangar OR Mangari OR Magarkura OR Mahali OR Mahli OR Mao OR "Naga Mao" OR Maram OR "Naga Maram" OR Meithei OR Meitei OR Manipuris OR Kathi OR Kathe OR Ponna OR Meiteilon OR Miju-Mishmi OR Kaman OR Mishing OR Mising OR Takam OR Tanis OR Amis OR Monpa OR

Mendba OR Moinba OR Monba OR Menpa OR Mongba OR Menba OR Monsang OR Moshang OR Monshang OR Mushang OR Mawshang OR Munda OR Colh OR Hor OR Kaur OR Mudus OR Mura OR Haroko OR Horohon OR Manki OR Mundu OR "Nicobarese Southern" OR Nicobara OR Nishi OR Nissi OR Dafla OR Nishang OR Nishing OR Nocte OR Bordari OR Panidori OR Namsangia OR Onge OR Ong OR Oraon OR Uraon OR Khurukh OR Paite OR Chin OR Kuki OR Lushai OR Tedim OR Sahte OR Zou OR Paliyan OR Paliyar OR Palleyan OR Palliyar OR Pangwali OR Pahari OR Pangi OR "Pangwali Pahari" OR Pangwala OR Piral OR Pochury OR Poumai OR Raika OR Rabari OR Rebari OR Rabha OR Rahbari OR Maru OR Godwar OR Pitalia OR Chalkia OR Rabbari OR Sorthia OR "Sorathi Charalia" OR Charmta OR Luni OR Kushar OR Tank OR "Muchhal Ka" OR Dhebariya OR Dheberya OR Vagadiya OR Vagariya OR Desi OR Kutchi OR Bhopa OR Gujarati OR Mogha OR Vishotar OR Sinai OR Rengma OR Sangtam OR Santali OR Hor OR Har OR Satar OR Santhali OR Santhal OR Sandal OR Sangtal OR Santal OR Sentali OR Samtali OR Santhiali OR Sonthal OR Saora OR Sora OR Saora OR Saonras OR Shabari OR Sabar OR Saura OR Savara OR Sawaria OR Swara OR Sabara OR Savara OR Sema OR Simi OR Sumi OR "Naga Sumi" OR Sentinel OR Sentinelese OR "Shom Peng" OR "Shom Pen" OR Shompeng OR Shompen OR Shobang OR Kalay OR Keyet OR Spitians OR Sulung OR Sullung OR Suling OR Sulong OR Puroik OR Pariok OR Tagin OR Tani OR "Apa Tani" OR Tangkhul OR Tagkhul OR Thangkhulm OR Champhung OR Luhuppa OR Luppa OR Somra OR Hao OR Tutsa OR Totcha OR Vaiphei OR Bhaipei OR Vaipei OR Veiphei OR Wancho OR "Banpara Naga" OR Joboka OR Warli OR Varli OR Yerukula OR Yerukala OR Yarukula OR Yerkula OR Yerukla OR Erukala OR Korava OR Yerukala-Korava OR Yerukula-Bhasha OR "Eruku Bhasha" OR Korchi OR Kurutha OR "Kurru Bhasha" OR Zangskari OR Zanskari OR Zaskari OR Zomi OR Zo

MALDIVES: SEAR D

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

MYANMAR OR BURMA: SEAR D

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Shan OR Karen OR Rakhine OR Mon OR Chin OR Kachin OR Karenni OR Akha OR Arakanese OR Maghi OR Marma OR Mogh OR Rakhine OR Chin OR Danau OR Danaw OR Danu OR Kachin OR Chingpaw OR Singphos OR Karen OR Pgaganyaw OR Plong OR Pwo OR Sgaw OR Skaw OR S'waw OR Karenni OR Kayah OR Kayan OR Kayaw OR Padaung OR Paku OR Kokang OR Kuki OR Mon OR Nagas OR Rohingya OR Shan OR Tavoyan OR Wa OR Hkawa OR Kala OR Kawa OR Lawa OR Va

NEPAL: SEAR D

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR "Adivasi Janajati" OR Angika OR Anga OR Angikar OR Chhika-Chhiki OR Awadhi OR "Awadhi Abadhi" OR Bahing OR "Bahing Rai" OR Bantawa OR "Bantawa Rai" OR Baraamu OR Baram OR Baramu OR Brahmu OR Bramu OR Bhramu OR Barhamu OR Bhojpuri OR Chukwa OR "Cukwa Ring" OR Pohing OR "Pohing Kha" OR Darai OR Darwai OR Dahri OR Daree OR Daroe OR Darmiya OR Darimiya OR Darmani OR Sauka OR Shauka OR Dhimal OR Haiko OR "Limbus of Terai" OR Dzongkha OR Jonkha OR "Bhotia of Bhutan" OR Zongkhar OR Drukke OR Drukha OR Bhutanese OR "Helambu Sherpa" OR "Yolmo Sherpa" OR Hyolmo OR Jerung OR Jero OR Jirel OR Jiripas OR Jiripa OR Jirpa OR Jiri OR Jirial OR Zaral OR Ziral OR Kagate OR Bhotia OR "Kagate Bhote" OR "Kagate Bhotia" OR Kagatey OR Kagati OR Limbu OR Yakthung OR Magar OR

Western OR Mangar OR Maithili OR Maitili OR Maithil OR Majhi OR Bhumar OR Manangba OR "Manang Bas" OR Nyishangba OR Nyi-Shang OR Manang OR Manangi OR Manangpa OR Manangbolt OR Neshyang OR Nesyangba OR Nyeshang OR Mugali OR Mugom OR Mugu OR Kham OR Khan OR Mugum OR Tamang OR Mustang OR Lo OR Lowa OR Mastang OR Sherpa OR Sharpa OR "Sharpa Bhotia" OR Xiaerba OR Serwa OR Tamang OR Thudam OR "Thudam Bhote" OR Thudambas OR Bhote OR Thulung OR "Thulunge Rai" OR "Thulu Luwa" OR Thululoa OR "Thulung La" OR "Thulung Lo" OR "Thulung Jemu" OR "Toaku Lwa" OR "Sub-Group of the Rai"

TIMOR*: SEAR D

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR "Tetum Prasa" OR Mambai OR Makasae OR "Tetum Terik" OR Baikenu OR Kemak OR Bunak OR Tokodede OR Fataluku OR Waima'a OR Galoli OR Naueti OR Idate OR Midiki OR Tentum OR Baikeno OR Makasai

AUSTRALIA: WPR A

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR "Torres Strait*"

BRUNEI: WPR A

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Dusun OR Bisaya OR Murut OR Kedayan OR Iban OR Tutong OR Penan

JAPAN: WPR A

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Ryūkyūans OR Okinawans OR Ainu OR Utari

"NEW ZEALAND": WPR A

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Māori

CAMBODIA: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR "Khmer Loeu" OR Kachac OR Chamic OR Kachak OR Kreung OR Krung OR Kru'ng OR Tampuon OR Campuon OR "Kha Tampuon" OR Proon* OR Tamphuan OR Tampuen OR Tumpun

CHINA: WPR A

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR "national minority" or Zhuang OR Manchu OR Hui OR Uyghur OR Yi OR Lolo OR "Tujia Achang" OR Bai OR Blang OR Bulang OR Wa OR Samtuan OR Samtao OR Saamtaav OR Pulang OR Bonan OR Bouyei OR Bouyi OR Buyei OR Buyi OR Dai OR Tai OR Baijue OR "Lu Dai" OR Daur OR De'ang OR Dong OR Gam OR Kam OR Tong OR Tung OR Dongxiang OR Tunghsiang OR Santa OR "Mongolian Huihui" OR Drung OR Ewenki OR Evenki OR Ewenke OR "Manchurian Solon" OR "Owenke Solon" OR "Solon Evenki" OR Suolun OR Tungus OR Gelo OR Hani OR Akha OR Biyo OR Bio OR Biyue OR Kado OR Mahei OR Pudu OR Putu OR Sansu OR Hezhen OR Hezhe OR Sushen OR Hmong OR Jing OR Jingpo OR Jino OR Kazak OR Kazakh OR Khmu OR Kirjiz OR Lahu OR Lhoba OR Li OR Lisu OR Maonan OR Miao OR "Black Hmong" OR "Black

Miao" OR Daishou OR Guoxiong OR "Long Skirt Miao" OR Mao OR "Red Hmong" OR "Red Miao" OR "Short Skirt Miao" OR "White Hmong" OR Moinba OR Mosuo OR Moso OR Musuo OR Mulam OR Naxi OR Nahsi OR Nasi OR Nakhi OR Lomi OR Mu OR Nisu OR Nu OR Oroqen OR Ozbek OR Pumi OR Qiang OR Salar OR She OR Shui OR Shuijia OR Sui OR "Sui Li" OR Suijia OR Suipo OR Tajik OR Tartar OR Tatar OR Tata'er OR Dada OR Daden OR Tu OR Tujia OR Uygur OR Va OR Xibe OR Yao OR "Baiku Yao" OR Baikuyao OR Bingduoyou OR Bunu OR "Guoshan Yan" OR Guoshanyao OR "Hon Yao" OR Jinmen OR Lajia OR Mian OR "Pan Yao" OR Panyao OR "Pindi Yao" OR Pindiyao OR "Shanzi Yao" OR Shanziyao OR Ajia OR "Black Yi" OR Yi OR Heiyi OR Qunuo OR Wajia OR "White Yi" OR Xiaxi OR Younuo OR "Hong Yao" OR "Red Yao" OR Yunou OR Yuno OR Yugur

"COOK ISLANDS": WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

FIJI: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Rotumans OR iTaukei

KIRIBATI: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR I-Kiribati OR Tuvalu OR Banaba

LAO*: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Phouthay OR Tai OR Makong OR Katang OR Lue OR Akha OR Aka OR Ekaw OR Ekwa OR Kaw OR Khka OR "Kon Ak'a" OR Hmong OR Maio OR Meo OR Khmu OR Kammu OR Khamu OR Lamet OR "Kha Lamet" OR Khamet OR Khamed OR Lemet OR Rmeet OR Lantan OR Lantien OR Malabri OR Mlabri OR "Phi Tong Luang" OR "Toong Luang" OR "Yellow Leaf" OR Yumbr OR Yumbri

MALAYSIA: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR "Anak Negeri" OR "Orang Ulu" OR Dayak OR "Orang Asli" OR Bajau OR Illanun OR Badjao OR Badjau OR Bajaw OR Bajo OR Suluk OR Obian OR "Orang Sama" OR "Sama Dilaut" OR "Sea Gypsies" OR Binadan OR Batek OR "Batek Negritos" OR Bidayuh OR "Bukar Sadong" OR Tebakang OR Bugis OR Buginese OR Luwu OR Ugi OR Chewong OR "Che'Wong" OR Iban OR "Sea Dayak" OR Jahai OR Jah OR Jehai OR Pangan OR "Jah Hut" OR Cheres OR Jakun OR Djakun OR "Orang Hulu" OR "Kadazan Dusun" OR "Tuaran Dusun" OR "Suang Lotud" OR Minokok OR Ringus OR "Tempasuk Dusun" OR Tindal OR "Orang Sungai" OR Kedayan OR Kedyan OR Kadayan OR Kadien OR Kensiu OR Negrito OR Lanoh OR Sakai OR Semnan OR "Mah Meri" OR Besisi OR Btsisek OR Melanaus OR Balingian OR Belanau OR Bruit OR Dalat OR Sarikei OR Muka OR Melanau OR Melenau OR Mendriq OR Mendrik OR Menri OR Mandriq OR Murut OR Timogun OR Tagal OR Nabas OR Penan OR Semai OR "Semai Senoi" OR Semang OR Semelai OR "Semaq Tasik" OR "Semoq Beri" OR Semaq OR Semalai OR "Semaq Beri" OR "Jakun of Tekai River" OR Senoi OR Sengoi OR Temiar OR "Temiar Senoi" OR Bumiputera OR Temuan OR Belanda OR Biduanda OR Benua OR Mantera OR Kenyah OR Kayan OR Lunbawang OR Punan OR Bisayah OR Kelabit OR Berawan OR Kejaman OR Ukit OR Sekapan OR Paitan

"MARSHALL ISLANDS": WPR B
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

MICRONESIA: WPR B
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

MONGOLIA: WPR B
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Bayad OR Bayaad OR Bayit OR Bait OR Dariganga OR Durvud OR Durbet OR Dörbed OR Dörvöd OR Kazakh OR Kazak OR Qazaq OR Khalkha OR Halh OR Mingat OR Myangad OR Torguud OR Torgut OR Tsaatan OR Dukha OR Tsachin

NAURU: WPR B
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

NIUE: WPR B
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

PALAU: WPR B
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

"PAPUA NEW GUINEA": WPR B
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Bougainvilleans

PHILIPPINES: WPR B
Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Tagalog OR Bisaya OR Binisaya OR Cebuano OR Ilocano OR Hiligaynon OR Ilonggo OR Bikol OR Bicol OR Waray OR Igorot OR Lumad OR Mangyan OR Abaknon OR Capul OR "Capul Samal" OR Capuleno OR Inabaknon OR Inbaknon OR Kapul OR Sama OR Applai OR Appais OR Kankanan-ey OR Katangnan OR "Lepanto Igorot" OR "Sagada Igorot" OR "Western Bontoc" OR "Western Bontok" OR Arumanen OR Aromanon OR Arumamen OR "Central Mindanao" OR Ilianen OR Liringanen OR Manobo OR Manuvu OR "South Cotabato" OR Attaw OR Bagobo OR Clata OR Diangan OR Giangan OR Guingan OR Guiangan OR Gulanga OR Jangan OR Klata OR Obo OR Banwaon OR Adgawanon OR Banuaonon OR Banwanon OR Higaonon-Banwaon OR "Bontok Igorots" OR Bontoc OR Kadaklan-Barlig OR Bukidnon OR Binokid OR Binukid OR "Central Bukidnon" OR Butuanon OR Lapaknon OR "Davao Chabakano" OR Chabakano OR "Chabakano Creole" OR Chavacano OR Creole OR Davao OR Zamboanga OR Dibabawon OR Dibabaon OR Mandaya OR "Dibabawon Manobo" OR "Digagaon Mandaya Manobo" OR "Orang Dibabawon" OR Higaonon OR Banuanon OR Higanon OR "Higaonon Manobo" OR "Misamis Higaonon" OR Talaandig OR "Jama Mapun" OR "Orang Cagayan" OR "Tao Cagayan" OR Kabihug OR Abian OR Aeta OR Agiyan OR Agta OR Bihug OR Bikol OR "Camarines Norte Agta" OR Manide OR Negrito* OR

Lambangian OR Teduray-Lambangian OR Tiruray OR Lapuyan OR Lapuyen OR "Subanun Lapuyan" OR Margosatubig OR Subanon OR Subanun OR Subanen OR Suban-on OR "Southern Subanun" OR "Manobo Agusan" OR "Agusan del Sur" OR Agusan OR Higanon OR Kidapawan OR Ubo OR Molbog OR Molebugan OR Molebuganon OR Molebuganori OR Palawan OR Palawano OR Palawanon OR Pala'wan OR Pinalawan OR Sangil OR Sanggil OR Sangire OR Sangihe OR "Sangir Pilipinas" OR Sangir OR Sangu OR Marore OR Sangirezen OR Talaoerezen OR Surigaonon OR Surigao OR Tagakaolo OR Kalagan OR Mansaka OR "Tagakaolo Kalagan" OR Tagakaulu OR "Tagakaulu Kalagan" OR Tagbanua OR Tagbanuas OR Tala-Andig OR Talandig OR "Tau´t Batu" OR "Tao't Bato" OR "Tao't Batu" OR "Taw Batu" OR TBoli OR Kiamba OR Tagabeli OR Tagabulu OR T'boli OR Tibole OR Tiboli

"REPUBLIC OF KOREA": WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

SAOMA: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

"SOLOMON ISLANDS": WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

TONGA: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

TUVALU: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous

VANUATU: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Wallisians OR Futunans OR i-Kiribati

