PATHOGENS AND GLOBAL HEALTH
2022, VOL. 116, NO. 4, 201–219
https://doi.org/10.1080/20477724.2021.2011579

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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

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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 analyzed 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

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

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 (Figure 3), however asymmetry of

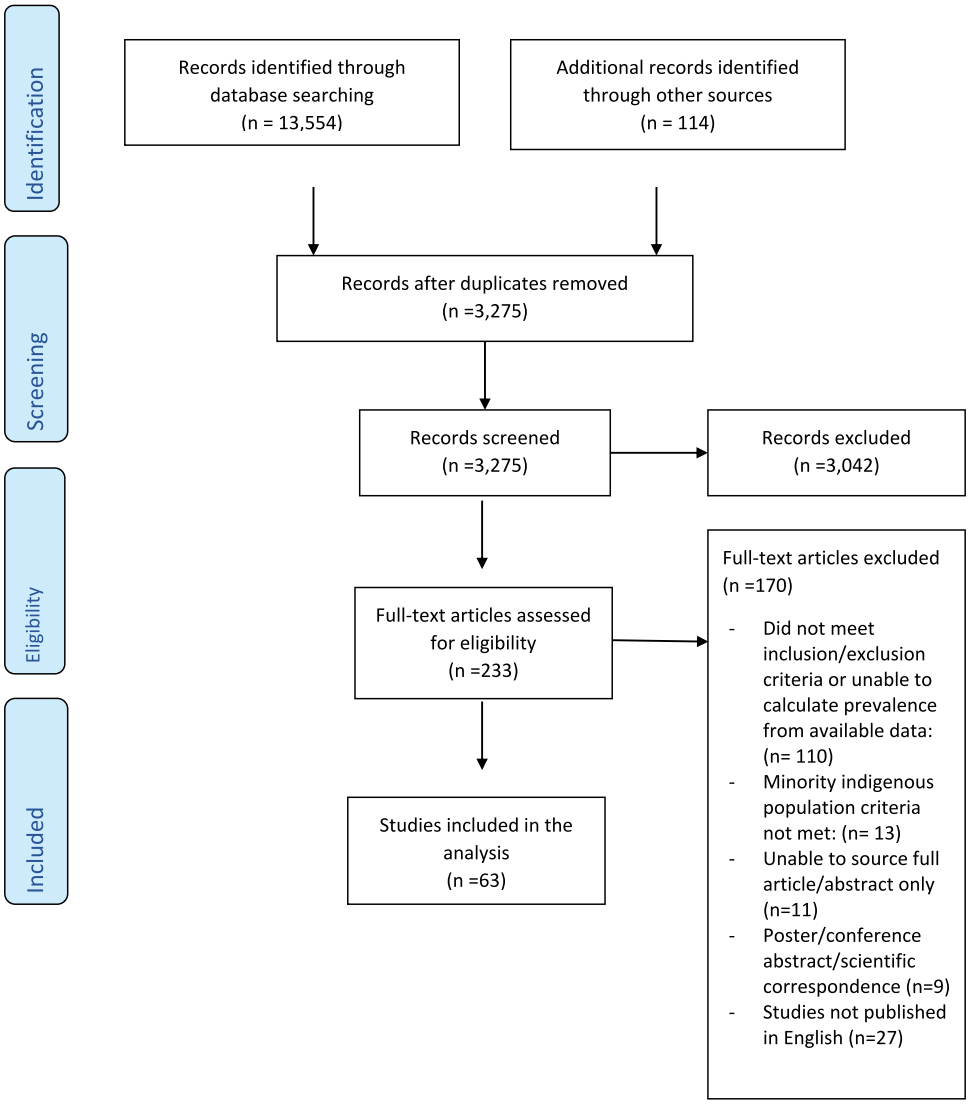

Figure 1. PRISMA summary of systematic review study selection process. *From*: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

