The Prevalence of Human T-Cell Lymphotropic Virus Type 1 in the General Population is Unknown

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Abstract

Human T-cell lymphotropic virus type 1 prevalence estimates are usually based on serological screening of blood donors, pregnant women, and other selected population groups. Previously, data on the global epidemiology of human T-cell lymphotropic virus type 1 infection have been summarized unsystematically and without a focus on general populations. To assess the implications of the virus for healthcare systems it is essential to know its past and present prevalence. The widely cited estimate that 10-20 million people are infected with human T-cell lymphotropic virus type 1 worldwide was calculated from data that are now 25 years old. This estimate may therefore no longer reflect the global epidemiology. The objective of this study was to collate published data that are truly representative of the general population through a systematic review of the literature. Fifty-nine relevant studies were identified and the 17 that met the inclusion criteria were all cross-sectional designs; none reported incidence. The prevalence of human T-cell lymphotropic virus type 1 was highest in the two studies of Japanese islands (36.4%; 95% CI: 29.9-42.8) and lowest in studies from Mongolia, Malaysia and India. In Haiti the prevalence was 3.8% (95% CI: 1.78-5.86); in Africa between 6.6% (95% CI: 4.0-9.9) and 8.5% (95% CI: 6.99-10.10) in Gabon, and 1.05% (95% CI: 0.63-1.47) in Guinea. Only three studies were from West Africa and none were from the South; the only study from India was from the north of the country. We conclude that there is a paucity of general population data from countries in which human T-cell lymphotropic virus type 1 is endemic, and that new studies are required to reevaluate the global burden of infection. **(AIDS Rev. 2009;11:205-14)**

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Key words

HTLV-1. HTLV-1 infection. Prevalence. General population.

Introduction

Several human T-cell lymphotropic viruses (HTLV) have been described and are designated HTLV-1 to HTLV-4. Of these, only HTLV-1 and HTLV-2 have been associated with disease in humans[1] and with lifelong carrier state. Type HTLV-2 has 65% sequence homology to HTLV-1. Infection with HTLV-1 is diagnosed by the detection of anti-HTLV antibodies, usually by enzyme-linked immunoassay (EIA or ELISA). Various screening assays have been used and, when reactive, need to be confirmed and typed by Western Blot. Until the 1990s, most serologic assays did not discriminate between HTLV-1 and cross-reacting HTLV-2 antibodies[2]. Stringent criteria for the diagnosis of HTLV-1 infection have been proposed by various organizations, including the HTLV European Research Network (HERN)[2-4].

Up to 10% of HTLV-1 carriers develop associated diseases, with adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) being the most severe. Infection

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Table 1. Summary of the inclusion and exclusion criteria of HTLV-1 studies

Inclusion criteria	Exclusion criteria
– Topic: incidence and/or prevalence of HTLV-1 infection – Diagnosis: screening by either ELISA, GPA and confirmatory testing by immunoblot (*gag* and *env*), RIPA or IF – Participants: adults and children from the general population – Study design: cohort and cross-sectional studies	– Studies without evidence of confirmatory testing on participants – Studies conducted on a select group of the population, i.e. • blood donors, • STD clinic patients, • sex workers, • injecting drug users, • neurological or hematological patients – Case reports, case series, and case control studies

with HTLV-1 causes significant morbidity (HAM/TSP: 50% become wheel chair dependant) and mortality (ATLL: median survival of 6-8 months). Other confirmed associations include uveitis, arthropathy, and HTLV-1-associated infective dermatitis[5-8].

It is reported that HTLV-1 has infected 10-20 million people worldwide[9], but the reality is that estimating the global prevalence of HTLV-1 on the basis of published reports is difficult because there are very few population-based studies, and selected populations where HTLV-1 infection has been found are overrepresented. The HTLV-1 infection is known to vary in prevalence or incidence across different geographic regions and population sectors. Serological screening of blood donors, pregnant women, and other selected population groups has been common. The value of data derived from blood donors is often limited due to the exclusion of individuals from high-risk groups and underrepresentation of ethnic minorities[2]. Comparisons between blood donor populations with those attending antenatal clinics are not without problems. In Europe it has been demonstrated that even between blood donors and pregnant women, there are considerable differences, especially when volunteer donors are used as they are biased towards low seroprevalence of viral blood-transmissible infections[2]. Data from pregnant women are not representative of all ages, yet HTLV-1 is reported to increase with age and may be predominant in females[10]. Amongst injecting drug users, a high prevalence of HTLV-2 has been found, but HTLV-1 is mostly rare in the same populations. Although HTLV-2 is frequently associated with HIV-1 infection, especially amongst injecting drug users in Europe and North America[11,12], it is not usually associated with disease *per se*. The epidemiology of both HTLV-3 and HTLV-4 is not well understood since only rare human infection in primate hunters in Cameroon has been reported[13,14]. Therefore, this review focuses on HTLV-1. Information on prevalence from representative samples of the general population is rare. The objective of this study was to collate data that are truly representative of the general population through a systematic review of the literature.