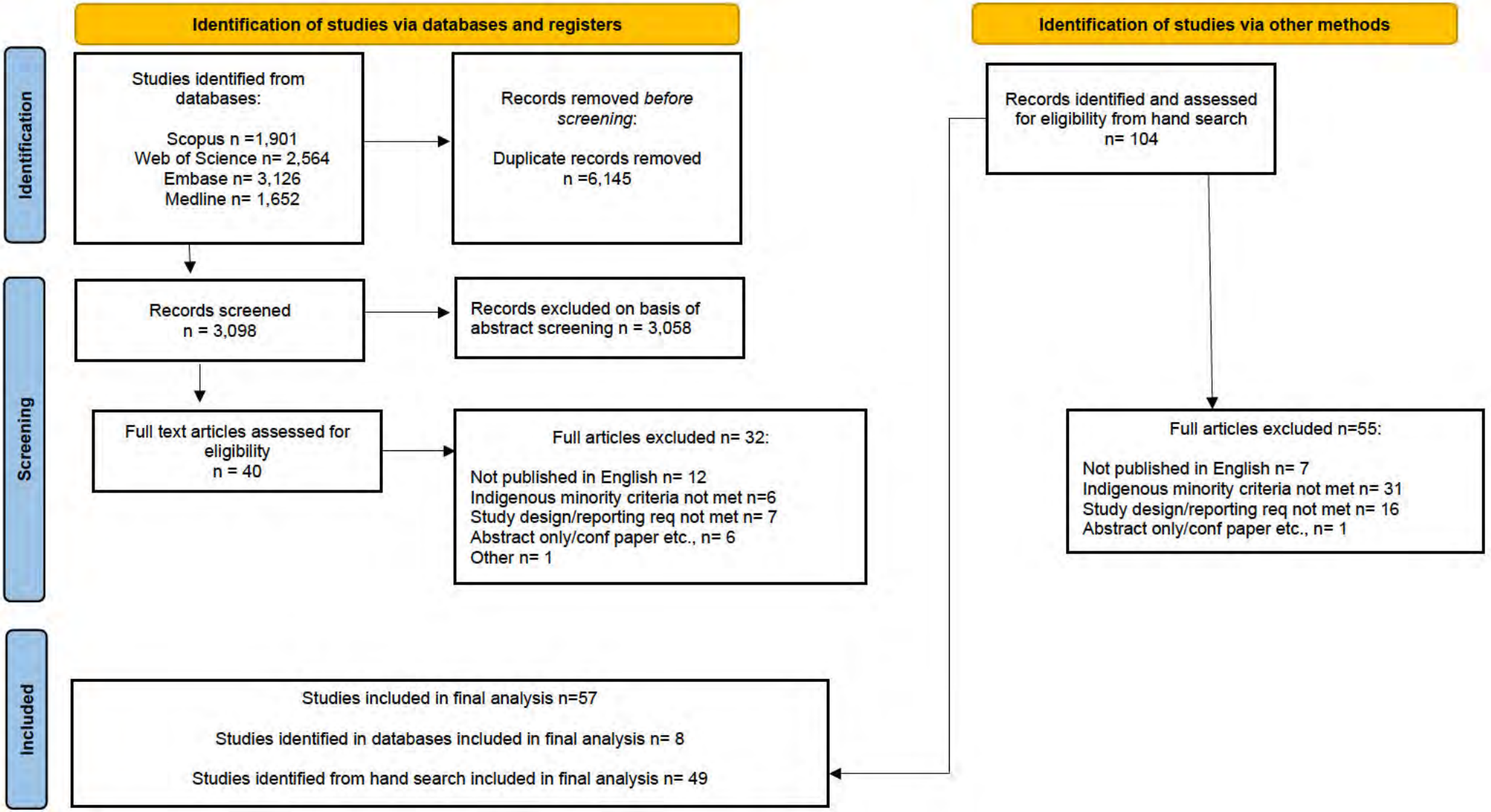
VIETNAM: WPR B

Indigenous OR aborigin* OR native OR "first nation*" OR "ethnic group" OR tribal OR tribe OR autochthonous OR Akha OR Aka OR Ak'a OR Ahka OR Hani OR "Ha Nhi" OR Ikaw OR Xo OR Khako OR "Kha ko" OR "Khao Ikor" OR Aini OR Yani OR "Hka Ko" OR "Khao Kha Ko" OR Arem OR A-Rem OR Chomrau OR Chombrau OR Umo OR Bahnar OR "Ba Na" OR "To Lo" OR Golar OR Jolong OR "Gio Lang"OR "Y Lang" OR "Ro Ngao" OR Reungao OR Rangao OR Ro-Ngao OR "Bahnar Rongao" OR Krum OR Krem OR Roh OR "Con Kde" OR "Kpang Cong" OR "Bo Mon" OR Bonom OR Bomom OR Alacong OR Alakong OR "A-La Cong" OR Brao OR Brau OR Braou OR Proue OR Proon OR Brou OR "Cao Lan" OR Caolan OR "Hon Ban" OR "San Chay" OR "San Chi Man Cao-Lan" OR Sán-Chi OR Mán OR "Cao Lan-Sán Chi" OR "Cho Ro" OR "Chau Ro" OR Chauro OR Chorao OR Choro OR Cho-ro OR Chrau OR "Do Ro" OR Zro OR "Chu Ru" OR Cadoe OR Chru OR Choru OR "Cho Ru" OR Chu OR Chu-ru OR Churu OR Cru OR Degar OR Kru OR Loang OR Seyu OR Ru OR Ede OR E-de OR Edeh OR De OR Dega OR Haqniq OR "Ha Nhi" OR Hanízú OR Hanhi OR "H Nhi" OR "Ha Nhi Gia" OR Uni OR "U Ni"

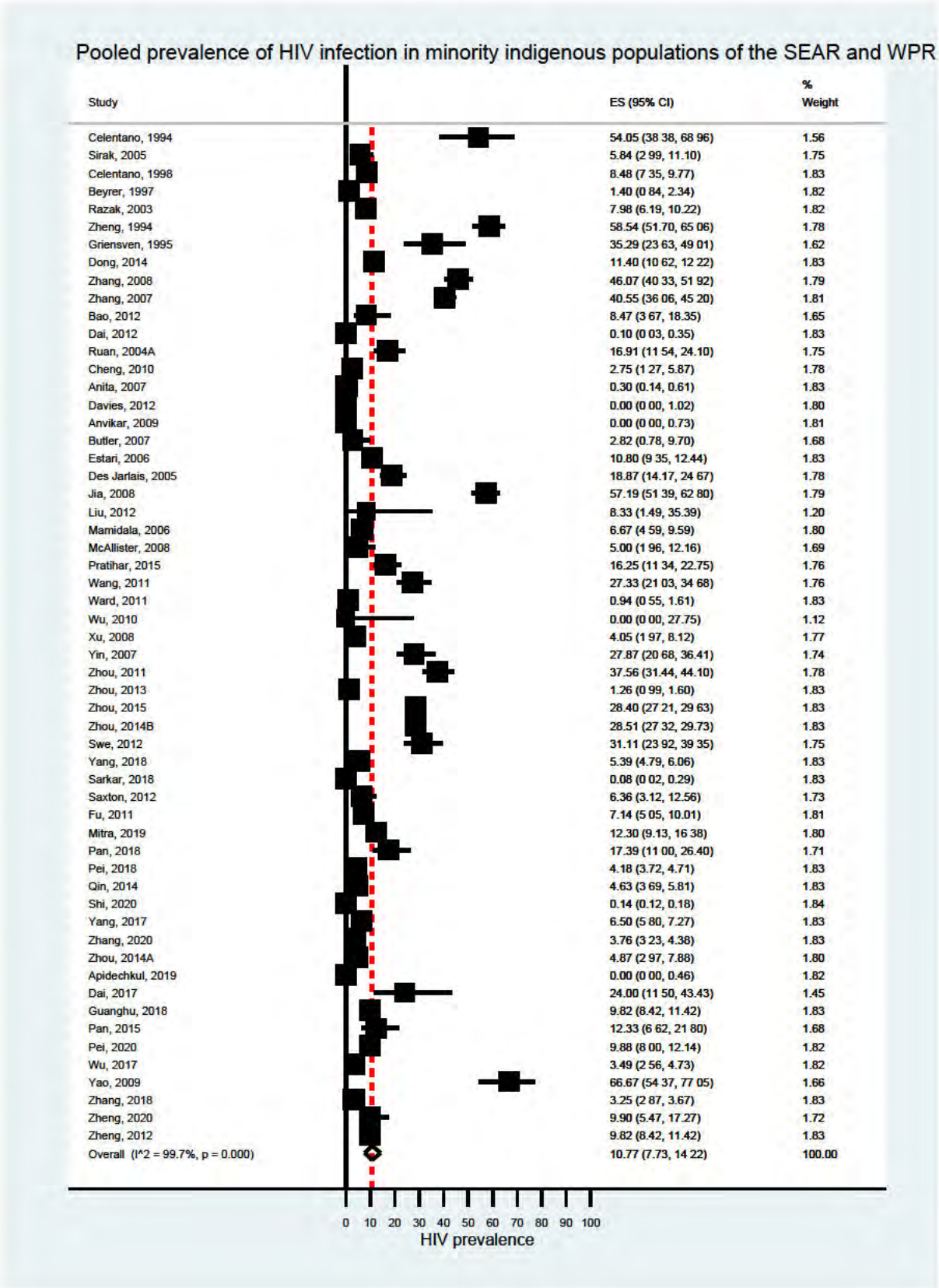
OR Xauni OR ”Xa U Ni” OR Koho OR Coho OR Co-ho OR Ko-ho OR Kohor OR K'ho OR Caho OR “Co Ho” OR “La Ha” OR “Xa Khan” OR “Xa Cah” OR “Xa Chien” OR “Xa Khao” OR “Xa Lay” OR “Xa Lga” OR “Khla Don” OR “Kla Dong” OR “Khla Liik” OR “La Hu” OR Luohei OR Launa OR Lahuna OR Laku OR Kaixien OR Namen OR Mussuh OR Muhso OR Musso OR Mussar OR Mussur OR Moso OR Lachi OR Lati OR “Cu Te” OR “Tho Den” OR “Black Tho” OR “Man La” OR Chi OR “La Chi” OR Pula OR Phula OR Fula OR Foula OR Lipupo OR Laji OR Lipulio OR Laqua OR “Y Pi” OR “Y Pong” OR Laghuu OR Laopa OR Xapho OR “Xa Pho” OR “Lahu Shi” OR “Yellow Lahu” OR Kouy OR Lu OR Duon OR Kon OR Leu OR “Lu Ge Zi” OR “Lu Ren” OR Lue OR Lugepo OR Nhuon OR Zhon OR Maa OR Ma OR “Chau Ma” OR “Ma Xop” OR “Ma To” OR “Ma Krung” OR “Ma Ngan” OR Maleng OR Pakatan OR Malieng OR Malang OR “Ma Leng” OR “Ma Lieng” OR Romam OR “Ro Mam” OR Ro-mam OR Sedang OR Hadang OR Hdang OR Hoteang OR Roteang OR Rotea OR Hotea OR “Xo Dang” OR Xodangg OR “Xa Dang” OR Cadong OR Tang OR Kmrang OR Kmrong OR Konelane OR Brila OR Stieng OR Budeh OR Xtieng OR “Xa Dieng” OR “Ba Ra” OR “Bu Dip” OR Budip OR “Bu Lanh” OR Rangah OR Tay OR Tho OR Ngan OR Phen OR “Thu Lao” OR “Pa Di”

Supplementary Data Table 1: **Key to modified Newcastle-Ottawa Quality Assessment Scale scoring**

Study Population	0= The study population is not clearly defined
	1=The study population is clearly defined
Representativeness of the sample	0=No description of the sampling strategy.
	1= Study sample comprises a select group of the study population (non-random sampling)
	2= Study sample is representative of the study population (all subjects or random sampling)
Ascertainment of specimen collection methods	0= The study does not detail specimen collection methodologies
	1= The study clearly defines specimen collection methodologies
Sample size	0= Not justified
	1= Justified and satisfactory (sample size and power calculation included)
Non-respondents	0= No description of the response rate or the characteristics of the responders and the non-responders.
	1= Comparability between respondents and non-respondents' characteristics are established.
Impact of Bias (selection bias, measurement bias, participant reporting, confounders)	0= Where appropriate, the study does not acknowledge or mitigate for potential bias. When comparisons are made between different study populations results are not adjusted for confounders
	1= Where relevant, the study acknowledges and mitigates for potential bias. When comparisons are made between different study populations results are adjusted for confounders
Assessment of the outcome (STH infection)	0= No definitive diagnosis or self-report
	1= Objective diagnostic methodology with units of measurement and /or definitions
Statistical analysis	0= The statistical test is inappropriate/not described/incomplete
	1= The statistical method used is clearly described and appropriate for the analysis undertaken. Where comparisons are made between population groups, the measurement of the association is presented, including confidence intervals and the probability level (*p* value)



Supplementary Data: Fig 1. PRISMA shortlisting (based on process summary by Page et al, 2021)(7)



Supplementary Data Fig 2: Pooled prevalence of HIV infection in minority indigenous popualtions of the SEAR and WPR based on the 57 studies

Supplementary Data Table 2: Prevalence of HIV in indigenous minority populations of China (based on data from x37 studies derived from the x57 studies)

Minority Population	Studies (n)	Study ID	First Author Year of Publication	Year of Data Collection*	Study population+	Study Population Age (years)	Study Population (n)	Number Positive
Bai	1	8	Cheng, 2010	2006-2007	Other		120	2
Dai	2	9	Fu, 2011	< 2011	General population	16-55	50	1
		24	Zhou, 2011	2009	Drug users		168	59
Hui	2	13	Pan, 2018	2013-2014	MSM	≥ 18	45	4
		31	Pan, 2015	2013-2014	MSM	≥ 18	45	4
Jingpo	2	9	Fu, 2011	< 2011	General population	16-55	370	29
		24	Zhou, 2011	2009	Drug users		53	24
Manchu	2	13	Pan, 2018	2013-2014	MSM	≥ 18	28	5
		31	Pan, 2015	2013-2014	MSM	≥ 18	28	5
Miao	2	6	Dai, 2012	2009	General population	≥ 2	49	0
		36	Zheng, 2020	2018	MSM	≥ 18	101	10
Tujia	1	16	Shi, 2020	2013-2016	General population		8,501	4
Uyghur	4	3	Zhang, 2008	2005	Drug users	≥ 18	280	129
		4	Zhang, 2007	2002	Drug users	≥ 18	439	178
		16	Shi, 2020	2013-2016	General population		17,438	40
		17	Wang, 2011	2007	Drug users	≥ 16	121	33
Yi	13	1	Dong, 2014	2010	General population	≥ 14	6,072	692
		2	Yang, 2018	2010-2016	General population		4,897	264
		6	Dai, 2012	2009	General population	≥ 2	1,154	2
		7	Ruan, 2004	2002	Drug users	≥ 18	136	23
		8	Cheng, 2010	2006-2007	Other		98	4
		14	Pei, 2018	2011-2016	General population	15-25	6,311	264
		15	Qin, 2014	2012	General population	15-45	1,532	71
		17	Wang, 2011	2007	Drug users	≥ 16	40	11
		20	Yang, 2017	2011-2013	General population		4,371	284

		27	Zhou, 2015	2004-2012	Drug users		5,355	1,521
		28	Zhou, 2014	2004-2012	Drug users	≥ 20	5,381	1,534
		32	Pei, 2020	< 2020	General population	45-49	800	79
		35	Zhang, 2018	2011-2015	General population	15-25	7,636	248
Zang	1	16	Shi, 2020	2013-2016	General population		9,126	5
Zhuang	3	6	Dai, 2012	2009	General population	≥ 2	874	0
		16	Shi, 2020	2013-2016	General population		28,641	42
		26	Zhou, 2013	2010	Commercial sex		4,071	49
Other	17	5	Bao, 2012	2009-2010	Drug users	≥ 18	59	5
		10	Des Jarlais, 2005	2002	Drug users		212	40
		11	Jia, 2008	2004-2005	Drug users	≥ 18	285	163
		12	Liu, 2012	2009	Commercial sex		12	1
		13	Pan, 2018	2013-2014	MSM	≥ 18	19	7
		18	Wu, 2010	2008	Drug users		10	0
		19	Xu, 2008	2006	Commercial sex	≥ 16	173	7
		21	Yin, 2007	2004	Drug users	≥ 18	122	34
		22	Zhang, 2020	2008-2016	Drug users		4,199	158
		23	Zheng, 1994	1992	Drug users		205	120
		25	Zhou, 2014	2012-2013	Commercial sex	≥ 16	308	15
		26	Zhou, 2013	2010	Commercial sex		1,021	15
		29	Dai, 2017	< 2017	MSM	≥ 18	25	6
		30	Guanghu, 2018	2013-2015	MSM	≥ 18	1,517	149
		33	Wu, 2017	2012	Commercial sex	> 50	1,118	39
		34	Yao, 2009	2007	Drug users	≥ 16	63	42
		37	Zheng, 2012	2013-2015	MSM	≥ 18	1,517	149

Supplementary Data Table 3: Pooled prevalance and bivariate regression of HIV infection within minority indigenous populations of China analyzed by study covariates.