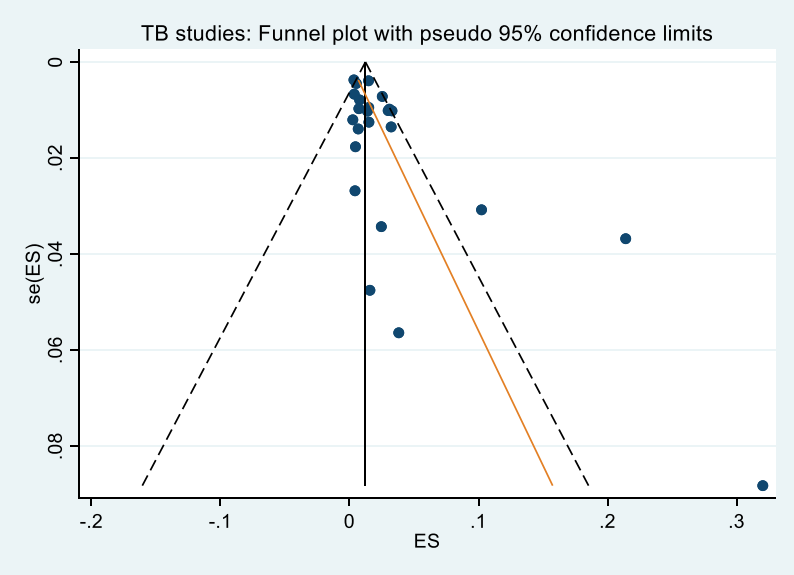

Figure 2. Funnel plot with pseudo 95% confidence limits for TB studies. Egger's test for small study effects gave a bias coefficient of 1.78 (95% CI 0.66, 2.91) *p*-value 0.003 indicating significant publication bias.

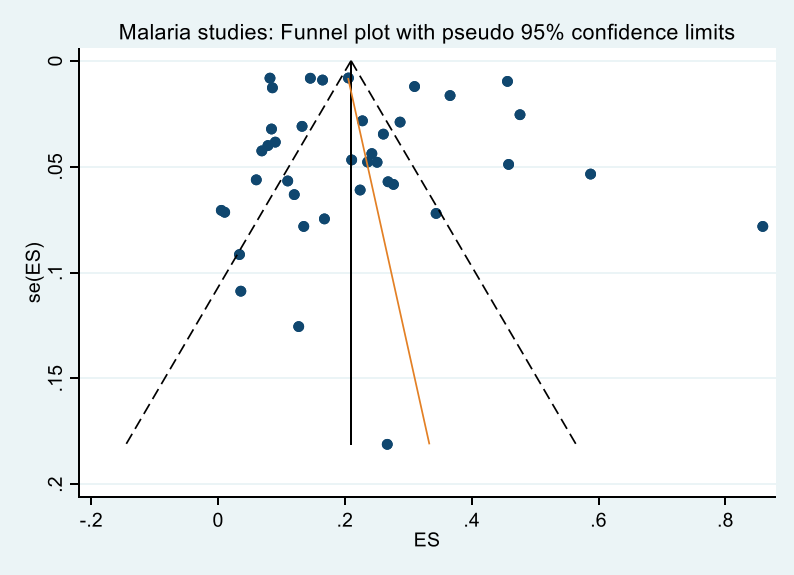

Figure 3. Funnel plot with pseudo 95% confidence limits for malaria studies. Egger's test for small study effects gave a bias coefficient of 0.74 (95% CI −2.33, 3.81) and a *p*-value of 0.63 indicating no significant publication bias.

the funnel plot (Figure 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.

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#	TB +ve (n)	Screening Method≠	Screened Population % Male	Population
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		
20	Rao, 2019	2013	SEAR	D	India		Culture	9,756	293	Chest symptoms		46.5
21	Roy, 1969	1968	WPR	B	Malaysia		Smear	1,055	108	X-ray		55
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, hemoptysis.

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 – Figure 4, which shows the significant heterogeneity between studies. The pooled prevalence of TB in minority indigenous people between

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: ^ 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.

ΔIndirect Fluorescent Antibody (IFA)

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

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

85.9% (95% CI 79.7, 90.4)[93]. These data are represented in a Forest Plot (Figure 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 ($p = 0.035$).