Methods

PubMed, EMBASE, and Ovid Global Health databases were searched from 1980, the year HTLV was identified[15], to end of 2007. Search terms included: human T-cell lymphotropic virus type 1, human T leukemia/ lymphoma virus type 1 or I, incidence, prevalence, sensitivity, specificity, diagnosis, enzyme linked immuno assay, and particle agglutination. These were used in combination with free text and thesaurus terms in different variations. Further attempts to locate papers were made by contacting published experts in the field. The same online databases were also searched for abstracts from conferences of the International Retrovirology Association published in the Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. Studies were limited to human studies, with no language restrictions. The inclusion and exclusion criteria used to select papers are summarized in table 1. Selected populations such as blood donors, pregnant women, and injecting drug users were excluded. Titles and abstracts of identified articles were reviewed for relevance. The two reviewers (Hlela and Shepperd) independently extracted data using a predefined proforma, which included the following: study design, method for selecting cases, diagnostic methods, study location, and outcomes. Methodological quality was assessed using the Standards for Reporting of Diagnostic Accuracy (STARD) criteria for diagnostic studies and criteria specific to prevalence studies[16] (Table 2).

Data analysis

The Chi-square (χ^2) test was used to assess the degree of statistical heterogeneity. Although we planned to

Table 2. Criteria for methodological quality of HTLV-1 prevalence studies

External validity	Internal validity
Population characteristics	Study design and testing methods
a. Definition of disease*	d. Type of study
– HTLV-1	– is it an applicable study design for the question asked
– HTLV- 1 and 2	e. Reference standard
b. Description of the selection criteria	– were the screening test results confirmed
– was there a clear description of the sampling methods used	f. Reported prevalence
	– are age-specific and gender-specific prevalences reported
c. Description of the study population	g. Reproducibility
– are important characteristics of the population specified†	– evidence for minimization of instrument bias

Pre-set criteria for assessment of methodological quality were formulated. Two aspects of validity were deemed important: external validity relating to the applicability of the study results to other populations and internal validity, implying accurate measurement apart from random error. Superscript labels a-c represents all factors considered in assessment of external validity of each included study. While *d-g* represents characteristics used to assess internal validity in each included study. *Disease equals HTLV-1 infection in this review; †two or more of: (i) age distribution, (ii) gender, (iii) ethnicity, (iv) socioeconomic data, e.g. income, educational level, (v) others.

calculate a pooled summary estimate, this was not pursued due to the high level of statistical heterogeneity, explained by variation in the diagnostic techniques employed by the different studies and in the study populations. Study data were entered into STATA software, version 7, to calculate individual study effect sizes and 95% CI.

Results

The primary search yielded 394 references, from which 59 relevant papers were identified and 17 met the inclusion criteria; all described prevalence of infection and all were published in English. Studies were excluded on the following grounds: lack of original data (n = 5), conducted in unrepresentative populations (n = 20), inappropriate study design (n = 4), no confirmatory testing done (n = 1) or testing performed on only some of the specimens (n = 1), prevalence not stated (n = 1) or prevalence not reported separately for HTLV-1 and HTLV-2 (n = 1). The different stages and categories of the search strategy are summarized in figure 1 and the geographic locations of the studies are depicted in figure 2.

Included studies comprised a total of 16,745 participants (age range 0-89 years) and were conducted between 1988 and 1999 and published between 1991 and 2006. All 17 studies investigated the prevalence of HTLV-1 infection in a general population using different representative groups, with 10 recruiting indigenous populations. One study investigated healthy individuals accompanying relatives to hospital (which might have introduced bias)[17], whilst two did not characterize their "healthy" population any further. In four papers the general population studied was not clearly characterized. The 17 papers reviewed are listed in table 3.

The prevalence of HTLV-1 varied considerably. No cases were identified in some Asian countries[18-20]. The highest prevalence was reported from the Japanese islands of Okinawa and Tsushima, 36.4% (95% CI: 29.9-42.8)[21]; 17.8% (95% CI: 16.0-19.4) in 1980 and 17.1% (95% CI: 15.2-18.9) in 1989/1990[22]. In Haiti the prevalence was 3.8% (95% CI: 1.78-5.86)[17]. In African studies the prevalence was between 6.6% (95% CI: 4.0-9.9)[23] and 8.5% (95% CI: 6.99-10.1) in Gabon[24] and 1.05% (95%: CI 0.63-1.47) in Guinea[25]. In Oceania a single-centre study carried out in Papua New Guinea reported a prevalence of 1.9% (95% CI: 1.42-2.42)[26], whilst a multi-regional study conducted in New Guinea from both Papua New Guinea and Irian Jaya (previously referred to as Asia, being politically Indonesia), Indonesia, reported an overall prevalence of 3.76% (95% CI: 2.69-4.83)[27]. In Brazil an Amazonian general population had a seroprevalence of 1.15% (95% CI: 0.14-2.46)[28], while in Salvador the rate was 1.7% (95% CI: 1.1-2.5)[29]. Prevalence rates in other studies conducted in Latin America were between 0.8% (95% CI: 0.5-4.6)[30] and 2.1%[31] within the Columbian Indian tribes, 0.70% (95% CI: 0.09-1.57) among the Mapuche of Chile[32], and 0.45% (95% CI: 0.43-1.33) among the Indians and natives from different regions of Argentina[33]. In studies with stratified data, HTLV-1 prevalence was higher in females and increased with age[17,22,24-26]. In two studies[23,30] prevalence was reported to increase with age but not with gender. Duorado, et al. reported prevalence ranging from 0.3% in the 0-15 year age group up to