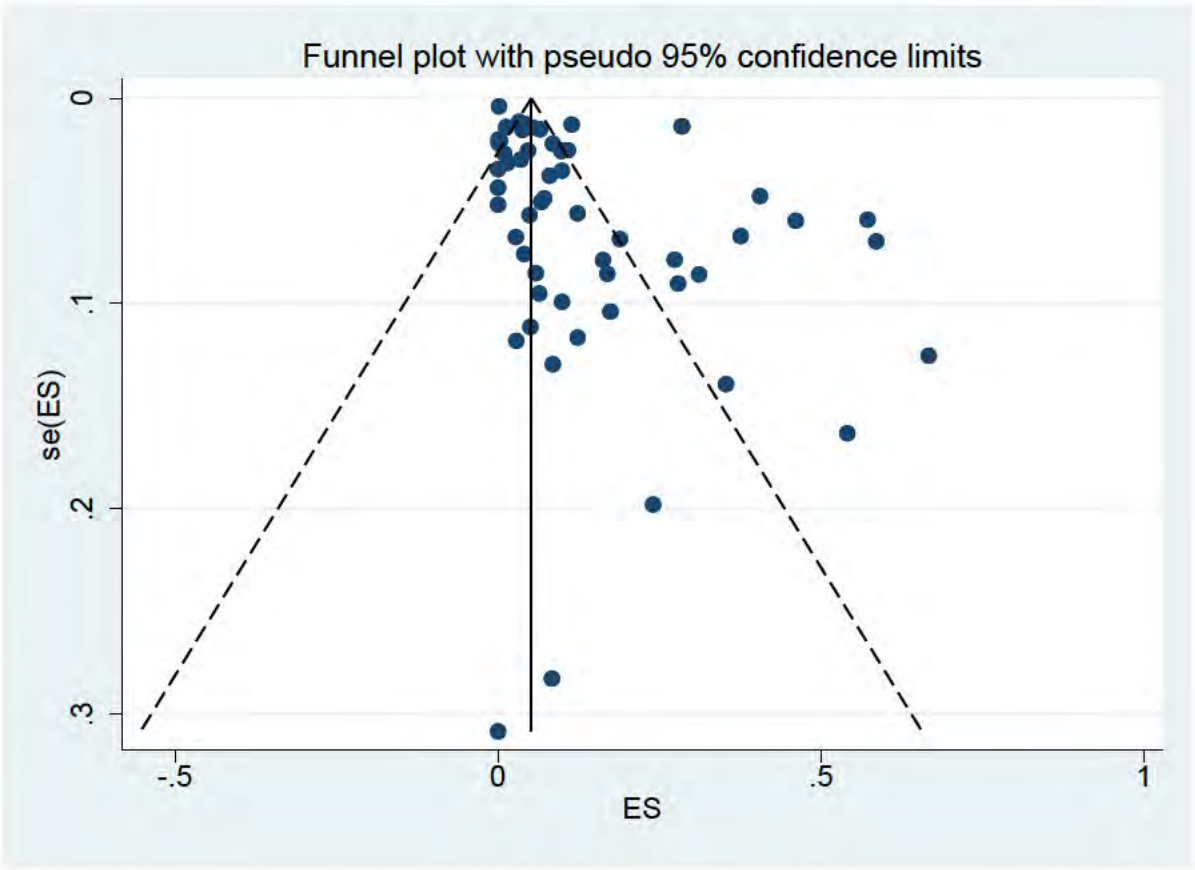
	Studies (n)	Pooled Prevalence HIV Infection (95% CI)	95% CI	*p* value
	37	13.62 (9.25, 18.65)		
Minority Ethnic Population				
Zhuang	3	0.29 (0.00, 1.19)	1.00	
Yi	13	9.44 (4.81, 15.39)	1.12 (1.05, 1.19)	0.001
Uyghur	4	23.62 (0.27, 66.42)	1.32 (1.07, 1.63)	0.010
Other	17	16.49 (10.10, 23.99)	1.22 (1.08, 1.38)	0.002
Bai	1	1.67 (0.46, 5.87)	-	-
Dai	2	25.06 (19.46, 31.10)	-	-
Hui	2	8.89 (3.60, 15.93)	-	-
Jingpo	2	10.90 (8.04, 14.12)	-	-
Manchu	2	17.86 (8.56, 29.34)	-	-
Miao	2	5.13 (1.97, 9.45)	-	-
Tujia	1	0.05 (0.02, 0.12)	-	-
Zang	1	0.05 (0.02, 0.13)	-	-
Sub-population Group				
General population	10	4.34 (1.55, 8.43)	1.00	
MSM	6	10.50 (9.25, 18.65)	1.09 (1.03, 1.14)	0.002
Commercial sex	5	2.61 (0.77, 5.22)	0.99 (0.96, 1.02)	0.463
Drug users	15	29.63 (20.20, 40.00)	1.30 (1.17, 1.45)	0.000
Others	1	2.75 (1.27, 5.87)		
Year of Data Collection				
1990-2000	1	58.54 (51.70, 65.06)	-	
2000-2010	15	19.61 (11.34, 29.42)	1.00	
2010-2020	21	8.25 (5.26, 11.79)	0.88 (0.78, 0.99)	0.034

Notes: Bivariate meta-regression analysis was only undertaken where there were 3 or more data sets

Supplementary Data Table 4: QA assessment of HIV studies based on modified Newcastle-Ottawa Quality Assessment Scale

Study #	First Author, Year of publication	Study Population	Representativeness of the sample	Ascertainment of specimen collection	Sample size	Non-respondents	Impact of Bias (selection bias, measurement bias, participant reporting, confounders)	Assessment of the outcome (STH infection)	Statistical analysis	Total Score	QA Grade
1	Celentano, 1994	1	1	1	0	1	1	1	1	7	medium
2	Dong, 2014	1	1	1	0	1	1	1	1	7	medium
3	Yang, 2018	1	1	1	0	1	1	1	1	7	medium
4	Zhang, 2008	1	1	1	0	0	0	1	1	5	medium
5	Zhang, 2007	1	1	1	0	0	1	1	1	6	medium
6	Bao, 2012	1	1	1	0	0	1	1	1	6	medium
7	Dai, 2012	1	1	1	0	0	0	1	1	5	medium
8	Sarkar, 2018	1	1	1	0	0	0	0	1	4	low
9	Siriak, 2005	1	1	1	0	0	1	1	1	6	medium
10	Celentano, 1998	1	1	1	0	0	1	1	1	6	medium
11	Beyrer, 1997	1	1	1	0	0	1	1	1	6	medium
12	Razak, 2003	1	1	1	0	1	0	1	1	6	medium
13	Ruan, 2004 A	1	1	1	0	0	1	1	1	6	medium
14	Cheng, 2010	1	1	1	0	0	0	1	1	5	medium
15	Anita, 2007	1	1	1	0	0	0	1	1	5	medium
16	Davies, 2012	1	1	1	0	0	1	1	1	6	medium
17	Saxton, 2012	1	1	1	0	1	1	1	1	7	medium
18	Anvikar, 2009	1	1	1	0	0	0	1	1	5	medium
19	Butler, 2007	1	1	1	0	1	1	1	1	7	medium
20	Estari, 2006	1	1	1	0	0	0	1	0	4	low
21	Fu, 2011	1	1	1	0	1	1	1	1	7	medium
22	Des Jarlais, 2005	1	1	1	0	0	1	1	1	6	medium
23	Jia, 2008	1	1	1	0	0	1	1	1	6	medium
24	Liu, 2012	1	1	1	1	0	1	1	1	7	medium
25	Mamidala, 2006	1	1	1	0	0	0	1	0	4	low
26	McAllister, 2008	1	1	1	0	1	0	1	1	6	medium

27	Mitra, 2019	1	1	1	0	0	0	1	1	5	medium
28	Pan, 2018	1	1	1	0	0	1	1	1	6	medium
29	Pei, 2018	1	1	1	0	0	1	1	1	6	medium
30	Pratihar, 2015	1	1	0	0	0	0	1	1	4	low
31	Qin, 2014	1	1	1	0	0	1	1	1	6	medium
32	Shi, 2020	1	1	1	0	0	1	1	1	6	medium
33	Wang, 2011	1	1	1	0	0	1	1	1	6	medium
34	Ward, 2011	1	1	1	0	0	1	0	1	5	medium
35	Wu, 2010	1	1	1	0	0	0	1	1	5	medium
36	Xu, 2008	1	1	1	0	1	1	1	1	7	medium
37	Yang, 2017	1	1	1	1	0	1	1	1	7	medium
38	Yin, 2007	1	1	1	0	0	1	1	1	6	medium
39	Zhang, 2020	1	1	0	0	0	1	1	1	5	medium
40	Zheng, 1994	1	1	1	1	0	0	1	1	6	medium
41	Zhou, 2011	1	1	1	0	0	0	1	1	5	medium
42	Zhou, 2014 A	1	1	1	0	1	1	1	1	7	medium
43	Zhou, 2013	1	1	1	1	0	1	1	1	7	medium
44	Zhou, 2015	1	1	1	0	0	1	1	1	6	medium
45	Zhou, 2014B	1	1	0	0	0	1	0	1	4	low
46	Apidechkul, 2019	1	1	1	1	1	1	1	1	8	high
47	Dai, 2017	1	1	1	1	0	1	1	1	7	medium
48	Griensven, 1995	1	1	1	0	0	1	1	1	6	medium
49	Guanghua, 2018	1	1	1	0	1	1	1	1	7	medium
50	Pan, 2015	1	1	1	0	1	1	1	1	7	medium
51	Pei, 2020	1	1	1	0	0	0	1	1	5	medium
52	Swe, 2012	1	1	0	0	0	1	0	1	4	low
53	Wu, 2017	1	1	1	0	1	1	1	1	7	medium
54	Yao, 2009	1	1	1	0	0	1	0	1	5	medium
55	Zhang, 2018	1	1	1	0	0	0	1	1	5	medium
56	Zheng, 2020	1	1	1	1	0	1	1	1	7	medium
57	Zheng, 2012	1	1	1	0	1	1	1	1	7	medium



Supplementary Data Fig 3: Funnel plot of HIV prevalence studies among minority indigenous populations

The funnel plot represents 57 studies and includes the 43 studies with comparative population data.

Egger's test produced a bias coefficient of 2.48 (95% CI 1.01, 3.96) *p*-value 0.001 indicating publication bias.

References:

1. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41.
2. World Health Organization. Global Burden of Disease Regions used for WHO-CHOICE Analyses n.d. [Available from: https://www.who.int/choice/demography/regions/en/.
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4. International Work Group for Indigenous Affairs. Who We Are Indigenous Peoples in Asia 2009 [updated 10.03.09. Briefing Paper]. Available from: https://www.iwgia.org/images/publications/0640_ho_are_e_IPs_in_Asia.pdf.
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6. Minority Rights Group International. World Directory of Minorities and Indigenous Peoples n.d. [Available from: https://minorityrights.org/directory/.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372.

Appendix 3 (of thesis): Paper II Supplementary Information

Appendix 1 (of paper II): PRISMA-P 2015 Checklist *

Section/topic	#	Checklist item	Information reported		Line number (s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2-3, 113, 124-126
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	52
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-20
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	311-313
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	126-127
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	306-308
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	309
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	25-31, 58-121
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	241-248
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	128-167, 177-206
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	128-136

Section/topic	#	Checklist item	Information reported		Line number (s)
			Yes	No	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	505-575; 584-614
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	170-171, 209-211
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	171-175, 209-210, 227-229
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	210-213 , 229-231, 623-649
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	214-221, 623-649
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	36-43, 241-248
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	226-238
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	41-43, 244-251
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	248-255
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	255-258
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	226-238
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	246-251

The above checklist has been downloaded from BCM Systematic Reviews[1] and has been adapted from the work undertaken by Moher et al, 2015 [2] with the rationale for the adaptation detailed in recommendations to prospective authors [3].

Appendix 2: Search Criteria

A. Countries

Countries comprising the SEAR and WPR are defined based on the WHO Global Burden of Disease (GBD) regional classification system [4].

SEAR Category B [#]	SEAR Category D [#]
Indonesia	Bangladesh
Sri Lanka	Bhutan
Thailand	Korea, Democratic People's Republic of
Timor-Leste	India
	Maldives
	Myanmar
	Nepal

WPR Category A [#]	WPR Category B [#]
Australia	Cambodia
Brunei	China
Japan	Cook Islands
New Zealand	Fiji
Singapore*	Kiribati
	Korea, Republic of
	Lao
	Malaysia
	Marshall Islands
	Micronesia
	Mongolia

Nauru

Niue

Palau

Papua New Guinea

Philippines

Samoa

Solomon Islands

Tonga

Tuvalu

Vanuatu

Vietnam

* Singapore will be excluded as it does not have any minority indigenous people according to the definitions utilized by this review.

Countries are classified according to mortality strata [4] :

Category A: very low child, very low adult mortality

Category B: low child, low adult mortality

Category C: Low child, high adult mortality (there are no Category C countries within the SEAR and WPR)

Category D: high child, high adult mortality

Category E: High child, very high adult mortality (there are no Category E countries within the SEAR and WPR)

Mortality strata are based upon the quintiles of distribution for adult and child mortality across WHO member states using 1999 population estimates [5].