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

	Studies (n)	Pooled[a] 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	1	13.64 (7.34, 23.93)
<15 years	15	2.40 (1.55, 3.41)
≥15 years		
Sex	9	1.01 (0.53, 1.63)
Female		2.89 (1.56, 4.59)
Male		
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: [a] Prevalence pooled when >1 data set, otherwise result is presented from a single study

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

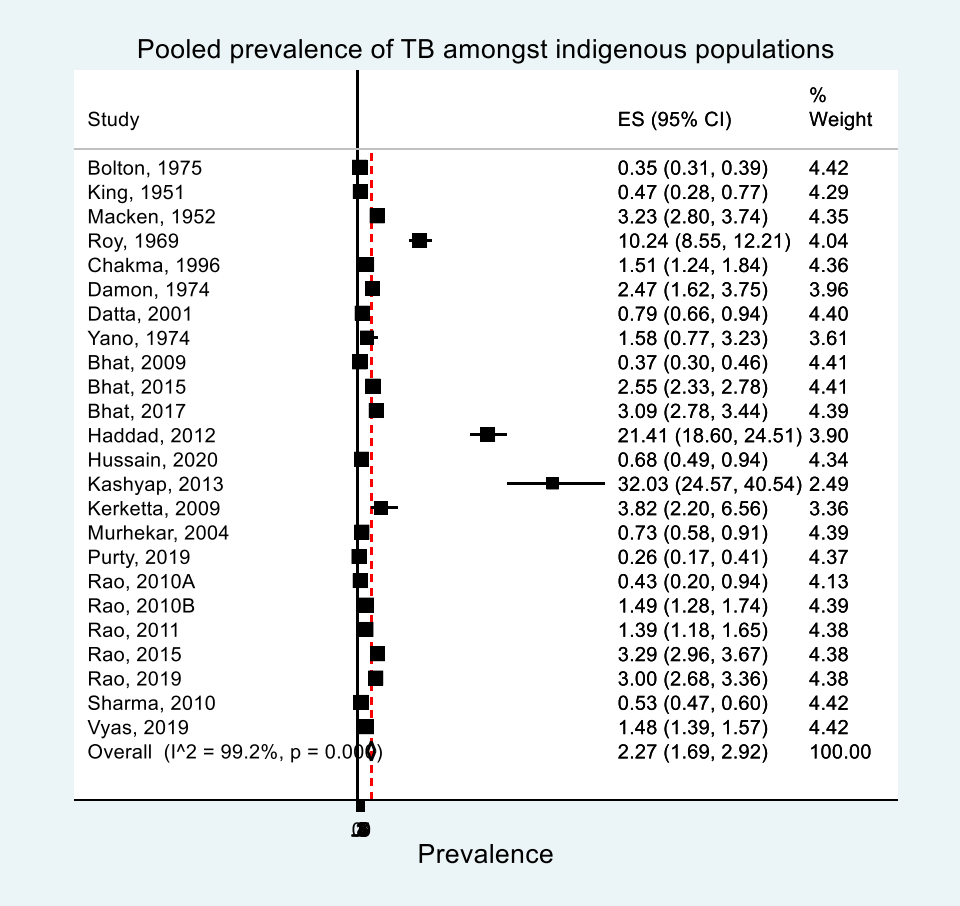

Figure 4. Pooled prevalence of TB within minority indigenous study populations. The forest plot shows overall effect sizes (ES) and their 95% confidence intervals (CI). I^2 statistic describes the percentage of variation due to heterogeneity.

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

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	1.00	0.218
Female	1.02 (0.99, 1.05)	
Male		
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