B. Parasites/Bacteria

The following search terms will be used to identify studies on TB, malaria, and STH infections: “soil transmitted helminth*” OR STH OR Ascaris OR Trichuris OR Nectator OR Ancylostoma OR hookworm* OR Strongyloides OR malaria* OR plasmodi* OR tuberculosis OR TB OR “Mycobacterium tuberculosis”

C. Indigenous Terms

In addition to generic indigenous terms, those relevant to each country have been derived from the World Directory Listing of Minorities and Indigenous People [6]; Native Planet-Indigenous Mapping [7] and International Working Group on Indigenous Affairs [8] and are detailed below:

INDONESIA: SEAR B
Indigenous OR aborigin* OR native OR first nation* OR “ethnic group” OR tribal OR tribe OR autochthonous OR “adat terpencil” OR Acehnese OR Achinese OR Atjeher OR “Orang Aceh” OR Acehnais OR Acehno OR Atjeh OR Atjehnese OR Achehnese OR Achenese OR Adabe OR Ataura OR Atauru OR Atauro OR Raklu-Un OR “Raklu Un” OR Adonara OR “Tusa Tadon” OR Waiwerang OR Vaiverang OR Sagu OR Alorese OR Ampanang OR Andio OR Masama OR Andio'o OR Imbao'o OR Aralle OR Tabulahan OR Asmat OR Asamat OR Asemer OR Asomat OR Bagusa OR “Batak Alas-Kluet” OR “Alas-Kluet Batak” OR “Batak Kluet-Alas” OR “Kluet-Alas Batak” OR “Alas Kluet” OR “Kluet Alas” OR Alas OR Kluet OR “Batak Angkola” OR “Orang Angkola” OR Anakola OR Angkola OR “Batak Dairi” OR Dairi OR “Dairi Batak” OR “Orang Batak Dairi” OR Pakpak OR “Pakpak Dairi” OR Sumut OR “Batak Karo” OR “Karo Batak” OR “Orang Batak Karo” OR Karonese OR “Batak Mandailing” OR “Mandailing Batak” OR Batta OR “Orang Mandailing” OR “Batak Simalungun” OR “Simalungun Batak” OR “Orang Batak Simalungun” OR Simelungun OR Simelungan OR Timur OR “Batak Toba” OR “Toba Batak” OR “Orang Batak Toba” OR “Silindung Batak” OR Bauzi OR Baudi OR Bauri OR Baudji OR Baudzi OR Damal OR Uhunduni OR Amung OR “Amung Kal” OR Amungme OR Amuy OR Enggipiloe OR Hamung OR Oehoendoeni OR Dani OR Gayo OR “Orang Gayo” OR Gayonese OR Ketengban OR Kupel OR Oktengban OR Kombai OR

Komboy OR Kubu OR Djambi OR “Orang Darat” OR Mentawai OR Mentawei OR Mentawi OR Minangkabau OR Minang OR Padang OR “Orang Minangkabau” OR Moni OR Migani OR Djonggunu OR Jonggunu OR Moronene OR Maronene OR Nias OR Batu OR Nuaulu OR “Southern Nuaulu” OR “Northern Nuaulu” OR Rejang OR “Keme Tun Djang” OR “Orang Rejang” OR Djang OR “Tun Djang” OR “Redjang Empat Petulai” OR “Djang Lebong” OR “Djang Bele Tebo” OR “Djang Musai” OR “Djang Lai” OR “Djang Bekulau” OR “Djang Abeus” OR “Djang Aweus” OR “Bang Hadji” OR Semitul OR Sawang OR Selako OR “Selako Dayak” OR Selakau OR Salakau OR Salako OR Silakau OR Tamiang OR Malayu OR Wandamen OR Wandamen-Windesi OR Windesi OR Windessi OR Bintuni OR Bentuni OR Bentoeni OR Wamesa OR Wolio OR Buton OR Butonese OR Walio

“SRI LANKA” OR CEYLON: SEAR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR “Ceylon Tamils” OR “Jaffna Tamils” OR “Indian Tamils” or “Estate Tamils” OR “Sri Lankan Moors” OR Burghers OR “Sri Lankan Chetty” OR Bharatha OR Wanniyala-Aetto OR Veddhas OR Sinhalese OR Tamil OR Wanniya-laeto OR Vedda OR Veddha OR Veddah OR Wanniyala-Aetto

THAILAND: SEAR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Akha OR Hmong OR Karen OR Lahu OR Lisu OR Mein OR Mon OR “Khmer Thai Isan” OR “Thai Lao” OR Khmer OR Kaw OR Bisu OR Mbi OR Mbisu OR Mibisu OR Misu OR “Hmong Daw” OR “White Meo” OR “White Hmong” OR “Hmong Njua” OR “Black Meo” OR “Blue Meo” OR H'tin OR T'in OR Ht'in OR Thin OR Tin OR Khatin OR Isan OR Lao OR Isaan OR Issan OR Esarn OR Karen S’gaw OR Khmu OR Khamu OR Kammu OR Kui OR Kuoy OR Kuy OR Suoy OR Suay OR Suai OR Lahu OR Musser OR Lisu OR Lisaw OR “lu Mien” OR Mien OR Yao OR “Yui Mien” OR Mani OR Manik OR Maniq OR Negrito OR Mannee OR Mlabri OR “Phi Tong Luang” OR Moken OR Salong OR Selung OR Salone OR “Sea Gypsy” OR Moklen OR “Chao Lay” OR Palaung OR “Silver Palaung” OR “Pale Palaung” OR Bulay OR Dlang OR Palay OR Palong OR Pulei OR Shwe OR Ta’ang OR “Tai Lue” OR “Dai Lue” OR “Urak Lawoi*” OR “Chao Lay” OR “Lumoh Lawoi” OR “Sea Gypsies” OR “Thai Mai” OR “Chao thale” OR “Chao khao” OR “Chon phao” OR “Chon phao mueang”

TIMOR*: SEAR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR “Tetum Prasa” OR Mambai OR Makasae OR “Tetum

Terik” OR Baikenu OR Kemak OR Bunak OR Tokodede OR Fataluku OR Waima’a OR Galoli OR Naueti OR Idate OR Midiki OR Tentum OR Baikeno OR Makasai

BANGLADESH: SEAR D
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Adivasis OR Jumma OR Chakmas OR Marma OR Tripura OR Mro OR Biharis OR Chakma OR Takam OR Chakama OR Tsakma OR Changma OR “Changma Vaj” OR “Changma Kodha” OR Chin OR Khumi OR Khumi OR Khami OR Kami OR Kumi OR Khweymi OR Khuni OR Darlong OR Dalong OR Zo OR Garo OR A'Chik OR Mande OR Mandi OR Lamdani OR Achchik OR Acchiks OR Achik OR Oraon OR Uraon OR Khurukh

BHUTAN: SEAR D
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Lhotshampas OR Chali OR Dakpa OR Sagtengpa OR Brokpa OR Brokkat OR Layap OR Lepcha OR Rong OR Rongke OR Rongpa OR Lhop OR Doya OR Lhokpu OR Lhops OR Lhopu OR Lhotshampas OR Gurkhali OR Nepali OR Paharia OR “Southern Bhutanese” OR Monpa OR Menba OR Moinba OR Monba OR Menpa OR Mongba OR Ngalop OR Bhote OR Sharchop OR Schachop OR Bhotia OR “Central Monba” OR “Cuona Monba” OR Memba OR Sarchapkkha OR “Southern Moonba” OR Tshalingpa OR “Bhotia Eastern” OR “Cona Monba” OR “Eastern Bhutanese” OR Mompa OR Sangla OR Sharchagpakha OR Tsangla

“DEMOCRATIC PEOPLE’S REPUBLIC OF KOREA”: SEAR D
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

INDIA: SEAR D
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Dalits OR Nagas OR Adivasis OR Adaman* OR Onges OR Jarawa OR Sentinelese OR “Adi Padam” OR Padam OR Miri OR Abor OR Arbor OR Abor-Miri OR Aimol OR Angami OR “Southern Angami” OR Japfuphiki OR “Western Angami” OR Jotsoma OR Khonoma OR Mezoma OR Chakhro OR “Northern Angami” OR Ao OR Awan OR “QuTB Shahi Awan” OR Badaga OR Badag OR Badagux OR Badugu OR Vadagu OR Baiga OR Bhumia OR Bhuiya OR Narotia OR Binjwar OR Bharotia OR Raibhaina OR Kathbhaina OR Kondwan OR Gonwaina OR Bangni OR Dafla OR Nishi OR “Nishi Bangni” OR Banjara OR Vanzara OR Lambadi OR Sugali OR Ghor OR Bharia OR Bhar OR Bharat OR Bhumia OR Bhumiya OR Paliha OR “Bhuinha Bhumia” OR Bhumiya OR Pando OR

Bhil OR Bhilbari OR Bhilboli OR Bhilla OR Bhili OR Bhilodi OR Vil OR Bhagoria OR Lengotia OR Birhor OR Bihor OR Birhar OR Birhore OR Mankidi OR Mankidia OR Bishnoi OR Marwadi OR Vishnoi OR Bodo OR Boro OR Bodi OR Bara OR Boroni OR Mechi OR Meche OR Mech OR Meci OR Kachari OR Bondo OR “Bondo Poraja” OR Bonda OR Remo OR Chakhesang OR Chang OR Chenchu OR Chenchucoolam OR Chenchwar OR Chenswar OR Choncharu OR Chote OR Chowte OR Chawtes OR Purum OR Dal OR “Dandami Marias” OR “Bison Horn Marias” OR “Kalpati Marias” OR “Singh Marias” OR “TalaguDDa Marias” OR Maria OR Dhodia OR Dhobi OR Dhori OR Dhore OR Dhowari OR Doria OR Didayi OR Gataq OR Getaq OR Geta' OR Gta' OR “Gta Asa” OR Didei OR Dire OR Gata' OR Didayee OR Digaro-Mishmi OR Digaru-Mishmi OR Taraon OR “Dimasa Kachari” OR Dimasa OR Dima-fisa OR Dogra OR Dogri OR Dogri-Kangri OR Dhogaryali OR Dogari OR “Dogri Jammu” OR “Dogri Pahari” OR Dogri-Kangr OR Gaddis OR Gaddies OR Garo OR Achik OR Abeng OR Ambeng OR Awe OR Ruga OR Atong OR Garrow OR Mande OR Gowlan OR Gujjars OR Halbaa OR Halba OR Halbi OR Hmar OR Mhar OR Mar OR Ho OR Lanka Kol OR “Bihar Ho” OR “Idu Mishmi” OR “Yidu Lobha” OR Chulikatas OR Irula OR Jaintias OR Jayantias OR Syntengs OR Pnars OR Hynniewtrep OR Jarawa OR “Jenu Kurumba” OR “Jennu Kurumba” OR “Jenu Kuruba” OR “Kadu Nayikas” OR Juang OR Patuas OR Puttooas OR Patra-Saara OR Patta-Savara OR Juango OR Kabui OR Rongmei OR Zeliangrong OR Puimei OR Inpui OR Kapwi OR Koboi OR Kubai OR “Kabui Naga” OR “Kacha Naga” OR “Kadu Kuruba” OR “Kadu Kurumba” OR Khasi OR Khoibu OR “Khoibu Maring” OR “Khoibu Maring Naga” OR Khond OR Kandhs OR “Raj Khonds” OR Kinnaure OR Kinners OR Kinnauris OR Kisan OR Nagasia OR Nagesia OR Nagesar OR Naksia OR Diharia OR Oraon OR Dhangad OR Dhangar OR Dhanka OR Kuda OR Kurukh OR Kurunkh OR Orao OR Uraon OR Kondh OR Kond OR Kui OR Buda Kondh OR “Bura Kandha” OR “Desia Kandha” OR “Dungaria Kondh” OR “Kutia Kandha” OR “Kandha Gauda” OR “Muli Kondh” OR “Malua Kondh” OR “Pengo Kandha” OR “Raja Kondh” OR “Raj Khond” OR “Desia Kondh” OR “Dongariya Kondh” OR Korku OR Bondhi OR Bopchi OR Kodaku OR Kurku OR Mouasi OR Muwasi OR Koya OR Koi OR “Koi Gondi” OR Kavor OR Koa OR Koitar OR Koyato OR Kaya OR Koyi OR Raj Koya OR Kavor OR Koitor OR Koithur OR Koitur OR Kutchi OR Kacchi OR Kanbis OR Bhanushali OR Rabari OR Ahirs OR Meghwals OR Lahules OR Lahulas OR Lahaulis OR Liangmai OR Kacha OR Liyang OR Lyengmai OR Liangmei OR Lyangmay OR Lohara OR Lohra OR Luhura OR Luhara OR Lotha OR “Naga Lotha” OR Madia OR Madia-Gond OR Maria OR Maria-Gond OR Madiya OR “Hill Madia” OR “Bison Horn Maria” OR Magahi OR Magadhi OR Magaya OR Maghai OR Maghaya OR Maghori OR Magi OR Magodhi OR Bihari OR Megahi OR “Magar Eastern” OR Magari OR Mangar OR Mangari OR Magarkura OR Mahali OR Mahli OR Mao OR “Naga Mao” OR Maram OR “Naga Maram” OR Meithei OR Meitei OR Manipuris OR Kathi OR Kathe OR Ponna OR Meiteilon OR Miju-Mishmi OR Kaman OR Mishing OR Mising OR Takam OR Tanis OR Amis OR Monpa OR Mendba OR Moinba OR Monba OR Menpa OR Mongba OR Menba OR Monsang OR

Moshang OR Monshang OR Mushang OR Mawshang OR Munda OR Colh OR Hor OR Kaur OR Mudus OR Mura OR Haroko OR Horohon OR Manki OR Mundu OR “Nicobarese Southern” OR Nicobara OR Nishi OR Nissi OR Dafla OR Nishang OR Nishing OR Nocte OR Bordari OR Panidori OR Namsangia OR Onge OR Ong OR Oraon OR Uraon OR Khurukh OR Paite OR Chin OR Kuki OR Lushai OR Tedim OR Sahte OR Zou OR Paliyan OR Paliyar OR Palleyan OR Palliyar OR Pangwali OR Pahari OR Pangi OR “Pangwali Pahari” OR Pangwala OR Piral OR Pochury OR Poumai OR Raika OR Rabari OR Rebari OR Rabha OR Rahbari OR Maru OR Godwar OR Pitalia OR Chalkia OR Rabbari OR Sorthia OR “Sorathi Charalia” OR Charmta OR Luni OR Kushar OR Tank OR “Muchhal Ka” OR Dhebariya OR Dheberya OR Vagadiya OR Vagariya OR Desi OR Kutchi OR Bhopa OR Gujarati OR Mogha OR Vishotar OR Sinai OR Rengma OR Sangtam OR Santali OR Hor OR Har OR Satar OR Santhali OR Santhal OR Sandal OR Sangtal OR Santal OR Sentali OR Samtali OR Santhiali OR Sonthal OR Saora OR Sora OR Saora OR Saonras OR Shabari OR Sabar OR Saura OR Savara OR Sawaria OR Swara OR Sabara OR Savara OR Sema OR Simi OR Sumi OR “Naga Sumi” OR Sentinel OR Sentinelese OR “Shom Peng” OR “Shom Pen” OR Shompeng OR Shompen OR Shobang OR Kalay OR Keyet OR Spitians OR Sulung OR Sullung OR Suling OR Sulong OR Puroik OR Pariok OR Tagin OR Tani OR “Apa Tani” OR Tangkhul OR Tagkhul OR Thangkhulm OR Champhung OR Luhuppa OR Luppa OR Somra OR Hao OR Tutsa OR Totcha OR Vaiphei OR Bhaipei OR Vaipei OR Veiphei OR Wancho OR “Banpara Naga” OR Joboka OR Warli OR Varli OR Yerukula OR Yerukala OR Yarukula OR Yerkula OR Yerukla OR Erukala OR Korava OR Yerukala-Korava OR Yerukula-Bhasha OR “Eruku Bhasha” OR Korchi OR Kurutha OR “Kurru Bhasha” OR Zangskari OR Zanskari OR Zaskari OR Zomi OR Zo

MALDIVES: SEAR D
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

MYANMAR OR BURMA: SEAR D
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Shan OR Karen OR Rakhine OR Mon OR Chin OR Kachin OR Karenni OR Akha OR Arakanese OR Maghi OR Marma OR Mogh OR Rakhine OR Chin OR Danau OR Danaw OR Danu OR Kachin OR Chingpaw OR Singphos OR Karen OR Pgaganyaw OR Plong OR Pwo OR Sgaw OR Skaw OR S'waw OR Karenni OR Kayah OR Kayan OR Kayaw OR Padaung OR Paku OR Kokang OR Kuki OR Mon OR Nagas OR Rohingya OR Shan OR Tavoyan OR Wa OR Hkawa OR Kala OR Kawa OR Lawa OR Va

NEPAL: SEAR D
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR “Adivasi Janajati” OR Angika OR Anga OR Angikar OR Chhika-Chhiki OR Awadhi OR “Awadhi Abadhi” OR Bahing OR “Bahing Rai” OR Bantawa OR “Bantawa Rai” OR Baraamu OR Baram OR Baramu OR Brahmu OR Bramu OR Bhramu OR Barhamu OR Bhojpuri OR Chukwa OR “Cukwa Ring” OR Pohing OR “Pohing Kha” OR Darai OR Darwai OR Dahri OR Daree OR Daroe OR Darmiya OR Darimiya OR Darmani OR Sauka OR Shauka OR Dhimal OR Haiko OR “Limbus of Terai” OR Dzongkha OR Jonkha OR “Bhotia of Bhutan” OR Zongkhar OR Drukke OR Drukha OR Bhutanese OR “Helambu Sherpa” OR “Yolmo Sherpa” OR Hyolmo OR Jerung OR Jero OR Jirel OR Jiripas OR Jiripa OR Jirpa OR Jiri OR Jirial OR Zaral OR Ziral OR Kagate OR Bhotia OR “Kagate Bhote” OR “Kagate Bhotia” OR Kagatey OR Kagati OR Limbu OR Yakthung OR Magar OR Western OR Mangar OR Maithili OR Maitili OR Maithil OR Majhi OR Bhumar OR Manangba OR “Manang Bas” OR Nyishangba OR Nyi-Shang OR Manang OR Manangi OR Manangpa OR Manangbolt OR Neshyang OR Nesyangba OR Nyeshang OR Mugali OR Mugom OR Mugu OR Kham OR Khan OR Mugum OR Tamang OR Mustang OR Lo OR Lowa OR Mastang OR Sherpa OR Sharpa OR “Sharpa Bhotia” OR Xiaerba OR Serwa OR Tamang OR Thudam OR “Thudam Bhote” OR Thudambas OR Bhote OR Thulung OR “Thulunge Rai” OR “Thulu Luwa” OR Thululoa OR “Thulung La” OR “Thulung Lo” OR “Thulung Jemu” OR “Toaku Lwa” OR “Sub-Group of the Rai”

AUSTRALIA: WPR A
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR “Torres Strait*”

BRUNEI: WPR A
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Dusun OR Bisaya OR Murut OR Kedayan OR Iban OR Tutong OR Penan

JAPAN: WPR A
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Ryūkyūans OR Okinawans OR Ainu OR Utari

“NEW ZEALAND”: WPR A
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Māori

CAMBODIA: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR “Khmer Loeu” OR Kachac OR Chamic OR Kachak OR Kreung OR Krung OR Kru'ng OR Tampuon OR Campuon OR “Kha Tampuon” OR Proon* OR Tamphuan OR Tampuen OR Tumpun

CHINA: WPR A
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR “national minority” or Zhuang OR Manchu OR Hui OR Uyghur OR Yi OR Lolo OR “Tujia Achang” OR Bai OR Blang OR Bulang OR Wa OR Samtuan OR Samtao OR Saamtaav OR Pulang OR Bonan OR Bouyei OR Bouyi OR Buyei OR Buyi OR Dai OR Tai OR Baijue OR “Lu Dai” OR Daur OR De'ang OR Dong OR Gam OR Kam OR Tong OR Tung OR Dongxiang OR Tunghsiang OR Santa OR “Mongolian Huihui” OR Drung OR Ewenki OR Evenki OR Ewenke OR “Manchurian Solon” OR “Owenke Solon” OR “Solon Evenki” OR Suolun OR Tungus OR Gelo OR Hani OR Akha OR Biyo OR Bio OR Biyue OR Kado OR Mahei OR Pudu OR Putu OR Sansu OR Hezhen OR Hezhe OR Sushen OR Hmong OR Jing OR Jingpo OR Jino OR Kazak OR Kazakh OR Khmu OR Kirjiz OR Lahu OR Lhoba OR Li OR Lisu OR Maonan OR Miao OR “Black Hmong” OR “Black Miao” OR Daishou OR Guoxiong OR “Long Skirt Miao” OR Mao OR “Red Hmong” OR “Red Miao” OR “Short Skirt Miao” OR “White Hmong” OR Moinba OR Mosuo OR Moso OR Musuo OR Mulam OR Naxi OR Nahsi OR Nasi OR Nakhi OR Lomi OR Mu OR Nisu OR Nu OR Oroqen OR Ozbek OR Pumi OR Qiang OR Salar OR She OR Shui OR Shuijia OR Sui OR “Sui Li” OR Suijia OR Suipo OR Tajik OR Tartar OR Tatar OR Tata’er OR Dada OR Daden OR Tu OR Tujia OR Uygur OR Va OR Xibe OR Yao OR “Baiku Yao” OR Baikuyao OR Bingduoyou OR Bunu OR “Guoshan Yan” OR Guoshanyao OR “Hon Yao” OR Jinmen OR Lajia OR Mian OR “Pan Yao” OR Panyao OR “Pindi Yao” OR Pindiyao OR “Shanzi Yao” OR Shanziyao OR Ajia OR “Black Yi” OR Yi OR Heiyi OR Qunuo OR Wajia OR “White Yi” OR Xiaxi OR Younuo OR “Hong Yao” OR “Red Yao” OR Yunou OR Yuno OR Yugur

“COOK ISLANDS”: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

FIJI: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Rotumans OR iTaukei

KIRIBATI: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR I-Kiribati OR Tuvalu OR Banaba

LAO*: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Phouthay OR Tai OR Makong OR Katang OR Lue OR Akha OR Aka OR Ekaw OR Ekwa OR Kaw OR Khka OR “Kon Ak'a” OR Hmong OR Maio OR Meo OR Khmu OR Kammu OR Khamu OR Lamet OR “Kha Lamet” OR Khamet OR Khamed OR Lemet OR Rmeet OR Lantan OR Lantien OR Malabri OR Mlabri OR “Phi Tong Luang” OR “Toong Luang” OR “Yellow Leaf” OR Yumbr OR Yumbri

MALAYSIA: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR “Anak Negeri” OR “Orang Ulu” OR Dayak OR “Orang Asli” OR Bajau OR Illanun OR Badjao OR Badjau OR Bajaw OR Bajo OR Suluk OR Obian OR “Orang Sama” OR “Sama Dilaut” OR “Sea Gypsies” OR Binadan OR Batek OR “Batek Negritos” OR Bidayuh OR “Bukar Sadong” OR Tebakang OR Bugis OR Buginese OR Luwu OR Ugi OR Chewong OR “Che’Wong” OR Iban OR “Sea Dayak” OR Jahai OR Jah OR Jehai OR Pangan OR “Jah Hut” OR Cheres OR Jakun OR Djakun OR “Orang Hulu” OR “Kadazan Dusun” OR “Tuaran Dusun” OR “Suang Lotud” OR Minokok OR Ringus OR “Tempasuk Dusun” OR Tindal OR “Orang Sungai” OR Kedayan OR Kedyan OR Kadayan OR Kadien OR Kensiu OR Negrito OR Lanoh OR Sakai OR Semnan OR “Mah Meri” OR Besisi OR Btsisek OR Melanaus OR Balingian OR Belanau OR Bruit OR Dalat OR Sarikei OR Muka OR Melanau OR Melenau OR Mendriq OR Mendrik OR Menri OR Mandriq OR Murut OR Timogun OR Tagal OR Nabas OR Penan OR Semai OR “Semai Senoi” OR Semang OR Semelai OR “Semaq Tasik” OR “Semoq Beri” OR Semaq OR Semalai OR “Semaq Beri” OR “Jakun of Tekai River” OR Senoi OR Sengoi OR Temiar OR “Temiar Senoi” OR Bumiputera OR Temuan OR Belanda OR Biduanda OR Benua OR Mantera OR Kenyah OR Kayan OR Lunbawang OR Punan OR Bisayah OR Kelabit OR Berawan OR Kejaman OR Ukit OR Sekapan OR Paitan

“MARSHALL ISLANDS”: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

MICRONESIA: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

MONGOLIA: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Bayad OR Bayaad OR Bayit OR Bait OR Dariganga OR Durvud OR Durbet OR Dörbed OR Dörvöd OR Kazakh OR Kazak OR Qazaq OR Khalkha OR Halh OR Mingat OR Myangad OR Torguud OR Torgut OR Tsaatan OR Dukha OR Tsachin

NAURU: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

NIUE: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

PALAU: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

“PAPUA NEW GUINEA”: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Bougainvilleans

PHILIPPINES: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Tagalog OR Bisaya OR Binisaya OR Cebuano OR

Ilocano OR Hiligaynon OR Ilonggo OR Bikol OR Bicol OR Waray OR Igorot OR Lumad OR Mangyan OR Abaknon OR Capul OR “Capul Samal” OR Capuleno OR Inabaknon OR Inbaknon OR Kapul OR Sama OR Applai OR Appais OR Kankanan-ey OR Katangnan OR “Lepanto Igorot” OR “Sagada Igorot” OR “Western Bontoc” OR “Western Bontok” OR Arumanen OR Aromanon OR Arumamen OR “Central Mindanao” OR Ilianen OR Liringanen OR Manobo OR Manuvu OR “South Cotabato” OR Attaw OR Bagobo OR Clata OR Diangan OR Giangan OR Guingan OR Guiangan OR Gulanga OR Jangan OR Klata OR Obo OR Banwaon OR Adgawanon OR Banuaonon OR Banwanon OR Higaonon-Banwaon OR “Bontok Igorots” OR Bontoc OR Kadaklan-Barlig OR Bukidnon OR Binokid OR Binukid OR “Central Bukidnon” OR Butuanon OR Lapaknon OR “Davao Chabakano” OR Chabakano OR “Chabakano Creole” OR Chavacano OR Creole OR Davao OR Zamboanga OR Dibabawon OR Dibabaon OR Mandaya OR “Dibabawon Manobo” OR “Digagaon Mandaya Manobo” OR “Orang Dibabawon” OR Higaonon OR Banuanon OR Higanon OR “Higaonon Manobo” OR “Misamis Higaonon” OR Talaandig OR “Jama Mapun” OR “Orang Cagayan” OR “Tao Cagayan” OR Kabihug OR Abian OR Aeta OR Agiyan OR Agta OR Bihug OR Bikol OR “Camarines Norte Agta” OR Manide OR Negrito* OR Lambangian OR Teduray-Lambangian OR Tiruray OR Lapuyan OR Lapuyen OR “Subanun Lapuyan” OR Margosatubig OR Subanon OR Subanun OR Subanen OR Suban-on OR “Southern Subanun” OR “Manobo Agusan” OR “Agusan del Sur” OR Agusan OR Higanon OR Kidapawan OR Ubo OR Molbog OR Molebugan OR Molebuganon OR Molebuganori OR Palawan OR Palawano OR Palawanon OR Pala’wan OR Pinalawan OR Sangil OR Sanggil OR Sangire OR Sangihe OR “Sangir Pilipinas” OR Sangir OR Sangu OR Marore OR Sangirezen OR Talaoerezen OR Surigaonon OR Surigao OR Tagakaolo OR Kalagan OR Mansaka OR “Tagakaolo Kalagan” OR Tagakaulu OR “Tagakaulu Kalagan” OR Tagbanua OR Tagbanuas OR Tala-Andig OR Talandig OR “Tau´t Batu” OR “Tao’t Bato” OR “Tao’t Batu” OR “Taw Batu” OR TBoli OR Kiamba OR Tagabeli OR Tagabulu OR T'boli OR Tibole OR Tiboli

“REPUBLIC OF KOREA”: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

SAOMA: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

“SOLOMON ISLANDS”: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

TONGA: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

TUVALU: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous

VANUATU: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Wallisians OR Futunans OR i-Kiribati

VIETNAM: WPR B
Indigenous OR aborigin* OR native OR “first nation*” OR “ethnic group” OR tribal OR tribe OR autochthonous OR Akha OR Aka OR Ak’a OR Ahka OR Hani OR “Ha Nhi” OR Ikaw OR Xo OR Khako OR “Kha ko” OR “Khao Ikor” OR Aini OR Yani OR “Hka Ko” OR “Khao Kha Ko” OR Arem OR A-Rem OR Chomrau OR Chombrau OR Umo OR Bahnar OR “Ba Na” OR “To Lo” OR Golar OR Jolong OR “Gio Lang”OR “Y Lang” OR “Ro Ngao” OR Reungao OR Rangao OR Ro-Ngao OR “Bahnar Rongao” OR Krum OR Krem OR Roh OR “Con Kde” OR “Kpang Cong” OR “Bo Mon” OR Bonom OR Bomom OR Alacong OR Alakong OR “A-La Cong” OR Brao OR Brau OR Braou OR Proue OR Proon OR Brou OR “Cao Lan” OR Caolan OR “Hon Ban” OR “San Chay” OR “San Chi Man Cao-Lan” OR Sán-Chi OR Mán OR “Cao Lan-Sán Chi” OR “Cho Ro” OR “Chau Ro” OR Chauro OR Chorao OR Choro OR Cho-ro OR Chrau OR “Do Ro” OR Zro OR “Chu Ru” OR Cadoe OR Chru OR Choru OR “Cho Ru” OR Chu OR Chu-ru OR Churu OR Cru OR Degar OR Kru OR Loang OR Seyu OR Ru OR Ede OR E-de OR Edeh OR De OR Dega OR Haqniq OR “Ha Nhi” OR Hanízú OR Hanhi OR “H Nhi” OR “Ha Nhi Gia” OR Uni OR ”U Ni” OR Xauni OR ”Xa U Ni” OR Koho OR Coho OR Co-ho OR Ko-ho OR Kohor OR K'ho OR Caho OR “Co Ho” OR “La Ha” OR “Xa Khan” OR “Xa Cah” OR “Xa Chien” OR “Xa Khao” OR “Xa Lay” OR “Xa Lga” OR “Khla Don” OR “Kla Dong” OR “Khla Liik” OR “La Hu” OR Luohei OR Launa OR Lahuna OR Laku OR Kaixien OR Namen OR Mussuh OR Muhso OR Musso OR Mussar OR Mussur OR Moso OR Lachi OR Lati OR “Cu Te” OR “Tho Den” OR “Black Tho” OR “Man La” OR Chi

OR “La Chi” OR Pula OR Phula OR Fula OR Foula OR Lipupo OR Laji OR Lipulio OR Laqua OR “Y Pi” OR “Y Pong” OR Laghuu OR Laopa OR Xapho OR “Xa Pho” OR “Lahu Shi” OR “Yellow Lahu” OR Kouy OR Lu OR Duon OR Kon OR Leu OR “Lu Ge Zi” OR “Lu Ren” OR Lue OR Lugepo OR Nhuon OR Zhon OR Maa OR Ma OR “Chau Ma” OR “Ma Xop” OR “Ma To” OR “Ma Krung” OR “Ma Ngan” OR Maleng OR Pakatan OR Malieng OR Malang OR “Ma Leng” OR “Ma Lieng” OR Romam OR “Ro Mam” OR Ro-mam OR Sedang OR Hadang OR Hdang OR Hoteang OR Roteang OR Rotea OR Hotea OR “Xo Dang” OR Xodangg OR “Xa Dang” OR Cadong OR Tang OR Kmrang OR Kmrong OR Konelane OR Brila OR Stieng OR Budeh OR Xtieng OR “Xa Dieng” OR “Ba Ra” OR “Bu Dip” OR Budip OR “Bu Lanh” OR Rangah OR Tay OR Tho OR Ngan OR Phen OR “Thu Lao” OR “Pa Di”

Each search will comprise:
A. country AND
B. parasites/bacteria terms AND
C. country relevant indigenous terms

Appendix 3: Example search strategy for Indonesia.