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

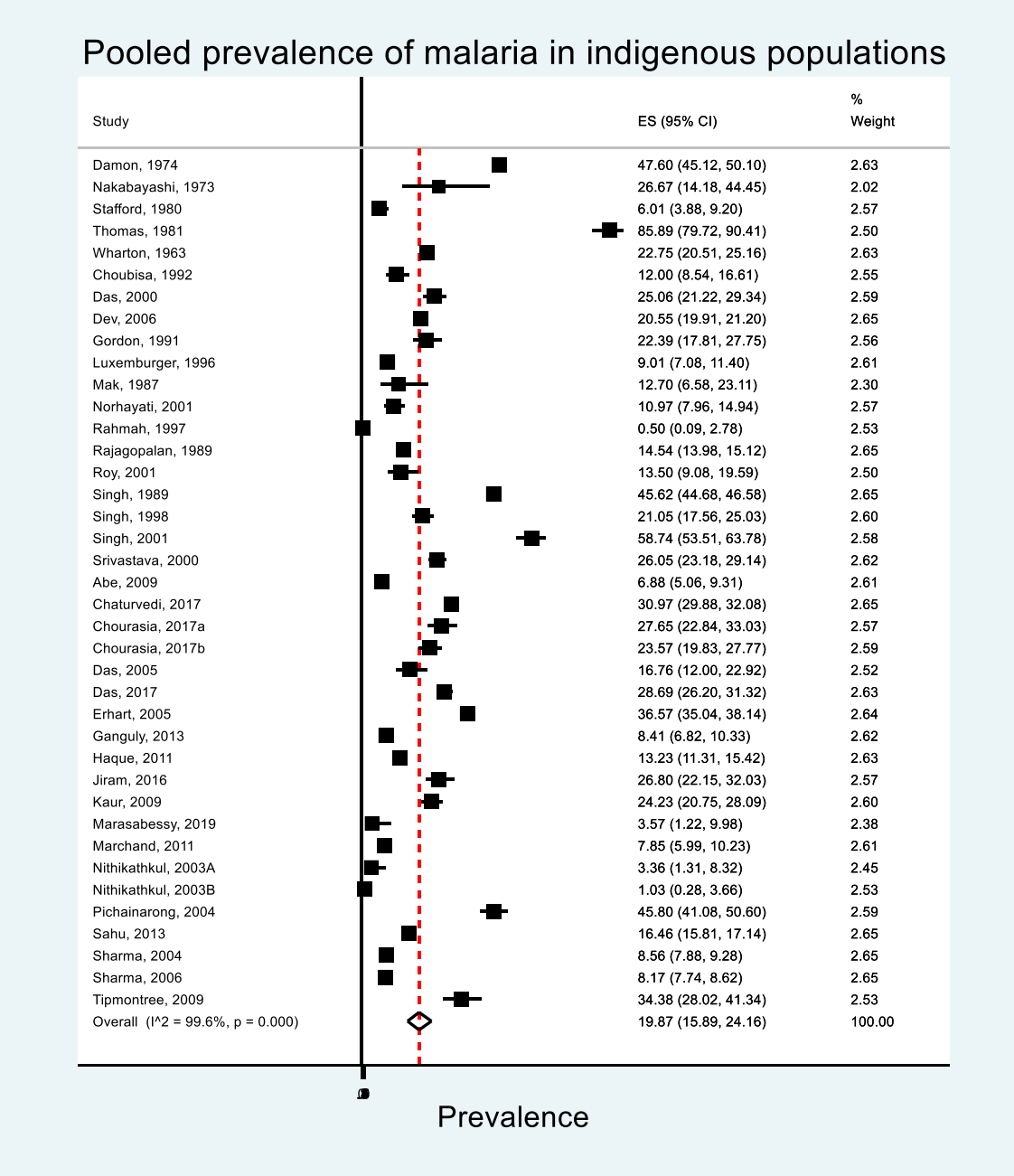

Figure 5. Pooled prevalence of malaria within minority indigenous study populations. The forest plot shows overall effect sizes (ES) and their 95% confidence intervals (CI). I^2 statistic describes the percentage of variation due to heterogeneity.

treatment programmes are disrupted and resources are re-allocated. [105–108] Modeling 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.

Acknowledgment(s)

Not applicable

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.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix 1: Summary of systematic review search terms

[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.

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*

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

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

#	References	Study Population 1 = The study population is clearly defined 0 = The study population is not clearly defined	Representativeness of the sample2 = Study sample is representative of the study population (all subjects or random sampling)1 = Study sample comprises a select group of the study population (nonrandom sampling)0 = No description of the sampling strategy.	Ascertainment of specimen collection methods1 = The study clearly defines specimen collection methodologies 0 = The study does not detail specimen collection methodologies	Sample size1 = Justified and satisfactory (sample size and power calculation included) 0 = Not justified	Non-respondents1 = 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 confounders0 = 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 analysis1 = 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

(*Continued*)

(Continued).

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

(*Continued*)

(Continued).

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