Indonesia **AND** “soil transmitted helminth*” OR STH OR Ascaris OR Trichuris OR Nectator OR Ancylostoma OR hookworm* OR Strongyloides OR malaria* OR plasmodi* OR tuberculosis OR TB OR “Mycobacterium tuberculosis” **AND** Indigenous OR aborigin* OR native OR first nation* OR “ethnic group” OR tribal OR tribe OR autochthonous OR “adat terpencil” OR Acehnese OR Achinese OR Atjeher OR “Orang Aceh” OR Acehnais OR Acehno OR Atjeh OR Atjehnese OR Achehnese OR Achenese OR Adabe OR Ataura OR Atauru OR Atauro OR Raklu-Un OR “Raklu Un” OR Adonara OR “Tusa Tadon” OR Waiwerang OR Vaiverang OR Sagu OR Alorese OR Ampanang OR Andio OR Masama OR Andio'o OR Imbao'o OR Aralle OR Tabulahan OR Asmat OR Asamat OR Asemer OR Asomat OR Bagusa OR “Batak Alas-Kluet” OR “Alas-Kluet Batak” OR “Batak Kluet-Alas” OR “Kluet-Alas Batak” OR “Alas Kluet” OR “Kluet Alas” OR Alas OR Kluet OR “Batak Angkola” OR “Orang Angkola” OR Anakola OR Angkola OR “Batak Dairi” OR Dairi OR “Dairi Batak” OR “Orang Batak Dairi” OR Pakpak OR “Pakpak Dairi” OR Sumut OR “Batak Karo” OR “Karo Batak” OR “Orang Batak Karo” OR Karonese OR “Batak Mandailing” OR “Mandailing Batak” OR Batta OR “Orang Mandailing” OR “Batak Simalungun” OR “Simalungun Batak” OR “Orang Batak Simalungun” OR Simelungun OR Simelungan OR Timur OR “Batak Toba” OR “Toba Batak” OR “Orang Batak Toba” OR “Silindung Batak” OR Bauzi OR Baudi OR Bauri OR Baudji OR Baudzi OR Damal OR Uhunduni OR Amung OR “Amung Kal” OR Amungme OR Amuy OR Enggipiloe OR Hamung OR Oehoendoeni OR Dani OR Gayo OR “Orang Gayo” OR Gayonese OR Ketengban OR Kupel OR Oktengban OR Kombai OR Komboy OR Kubu OR Djambi OR “Orang Darat” OR Mentawai OR Mentawei OR Mentawi OR Minangkabau OR Minang OR Padang OR “Orang Minangkabau” OR Moni OR Migani OR Djonggunu OR Jonggunu OR Moronene OR Maronene OR Nias OR Batu OR Nuaulu OR “Southern Nuaulu” OR “Northern Nuaulu” OR Rejang OR “Keme Tun Djang” OR “Orang Rejang” OR Djang OR “Tun Djang” OR “Redjang Empat Petulai” OR “Djang Lebong” OR “Djang Bele Tebo” OR “Djang Musai” OR “Djang Lai” OR “Djang Bekulau” OR “Djang Abeus” OR “Djang Aweus” OR “Bang Hadji” OR Semitul OR Sawang OR Selako OR “Selako Dayak” OR Selakau OR Salakau OR Salako OR Silakau OR Tamiang OR Malayu OR Wandamen OR Wandamen-Windesi OR Windesi OR Windessi OR Bintuni OR Bentuni OR Bentoeni OR Wamesa OR Wolio OR Buton OR Butonese OR Walio

Appendix 4: Data extraction tool.

The following headings will be used for data extraction within Excel (version 2014):

- First author
- Year of publication
- Year of study/data collection
- Study design
- Country
- Village, region/state
- Population group(s) (minority indigenous/other)
- Name of population group(s) (e.g., Aeta, Bulang, Penan)
- Study site (e.g., school, community etc)
- Sample type(s) (e.g., blood, fecal)
- Number of samples taken and analyzed per participant
- Infectious agent(s) (e.g., A.lumbricoides, P.falciparum)
- Diagnostic method(s) (e.g., smear microscopy, culture, chest X-ray, and GenXeprt for active TB; microscopy, RDT, PCR, splenomegaly for malaria and microscopy, PCR, serology, for STH)
- Study population (children, adult, both)
- Study population age group (<15 years; ≥15 years)
- Study population median age

- Study population size (n)
- Male (# male within the study population)
- Female (# female within the study population)
- Number of people infected
- Co-infection (name of infectious agent)
- Prevalence of co-infection (# co-infected)
- Comments/notes

Appendix 5: Quality and bias assessment.

The following adaption to the Newcastle-Ottawa Scale [9] will be utilized for this review:

Newcastle-Ottawa Scale adapted for cross-sectional studies (Maximum total= 9 points)

Study Population

1 The study population is clearly defined

0 The study population is not clearly defined

Representativeness of the sample

2 Study sample is representative of the study population (all subjects or random sampling)

1 Study sample comprises a select group of the study population (non-random sampling)

0 No description of the sampling strategy.

Ascertainment of specimen collection methods

1 The study clearly defines specimen collection methodologies

0 The study does not detail specimen collection methodologies

Sample size

1 Justified and satisfactory (sample size and power calculation included)

0 Not justified

Non-respondents

1 Comparability between respondents and non-respondent's characteristics are established

0 No description of the response rate or the characteristics of the responders and the non-responders.

Comparability:

Impact of Bias (selection bias, measurement bias, participant reporting, confounders)

1 Where relevant, the study acknowledges and mitigates for potential bias. When comparisons are made between different study populations results are adjusted for confounders

0 Where appropriate, the study does not acknowledge or mitigate for potential bias. When comparisons are made between different study populations results are not adjusted for confounders

Assessment of the outcome (TB, Malaria, STH infection)

1 Objective diagnostic methodology with units of measurement and /or definitions

0 No definitive diagnosis or self-report

Statistical analysis

1 The statistical method used is clearly described and appropriate for the analysis undertaken. Where comparisons are made between population groups, the measurement of the association is presented, including confidence intervals and the probability level (p value)

0 The statistical method is inappropriate/not described/incomplete

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Appendix 4: Paper IV Supplementary Information

S1 Table A: PRISMA Checklist [1]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figs 3,4,5,6,7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 2,4,6,8,10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Tables 3,5,7,9,11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41.

S1 Table B: Systematic review search terms summary

Descriptor	Search Terms
STH search terms	*"soil transmitted helminth*"* OR *STH* OR *Ascaris* OR *Trichuris* OR *Nectator* OR *Ancylostoma* OR *Strongyloides* OR *hookworm** **AND**
[Δ] Countries within the SEAR and WPR	*Indonesia* OR "*Sri Lanka*" OR *Ceylon* OR *Thailand* OR *Timor** OR *Bangladesh* OR *Bhutan* OR "*Democratic People's Republic of Korea*" OR *India* OR *Maldives* OR *Myanmar* OR *Burma* OR *Nepal* OR *Australia* OR *Brunei* OR *Japan* OR "New Zealand" OR Cambodia OR China OR "*Cook Islands*" OR *Fiji* OR *Kiribati* OR *Lao** OR *Malaysia* OR "*Marshall Islands*" OR *Micronesia* OR Mongolia OR Nauru OR Niue OR Palau OR "*Papua New Guinea*" OR *Philippines* OR "*Republic of Korea*" OR *Samoa* OR "*Solomon Islands*" OR *Tonga* OR *Tuvalu* OR *Vanuatu* OR *Vietnam* **AND**
[α] Indigenous search terms	*Indigenous* OR *aborigin** OR *native* OR *"first nation*"* OR *"ethnic group"* OR *tribal* OR *tribe* OR *autochthonous*

[Δ] The WHO Global Burden of Disease (GBD) regional classification system[1] was used to define the countries located within the SEAR and WPR. Singapore was omitted from the search as there are no minority indigenous populations according to the classification criteria used in this review.

[α] In addition to the above generic indigenous search terms, those relevant to each country were included. The country specific search terms were derived from the International Working Group on Indigenous Affairs[2], Native Planet- Indigenous Mapping[3], and the World Directory Listing of Minorities and Indigenous People[4]. If indigenous minority study populations were not identified according to the search criteria list, but the author identified them as such, they were included within the analysis.

References

1. World Health Organization. Global Burden of Disease Regions used for WHO-CHOICE Analyses n.d. [Available from: https://www.who.int/choice/demography/regions/en/.
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3. Native Planet. Indigenous Mapping: Ethnic Communities from Asia n.d. [Available from: https://www.nativeplanet.org/indigenous/ethnicdiversity/indigenous_data_asia.shtml.
4. Minority Rights Group International. World Directory of Minorities and Indigenous Peoples n.d. [Available from: https://minorityrights.org/directory/.

S1 Table C: QA assessment of STH studies based on modified Newcastle-Ottawa Quality Assessment Scale

Study #	First Author, Year of publication	Study Population	Representativeness of the sample	Ascertainment of specimen collection [illegible]	Sample size	Non-respondents	Impact of Bias (selection bias, measurement bias, participant reporting, confounders)	Assessment of the outcome (STH infection)	Statistical analysis	Total Score	QA Grade
1	Adli, 2019	1	1	1	0	0	0	1	0	4	low
2	Adli, 2020	1	1	1	0	0	0	1	0	4	low
3	Ahmad, 2013	1	1	1	1	0	1	1	1	7	medium
4	Ahmed, 2011	1	1	1	0	1	0	1	1	6	medium
5	Al-Delaimy, 2014A	1	1	1	1	1	1	1	1	8	high
6	Al-Delaimy, 2014B	1	1	1	1	1	1	1	1	8	high
7	Al-Mekhlafi, 2005	1	1	1	0	0	1	1	1	6	medium
8	Al-Mekhlafi, 2006	1	1	1	0	0	0	1	1	5	medium
9	Al-Mekhlafi, 2007	1	1	1	0	1	0	1	1	6	medium
10	Al-Mekhlafi, 2019	1	1	1	1	1	1	1	1	8	high
11	Anuar, 2014	1	1	1	0	0	1	1	1	6	medium
12	Ash, 2017	1	1	1	0	1	1	1	1	7	medium
13	Bangs, 1996	1	1	1	0	1	1	1	0	6	medium
14	Belizario, 2011	1	1	1	1	0	1	1	1	7	medium
15	Brandon-Mong, 2017	1	1	1	0	0	0	1	1	5	medium
16	Chakma, 2000	1	1	1	0	1	0	1	0	5	medium
17	Chin, 2016	1	1	1	1	0	1	1	1	7	medium
18	Choubisa, 1992	1	1	1	0	0	0	1	0	4	low
19	Choubisa, 2012	1	1	1	0	0	0	1	1	5	medium
20	Damon, 1974	1	1	1	0	1	0	1	0	5	medium
21	DeGuia, 2019	1	1	1	1	1	0	1	0	6	medium
22	Elyana, 2016	1	1	1	1	0	1	1	1	7	medium
23	Farook, 2002	1	1	1	0	1	0	1	1	6	medium

24	Fryar, 1997	1	1	1	0	0	0	1	0	4	low
25	Geik, 2015	1	1	1	1	0	0	1	1	6	medium
26	Ghani, 2013	1	1	1	0	1	0	1	0	5	medium
27	Hall, 1994	1	1	1	0	0	1	1	1	6	medium
28	Hanapian, 2014	1	1	1	0	1	0	1	1	6	medium
29	Hartini, 2013	1	1	1	0	1	0	1	1	6	medium
30	Holt, 2017	1	1	1	0	0	1	1	1	6	medium
31	Hung, 2016	1	1	1	0	0	0	1	1	5	medium
32	Kaliappan, 2013	1	1	1	0	1	1	1	1	7	medium
33	Kalra, 1982	1	1	1	0	1	0	1	1	6	medium
34	Kearns, 2017	1	1	1	1	1	0	1	1	7	medium
35	Lee, 2014	1	1	1	0	0	1	1	1	6	medium
36	Lili, 2000	1	1	1	0	0	0	1	0	4	low
37	Lyndem, 2002	1	1	1	0	1	0	1	0	5	medium
38	Meloni, 1993	1	1	1	0	0	0	1	0	4	low
39	Miller, 2018	1	1	1	0	1	0	1	1	6	medium
40	Mohd-Shadaruddin, 2018	1	1	1	1	0	1	1	1	7	medium
41	Muslim, 2019	1	1	1	1	1	1	1	1	8	high
42	Nasr, 2013	1	1	1	0	1	0	1	1	6	medium
43	Neo, 1987	1	1	1	0	1	0	1	0	5	medium
44	Ng, 2014	1	1	1	0	1	1	1	1	7	medium
45	Ngui, 2015	1	1	1	1	0	1	1	1	7	medium
46	Ngui, 2016	1	1	1	1	0	0	1	1	6	medium
47	Nithikathkul, 2003	1	1	1	0	0	0	1	0	4	low
48	Nithikathkul, 2007	1	1	1	0	1	0	1	0	5	medium
49	Nor Aini, 2007	1	1	1	0	1	1	1	1	7	medium
50	Norhayati, 1995	1	1	1	0	0	0	1	1	5	medium
51	Norhayati, 1997	1	1	1	0	0	0	1	1	5	medium
52	Norhayati, 1998	1	1	1	0	0	0	1	1	5	medium
53	Piangjai, 2003	1	1	1	0	0	1	1	1	6	medium

54	Prownebon, 2013	1	1	1	0	0	0	1	1	5	medium
55	Rahmah, 1997	1	1	1	0	1	0	1	0	5	medium
56	Rajeswari, 1994	1	1	1	0	1	0	1	0	5	medium
57	Rajoo, 2017	1	1	1	1	0	1	1	1	7	medium
58	Ranjitkar, 2014	1	1	1	0	0	1	1	1	6	medium
59	Rao, 2002	1	1	1	0	0	0	1	1	5	medium
60	Rao, 2006	1	1	1	0	1	0	1	1	6	medium
61	Reynoldson, 1997	1	1	1	0	1	0	1	1	6	medium
62	Ribas, 2017	1	1	1	0	0	0	1	1	5	medium
63	Ritchie, 1954	1	1	1	0	0	0	1	0	4	low
64	Sagin, 2002	1	1	1	0	0	0	1	0	4	low
65	Saksirisampant, 2004	1	1	1	0	1	0	1	1	6	medium
66	Shield, 2015	1	1	1	0	0	1	1	1	6	medium
67	Singh, 1993	1	1	1	0	1	0	1	0	5	medium
68	Sinniah, 2012	1	1	1	0	1	0	1	0	5	medium
69	Sinniah, 2014	1	1	1	0	1	1	1	0	6	medium
70	Stafford, 1980	1	1	1	0	0	1	1	0	5	medium
71	Steinmann, 2008	1	1	1	0	1	1	1	1	7	medium
72	Sugunan, 1996	1	1	1	0	0	0	1	1	5	medium
73	Tienboon, 2007	1	1	1	0	0	0	1	1	5	medium
74	Verle, 2003	1	1	1	0	1	0	1	1	6	medium
75	Wong, 2016	1	1	1	0	0	0	1	0	4	low
76	Yanola, 2018	1	1	1	0	0	1	1	1	6	medium
77	Yap, 2012	1	1	1	0	0	1	1	1	6	medium
78	Yoshida, 1968	1	1	1	0	0	0	1	0	4	low
79	Zulkifli, 1999A	1	1	1	0	1	0	1	1	6	medium
80	Zulkifli, 1999B	1	1	1	0	1	0	1	0	5	medium
81	Zulkifli, 2000	1	1	1	0	1	1	1	1	7	medium

S1 Table D: Key to modified Newcastle-Ottawa Quality Assessment Scale scoring

Study Population	0= The study population is not clearly defined
	1=The study population is clearly defined
Representativeness of the sample	0=No description of the sampling strategy.
	1= Study sample comprises a select group of the study population (non-random sampling)
	2= Study sample is representative of the study population (all subjects or random sampling)
Ascertainment of specimen collection methods	0= The study does not detail specimen collection methodologies
	1= The study clearly defines specimen collection methodologies
Sample size	0= Not justified
	1= Justified and satisfactory (sample size and power calculation included)
Non-respondents	0= No description of the response rate or the characteristics of the responders and the non-responders.
	1= Comparability between respondents and non-respondents' characteristics are established.
Impact of Bias (selection bias, measurement bias, participant reporting, confounders)	0= Where appropriate, the study does not acknowledge or mitigate for potential bias. When comparisons are made between different study populations results are not adjusted for confounders
	1= Where relevant, the study acknowledges and mitigates for potential bias. When comparisons are made between different study populations results are adjusted for confounders
Assessment of the outcome (STH infection)	0= No definitive diagnosis or self-report
	1= Objective diagnostic methodology with units of measurement and /or definitions
Statistical analysis	0= The statistical test is inappropriate/not described/incomplete
	1= The statistical method used is clearly described and appropriate for the analysis undertaken. Where comparisons are made between population groups, the measurement of the association is presented, including confidence intervals and the probability level (*p* value)

The average QA score across STH studies was 5.7 out of a total possible score of 9.

Appendix 5: Paper V Supplementary Information

Additional file 1

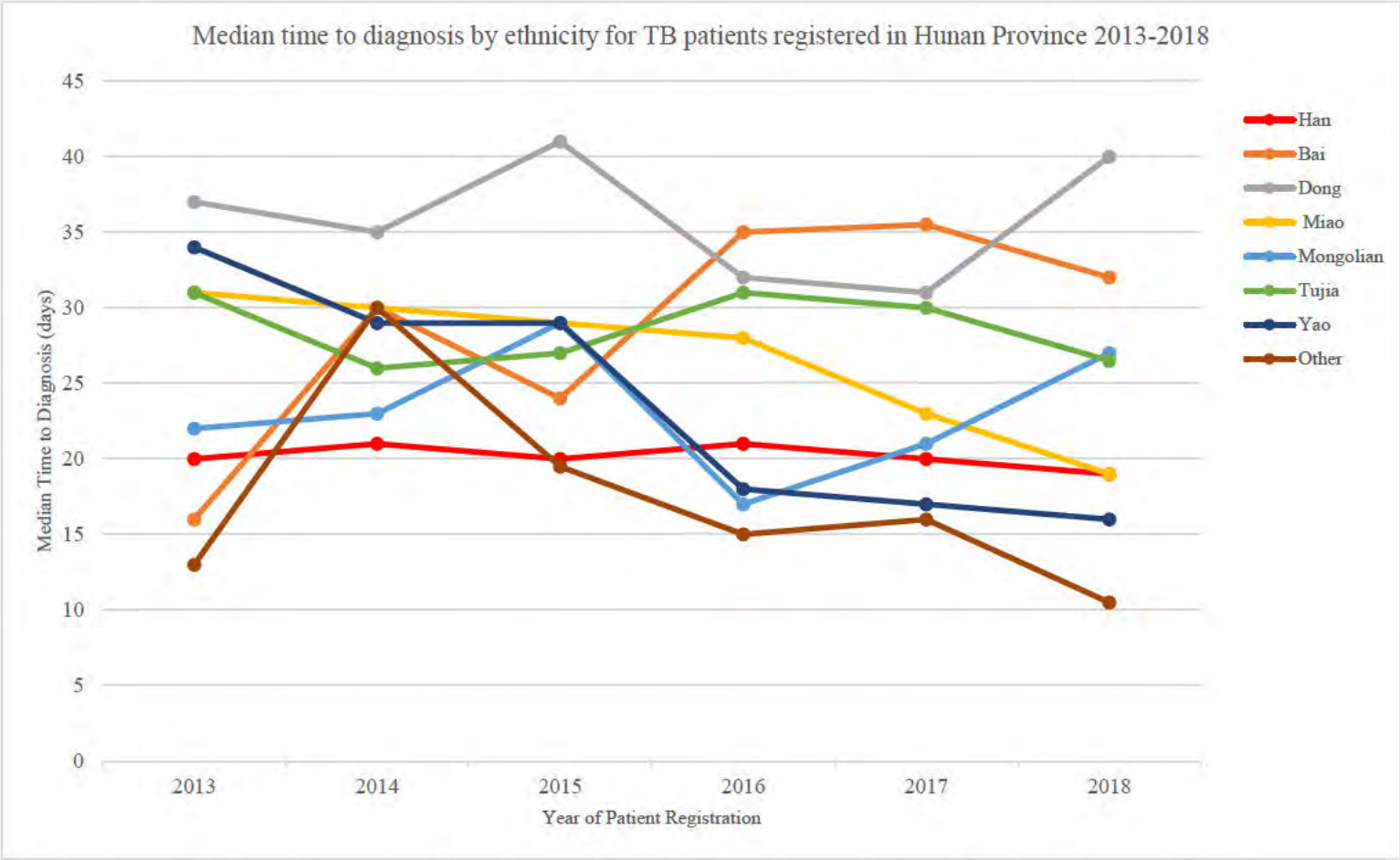

Fig S1: Median time to diagnosis by ethnicity for TB patients registered in Hunan Province 2013-2018

Table S1: Sensitivity Analysis: Univariable and multivariable regression of factors associated with 14-day diagnosis delay in TB patients registered in Hunan Province, 2013-2018

	Univariable odds ratio (95% CI)	Univariable *p* value	Multivariable odds ratio (95% CI)	Multivariable *p* value
Ethnicity				
Han	1.00		1.00	
Tujia	1.26 (1.22, 1.31)	0.001	1.34 (1.29, 1.39)	0.000
Miao	1.44 (1.37, 1.50)	0.000	1.48 (1.42, 1.56)	0.000
Dong	1.58 (1.48, 1.69)	0.000	1.68 (1.57, 1.80)	0.000
Yao	1.15 (1.06, 1.25)	0.001	1.24 (1.14, 1.34)	0.000
Bai	1.18 (0.99, 1.42)	0.068	1.33 (1.10, 1.60)	0.003
Mongolian	1.14 (0.92, 1.42)	0.235	1.13 (0.90, 1.41)	0.296
Other*	0.77 (0.61, 0.96)	0.024	0.88 (0.69, 1.11)	0.283
Sex				
Male	1.00			
Female	1.01 (0.997, 1.03)	0.110	1.04 (1.02, 1.06)	0.000
Age	1.01 (1.01, 1.01)	0.000	1.00 (1.003, 1.004)	0.000
Occupation				
Commercial services/civil servant	1.00		1.00	
Agriculture~	1.47 (1.40, 1.53)	0.000	1.23 (1.17, 1.29)	0.000
Housekeeping$^{\$}$	1.25 (1.19, 1.32)	0.000	1.18 (1.12, 1.24)	0.000
Education$^{\Delta}$	0.81 (0.76, 0.86)	0.000	0.85 (0.80, 0.90)	0.000
Migrant worker	1.40 (1.27, 1.53)	0.000	1.19 (1.09, 1.31)	0.000
Healthcare	1.00 (0.88, 1.14)	0.971	0.96 (0.84, 1.10)	0.554
Hospitality	0.87 (0.74, 1.03)	0.098	0.89 (0.75, 1.05)	0.170
Other	1.07 (1.01, 1.13)	0.017	0.96 (0.90, 1.01)	0.112

Year				
2013	1.00		1.00	
2014	1.04 (1.01, 1.06)	0.005	1.02 (0.99, 1.04)	0.144
2015	1.06 (1.04, 1.09)	0.000	1.05 (1.02, 1.07)	0.000
2016	1.13 (1.10, 1.16)	0.000	1.11 (1.09, 1.14)	0.000
2017	1.00 (0.98, 1.03)	0.777	1.01 (0.99, 1.04)	0.340
2018	0.92 (0.90, 0.95)	0.000	0.99 (0.96, 1.01)	0.311
Residential Address				
Local	1.00		1.00	
Intra-provincial	1.12 (1.07, 1.19)	0.000	1.43 (1.36, 1.51)	0.000
Inter-provincial	0.80 (0.74, 0.87)	0.000	1.02 (0.94, 1.12)	0.608
Foreign nationality	1.17 (0.66, 2.08)	0.582	1.25 (0.70, 2.25)	0.454
Patient Classification				
Consultation symptoms	1.00		1.00	
Referral	0.57 (0.56, 0.58)	0.000	0.56 (0.55, 0.57)	0.000
Contact tracing	0.59 (0.58, 0.60)	0.000	0.60 (0.59, 0.61)	0.000
Health check	0.15 (0.14, 0.16)	0.000	0.16 (0.15, 0.17)	0.000
Other	0.48 (0.43, 0.54)	0.000	0.51 (0.45, 0.57)	0.000
Diagnosis Institution				
CDC	1.00		1.00	
Hospital	0.96 (0.94, 0.98)	0.001	1.00 (0.97, 1.03)	0.897
TB dispensary	1.31 (1.23, 1.40)	0.000	1.24 (1.16, 1.32)	0.000
Other	0.91 (0.56, 1.47)	0.700	1.08 (0.66, 1.77)	0.769
Severely Ill				
No	1.00		1.00	
Yes	1.27 (1.22, 1.32)	0.000	1.33 (1.28, 1.39)	0.000

[~] Agriculture includes famer, herdsman, fisherman.
[$] Housekeeping includes housekeeping, childcare, retired and unemployed.
[Δ] Education includes students and teachers.
*Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups.

Table S2: Univariable and multivariable negative binomial regression assessment of factors associated with time to diagnosis in TB patients registered in Hunan Province, 2013-2018

	Univariable coefficient (95% CI)	Univariable *p* value	Multivariable coefficient (95% CI)	Multivariable *p* value
Ethnicity				
Han	0.00		0.00	
Tujia	0.17 (0.15, 0.20)	0.000	0.23 (0.20, 0.25)	0.000
Miao	0.06 (0.02, 0.09)	0.001	0.13 (0.09, 0.16)	0.000
Dong	0.51 (0.47, 0.56)	0.000	0.52 (0.47, 0.57)	0.000
Yao	-0.06 (-0.12, -0.001)	0.046	0.05 (-0.008, 0.11)	0.089
Bai	0.69 (0.56, 0.82)	0.000	0.60 (0.47, 0.74)	0.000
Mongolian	-0.05 (-0.21, 0.11)	0.560	-0.07 (-0.24, 0.09)	0.367
Other*	-0.24 (-0.42, -0.07)	0.007	-0.10 (-0.27, 0.08)	0.287
Sex				
Male	0.00		0.00	
Female	-0.01 (-0.02, -0.002)	0.017	0.02 (0.005, 0.03)	0.005
Age	0.01 (0.01, 0.01)	0.000	0.01 (0.01, 0.01)	0.000
Occupation				
Commercial services/civil servant	0.00		0.00	
Agriculture~	0.29 (0.26, 0.32)	0.000	0.13 (0.10, 0.17)	0.000
Housekeeping$^{\$}$	0.26 (0.22, 0.30)	0.000	0.10 (0.06, 0.14)	0.000
Education$^{\Delta}$	-0.42 (-0.46, -.037)	0.000	-0.18 (-0.22, -0.13)	0.000
Migrant worker	0.16 (0.09, 0.22)	0.000	0.14 (0.07, 0.21)	0.000
Healthcare	-0.41 (-0.51, -0.31)	0.000	-0.34 (-0.44, -0.24)	0.000
Hospitality	-0.45 (-0.58, -0.32)	0.000	-0.29 (-0.42, -0.17)	0.000
Other	0.003 (-0.04, 0.04)	0.883	-0.03 (-0.07, 0.01)	0.142
Year				
2013	zero		zero	
2014	0.04 (0.02, 0.06)	0.000	-0.02 (0.004, 0.04)	0.016
2015	-0.004 (-0.02, 0.01)	0.698	-0.02 (-0.04, -0.002)	0.026

2016	-0.009 (-0.03, 0.009)	0.337	-0.0009 (-0.02, 0.02)	0.924
2017	-0.06 (-0.07, -0.04)	0.000	-0.03 (-0.05, -0.02)	0.000
2018	-0.08 (-0.10, -0.06)	0.000	-0.003 (-0.02, 0.02)	0.796
Residential Address				
Local	0.00		0.00	
Intra-provincial (within province)	0.002 (-0.04, 0.04)	.923	0.14 (0.10, 0.18)	0.000
Inter-provincial (between provinces)	-0.31 (-0.38, -0.25)	0.000	-0.09 (-0.16, -0.03)	0.006
Foreign nationality	0.06 (-0.36, 0.47)	0.794	0.29 (-0.13, 0.70)	0.174
Patient Enrolment Classification				
Consultation due to symptoms	0.00		0.00	
Referral	-0.09 (-0.10, -0.07)	0.000	-0.08 (-0.09, -0.07)	0.000
Contact tracing	0.04 (0.03, 0.05)	0.000	0.05 (0.04, 0.06)	0.000
Health check	-1.30 (-1.36, -1.25)	0.000	-1.07 (-1.13, -1.02)	0.000
Other	-0.28 (-0.36, -0.19)	0.000	-0.28 (-0.36, -0.19)	0.000
Diagnosis Institution				
CDC	0.00		0.00	
Hospital	-0.21 (-0.22, -0.19)	0.000	-0.19 (-0.21, -0.17)	0.000
TB dispensary	-0.23 (-0.28, -0.19)	0.000	-0.22 (-0.26, -0.17)	0.000
Other	-0.58 (-0.94, -0.21)	0.002	-0.31 (-0.67, 0.05)	0.091
Severely Ill				
No	0.00		0.00	
Yes	0.05 (0.02, 0.07)	0.001	0.05 (0.02, 0.08)	0.001

Table S3: Sensitivity Analysis: Univariable and multivariable regression assessment of factors associated with 1-day treatment delay in TB patients registered in Hunan Province, 2013-2018

	Number of patients (%)	Univariable odds ratio (95% CI)	Univariable *p* value	Multivariable odds ratio (95% CI)	Multivariable *p* value
Ethnicity					
Han	288,802 (90.59)	1.00		1.00	
Tujia	13,680 (4.29)	0.99 (0.95, 1.02)	0.483	1.14 (1.10, 1.19)	0.000
Miao	8,460 (2.65)	1.05 (1.00, 1.09)	0.035	1.22 (1.16, 1.28)	0.000
Dong	4,033 (1.27)	0.83 (0.78, 0.89)	0.000	0.85 (0.79, 0.90)	0.000
Yao	2,662 (0.84)	0.55 (0.51, 0.60)	0.000	0.55 (0.51, 0.60)	0.000
Bai	509 (0.16)	1.24 (1.05, 1.48)	0.014	1.36 (1.13, 1.63)	0.001
Mongolian	349 (0.11)	0.93 (0.75, 1.15)	0.507	0.90 (0.72, 1.14)	0.387
Other*	293 (0.09)	0.96 (0.76, 1.21)	0.729	0.90 (0.70, 1.15)	0.397
Sex					
Male	231,495 (72.62)	1.00		1.00	
Female	87,297 (27.38)	1.09 (1.07, 1.11)	0.000	1.03 (1.02, 1.05)	0.000
Age	318,792 (100)	0.996 (0.996, 0.996)	0.000	0.998 (0.998, 0.999)	0.000
Occupation					
Commercial services/civil servant	7,818 (2.45)	1.00		1.00	
Agriculture~	249,093 (78.14)	0.42 (0.40, 0.44)	0.000	0.53 (0.50, 0.56)	0.000
Housekeeping[$]	30,802 (9.66)	0.78 (0.75, 0.83)	0.000	0.78 (0.74, 0.83)	0.000
Education[Δ]	10,679 (3.35)	0.68 (0.64, 0.73)	0.000	0.67 (0.63, 0.72)	0.000
Migrant worker	2,601 (0.82)	0.46 (0.42, 0.50)	0.000	0.66 (0.60, 0.73)	0.000
Healthcare	1,009 (0.32)	0.84 (0.73, 0.96)	0.009	0.86 (0.74, 0.99)	0.038
Hospitality	612 (0.19)	1.03 (0.87, 1.23)	0.696	1.08 (0.90, 1.30)	0.416
Other	16,178 (5.07)	0.60 (0.57, 0.64)	0.000	0.74 (0.70, 0.79)	0.000
Year					
2013	56,198 (17.63)	1.00		1.00	
2014	55,815 (17.51)	0.97 (0.95, 0.99)	0.015	0.96 (0.94, 0.98)	0.002
2015	55,196 (17.31)	0.91 (0.89, 0.94)	0.000	0.90 (0.87, 0.92)	0.000
2016	49,996 (15.68)	0.87 (0.85, 0.89)	0.000	0.85 (0.83, 0.87)	0.000

2017	49,843 (15.63)	0.99 (0.97, 1.02)	0.577	0.94 (0.92, 0.97)	0.000
2018	51,744 (16.23)	1.01 (0.99, 1.04)	0.232	0.91 (0.88, 0.93)	0.000
Residential Address					
Local	310,343 (97.35)	1.00		1.00	
Intra-provincial (within province)	6,215 (1.95)	1.28 (1.22, 1.35)	0.000	0.76 (0.72, 0.80)	0.000
Inter-provincial (between provinces)	2,182 (0.68)	1.78 (1.63, 1.94)	0.000	1.17 (1.07, 1.28)	0.001
Foreign nationality	52 (0.02)	0.41 (0.22, 0.77)	0.006	0.49 (0.25, 0.96)	0.036
Patient Enrolment Classification					
Consultation due to symptoms	117,834 (36.96)	1.00		1.00	
Referral	103,261 (32.39)	2.96 (2.91, 3.01)	0.000	3.01 (2.95, 3.07)	0.000
Contact tracing	93,183 (29.23)	6.76 (6.63, 6.89)	0.000	6.90 (6.76, 7.04)	0.000
Health check	3,179 (1.00)	1.60 (1.49, 1.73)	0.000	1.48 (1.37, 1.59)	0.000
Other	1,335 (0.42)	8.99 (7.95, 10.16)	0.000	8.38 (7.40, 9.48)	0.000
Diagnosis Institution					
CDC	278,707 (88.15)	1.00		1.00	
Hospital	33,104 (10.47)	0.79 (0.78, 0.81)	0.000	0.80 (0.77, 0.82)	0.000
TB dispensary	4,276 (1.35)	3.72 (3.47, 3.99)	0.000	7.06 (6.56, 7.59)	0.000
Other	69 (0.02)	0.94 (0.58, 1.51)	0.784	1.06 (0.63, 1.76)	0.831
Severely Ill					
No	306,534 (96.15)	1.00		1.00	
Yes	12,258 (3.85)	0.96 (0.93, 0.99)	0.026	0.84 (0.80, 0.87)	0.000

[~] Agriculture includes famer, herdsman, fisherman.

[$] Housekeeping includes housekeeping, childcare, retired and unemployed.

[Δ] Education includes students and teachers.

*Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups.

Table S4: Univariable and multivariable negative binomial regression assessment of factors associated with time from diagnosis to treatment commencement in TB patients registered in Hunan Province, 2013-2018

	Univariable coefficient (95% CI)	Univariable *p* value	Multivariable coefficient (95% CI)	Multivariable *p* value
Ethnicity				
Han	0.00		0.00	
Tujia	-0.09 (-0.13, -0.05)	0.000	0.008 (-0.03, 0.05)	0.697
Miao	-0.35 (-0.40, -0.30)	0.000	-0.24 (-0.29, -0.19)	0.000
Dong	0.05 (-0.02, 0.13)	0.150	0.14 (0.07, 0.21)	0.000
Yao	-1.22 (-1.31, -1.13)	0.000	-1.09 (-1.18, -1.00)	0.000
Bai	0.26 (0.05, 0.46)	0.014	0.35 (0.15, 0.55)	0.000
Mongolian	-0.20 (-0.45, 0.05)	0.115	-0.24 (-0.48, -0.003)	0.047
Other*	-0.20 (-0.47, 0.07)	0.141	-0.30 (-0.57, -0.04)	0.022
Sex				
Male	0.00		0.00	
Female	0.09 (0.07, 0.11)	0.000	0.11 (0.09, 0.13)	0.000
Age	0.002 (0.001, 0.002)	0.000		
Occupation				
Commercial services/civil servant	0.00		0.00	
Agriculture~	-0.40 (-0.45, -0.35)	0.000	-0.27 (-0.32, -0.22)	0.000
Housekeeping[$]	-0.11 (-0.16, -0.05)	0.000	-0.15 (-0.20, -0.09)	0.000
Education[Δ]	-0.31 (-0.38, -0.25)	0.000	-0.25 (-0.31, -0.18)	0.000
Migrant worker	-0.52 (-0.63, -0.42)	0.000	-0.25 (-0.31, -0.18)	0.000
Healthcare	-0.12 (-0.27, 0.03)	0.127	-0.15 (-0.30, 0.001)	0.052
Hospitality	-0.10 (-0.29, 0.10)	0.334	0.05 (-0.14, 0.23)	0.633
Other	-0.21 (-0.28, -0.15)	0.000	-0.20 (-0.26, -0.14)	0.000
Year				
2013	0.00		0.00	
2014	-0.04 (-0.07, -0.02)	0.001	-0.10 (-0.13, -0.08)	0.000
2015	-0.03 (-0.06, -0.001)	0.041	-0.002 (-0.03, 0.02)	0.893

2016	-0.13 (-0.16, -0.10)	0.000	-0.10 (-0.13, -.008)	0.000
2017	-0.02 (-0.05, 0.01)	0.231	0.05 (0.02, 0.07)	0.001
2018	0.01 (-0.01, 0.04)	0.298	0.11 (0.08, 0.14)	0.000
Residential Address				
Local	0.00		0.00	
Intra-provincial (within province)	0.32 (0.26, 0.38)	0.000	0.05 (-0.006, 0.11)	0.080
Inter-provincial (between provinces)	0.29 (0.20, 0.39)	0.000	0.14 (0.05, 0.24)	0.003
Foreign nationality	-0.01 (-0.65, 0.63)	0.975	0.17 (-0.44, 0.79)	0.574
Patient Enrolment Classification				
Consultation due to symptoms	0.00		0.00	
Referral	0.67 (0.65, 0.69)	0.000	0.69 (0.67, 0.71)	0.000
Contact tracing	1.44 (1.43, 1.46)	0.000	1.47 (1.45, 1.49)	0.000
Health check	-0.13 (-0.21, -0.05)	0.002	-0.07 (-0.15, 0.02)	0.113
Other	1.44 (1.32, 1.56)	0.000	1.44 (1.31, 1.56)	0.000
Diagnosis Institution				
CDC	0.00		0.00	
Hospital	-0.32 (-0.35, -0.30)	0.000	-0.51 (-0.54, -0.48)	0.000
TB dispensary	-0.08 (-0.15, -0.005)	0.036	0.47 (0.40, 0.54)	0.000
Other	-0.59 (-1.15, -0.03)	0.038	-0.48 (-1.02, 0.05)	0.077
Severely Ill				
No	0.00		0.00	
Yes	-0.13 (-0.18, -0.09)	0.000	-0.28 (-0.32, -0.24)	0.000

Table S5: Median time from diagnosis to treatment commencement for **new** TB patients registered in Hunan Province, 2013-2018, by demographic characteristics.

	Number of **new** patients (%)	Treatment time (days) **new** patients
All patients	305,218	1 (IQR 0–15)
Ethnicity		
Han	276,961 (90.74)	1 (IQR 0–16)
Tujia	12,763 (4.18)	1 (IQR 0–10)
Miao	8,074 (2.65)	1 (IQR 0–9)
Dong	3,827 (1.25)	1 (IQR 0–9)
Yao	2,512 (0.82)	0 (IQR 0–2)
Bai	458 (0.15)	2 (IQR 0–11)
Mongolian	337 (0.11)	1 (IQR 0–13)
Other*	282 (0.09)	1 (IQR 0–9)
Sex		
Male	220,703 (72.31)	1 (IQR 0–14)
Female	84,515 (27.69)	1 (IQR 0–17)
Age		
< 18 years	7,111 (2.34)	2 (IQR 0–17)
≥ 18 years	298,107 (97.67)	1 (IQR 0–15)
Occupation		
Agriculture~	237,797 (77.91)	1 (IQR 0–12)
Housekeeping$	29,469 (9.66)	4 (IQR 0–27)
Education$^{\Delta}$	10,583 (3.47)	2 (IQR 0–20)
Commercial services/civil servant	7,610 (2.49)	7 (IQR 0–30)
Migrant worker	2,511 (0.82)	1 (IQR 0–10)
Healthcare	988 (0.32)	4 (IQR 0–25)
Hospitality	599 (0.20)	6 (IQR 0–27)
Other	15,661 (5.13)	2 (IQR 0–23)
Year		
2013	53,830 (17.64)	1 (IRQ 0–14)
2014	53,543 (17.54)	1 (IQR 0–14)
2015	52,989 (17.36)	1 (IQR 0–14)
2016	47,991 (15.72)	1 (IQR 0–13)
2017	47,778 (15.65)	1 (IQR 0–16)
2018	49,087 (16.08)	1 (IQR 0–19)
Residential Address		
Local	297,023 (97.32)	1 (IQR 0–15)
Intra-provincial (within province)	6,015 (1.97)	2 (IQR 0–30)
Inter-provincial (between provinces)	2,131 (0.70)	5 (IQR 0–28)
Foreign nationality	49 (0.02)	0 (IQR 0–1)
Patient Enrolment Classification		
Consultation due to symptoms	110,843 (36.32)	0 (IQR 0–1)
Referral	99,528 (32.61)	1 (IQR 0–12)
Contact tracing	90,476 (29.64)	16 (IQR 0–38)
Health check	3,139 (1.03)	0 (IQR 0–3)
Other	1,232 (0.40)	9 (IQR 2–28)
Diagnosis Institution		
CDC	267,390 (87.61)	1 (IQR 0–15)

Hospital	31,116 (10.20)	0 (IQR 0–9)
TB dispensary	4,120 (1.35)	11 (IQR 2–18)
Other	68 (0.02)	1 (IQR 0–6.5)
Severely Ill		
No	293,371 (96.12)	1 (IQR 0–15)
Yes	11,847 (3.88)	1 (IQR 0–13)

~ Agriculture includes famer, herdsman, fisherman.
$ Housekeeping includes housekeeping, childcare, retired and unemployed.
Δ Education includes students and teachers.
*Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups.

Table S6: Univariable and multivariable regression of factors associated with >15-day treatment delay in **new** TB patients registered in Hunan Province, 2013-2018

	Number of new patients (%)	Univariable odds ratio (95% CI)	Univariable *p* value	Multivariable odds ratio (95% CI)	Multivariable *p* value
All patients	305,218				
Ethnicity					
Han	276,961 (90.74)	1.00		1.00	
Tujia	12,763 (4.18)	0.74 (0.71, 0.77)	0.000	0.91 (0.87, 0.96)	0.000
Miao	8,074 (2.65)	0.61 (0.58, 0.65)	0.000	0.75 (0.70, 0.80)	0.000
Dong	3,827 (1.25)	0.79 (0.73, 0.86)	0.000	0.91 (0.83, 0.99)	0.021
Yao	2,512 (0.82)	0.20 (0.17, 0.24)	0.000	0.21 (0.17, 0.24)	0.000
Bai	458 (0.15)	0.74 (0.59, 0.93)	0.009	0.90 (0.71, 1.15)	0.408
Mongolian	337 (0.11)	0.86 (0.67, 1.12)	0.266	0.79 (0.59, 1.05)	0.100
Other*	282 (0.09)	0.70 (0.52, 0.95)	0.020	0.72 (0.52, 0.999)	0.049
Sex					
Male	220,703 (72.31)	1.00		1.00	
Female	84,515 (27.69)	1.11 (1.09, 1.13)	0.000	1.07 (1.05, 1.10)	0.000
Age	305,218	0.999(0.998, 0.999)	0.000	1.0009 (1.0004, 1.002)	0.001
Occupation					
Commercial services/civil servant	7,610 (2.49)	1.00		1.00	
Agriculture~	237,797 (77.91)	0.45 (0.43, 0.48)	0.000	0.57 (0.54, 0.61)	0.000
Housekeeping$	29,469 (9.66)	0.85 (0.81, 0.90)	0.000	0.80 (0.76, 0.85)	0.000
Education$^{\Delta}$	10,583 (3.47)	0.64 (0.60, 0.68)	0.000	0.67 (0.62, 0.72)	0.000
Migrant worker	2,511 (0.82)	0.41 (0.37, 0.46)	0.000	0.63 (0.56, 0.71)	0.000
Healthcare	988 (0.32)	0.81 (0.70, 0.93)	0.003	0.81 (0.70, 0.95)	0.009
Hospitality	599 (0.20)	0.88 (0.74, 1.05)	0.156	0.92 (0.76, 1.11)	0.373
Other	15,661 (5.13)	0.68 (0.64, 0.72)	0.000	0.81 (0.76, 0.87)	0.000
Year					
2013	53,830 (17.64)	1.00		1.00	

2014	53,543 (17.54)	0.99 (0.97, 1.02)	0.680	0.95 (0.92, 0.98)	0.001
2015	52,989 (17.36)	0.97 (0.94, 0.996)	0.026	0.93 (0.90, 0.96)	0.000
2016	47,991 (15.72)	0.94 (0.91, 0.97)	0.000	0.90 (0.87, 0.93)	0.000
2017	47,778 (15.65)	1.07 (1.04, 1.10)	0.000	0.99 (0.96, 1.02)	0.541
2018	49,087 (16.08)	1.18 (1.15, 1.21)	0.000	1.09 (1.05, 1.12)	0.000
Residential Address					
Local	297,023 (97.32)	1.00		1.00	
Intra-provincial (within province)	6,015 (1.97)	1.73 (1.64, 1.82)	0.000	0.96 (0.91, 1.02)	0.211
Inter-provincial (between provinces)	2,131 (0.70)	1.74 (1.59, 1.90)	0.000	1.14 (1.03, 1.26)	0.010
Foreign nationality	49 (0.02)	0.70 (0.34, 1.45)	0.341	1.10 (0.50, 2.40)	0.821
Patient Enrolment Classification					
Consultation due to symptoms	110,843 (36.32)	1.00		1.00	
Referral	99,528 (32.61)	3.61 (3.51, 3.72)	0.000	3.60 (3.50, 3.71)	0.000
Contact tracing	90,476 (29.64)	14.40 (14.02, 14.79)	0.000	14.40 (14.01, 14.80)	0.000
Health check	3,139 (1.03)	1.14 (0.998, 1.31)	0.053	1.09 (0.95, 1.25)	0.214
Other	1,232 (0.40)	8.57 (7.62, 9.64)	0.000	7.90 (7.01, 8.89)	0.000
Diagnosis Institution					
CDC	267,390 (87.61)	1.00		1.00	
Hospital	31,116 (10.20)	0.75 (0.73, 0.77)	0.000	0.73 (0.70, 0.76)	0.000
TB dispensary	4,120 (1.35)	1.38 (1.29, 1.47)	0.000	3.22 (3.00, 3.46)	0.000
Other	68 (0.02)	0.64 (0.34, 1.20)	0.165	0.79 (0.40, 1.56)	0.498
Severely Ill					
No	293,371 (96.12)	1.00		1.00	
Yes	11,847 (3.88)	0.84 (0.81, 0.88)	0.000	0.71 (0.68, 0.75)	0.000

[~] Agriculture includes famer, herdsman, fisherman.
[$] Housekeeping includes housekeeping, childcare, retired and unemployed.
[Δ] Education includes students and teachers.
*Other are represented by: Buyi, Dai, Gelao, Hani, Hui, Jingpo, Kazakh, Kirgiz, Korean, Lahu, Li, Lisu, Manchu, Salar, She, Tibetan, Tu, Uighur, Wa, Yao, Yi, and Zhuang ethnic groups.

Additional file

Fig S1: Median time to diagnosis for TB patients registered in Hunan Province 2013-2018.

Table S1: Sensitivity Analysis: Univariable and multivariable regression of factors associated with 14-day diagnosis delay in TB patients registered in Hunan Province, 2013-2018

Table S2: Univariable and multivariable negative binomial regression assessment of factors associated with time to diagnosis in TB patients registered in Hunan Province, 2013-2018

Table S3: Sensitivity Analysis: Univariable and multivariable regression assessment of factors associated with 1-day treatment delay in TB patients registered in Hunan Province, 2013-2018

Table S4: Univariable and multivariable negative binomial regression assessment of factors associated with time from diagnosis to treatment commencement in TB patients registered in Hunan Province, 2013-2018

Table S5: Median time from diagnosis to treatment commencement for **new** TB patients registered in Hunan Province, 2013-2018, by demographic characteristics.

Table S6: Univariable and multivariable regression of factors associated with >15-day treatment delay in **new** TB patients registered in Hunan Province, 2013-2018