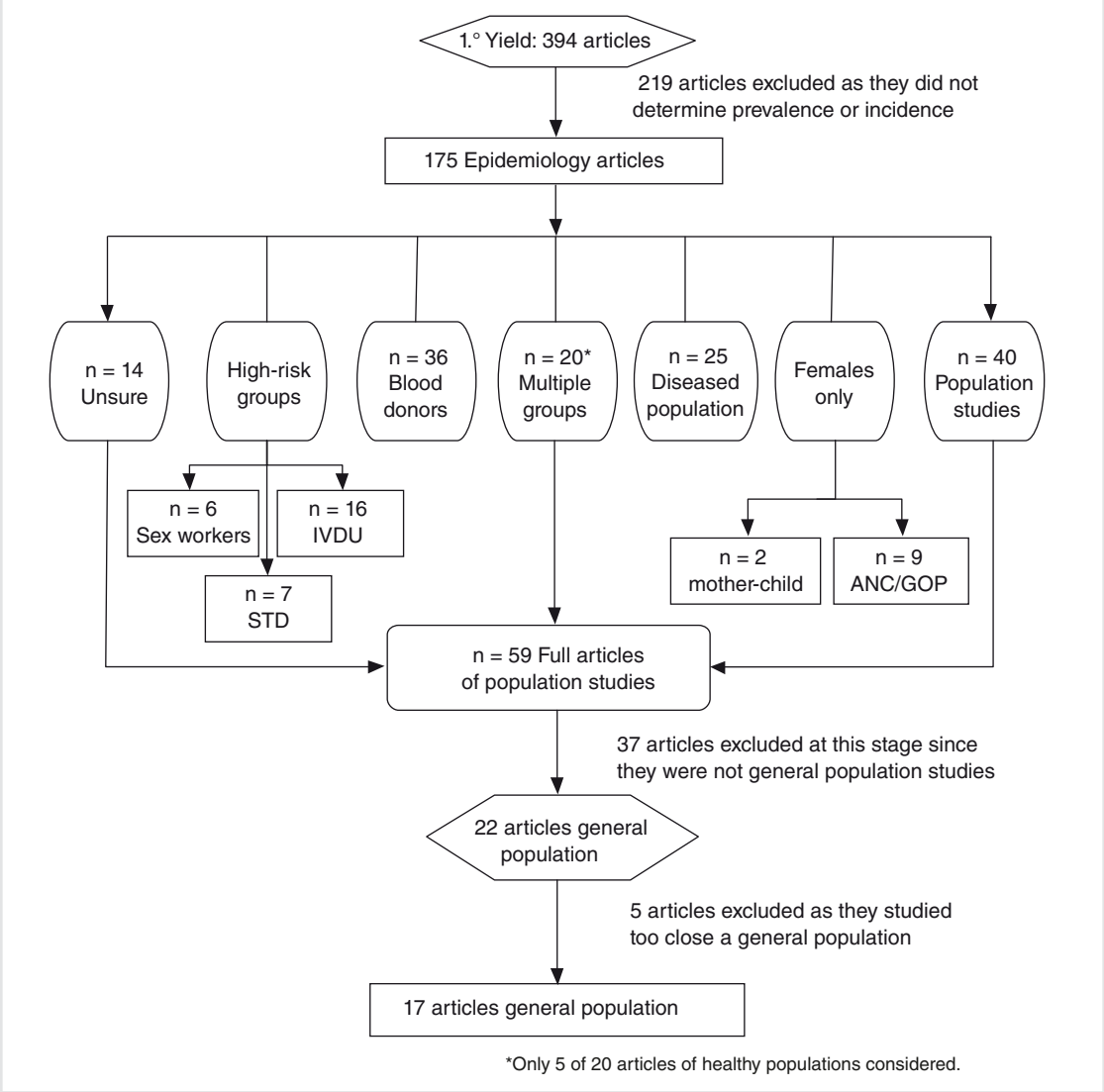

Figure 1. *Flow chart with stages and strategies followed in the selection of studies for this review. IVDU: intravenous drug users; STD: sexually transmitted disease; ANC/GOP: antenatal clinic/general outpatients.*

8.4% in individuals 51 years or older in Salvador, Brazil[30].

Results of the quality assessment are shown in table 4. A chi-squared test for heterogeneity was 949.80 (d.f. = 14; $p < 0.001$); I^2 (variation in the effect size attributable to heterogeneity) = 98.5%. Studies from the Japanese islands contributed significantly to the variation noted. Data were stratified according to the suspected sources of heterogeneity (i.e. geographic region, study population, and diagnostic methods). However, variation remained significant and an overall estimate of effect was not determined.

Discussion

The most widely quoted figure for the global prevalence of HTLV-1 is the 10-20 million estimate of de Thé and Bomford in the 1996 review of the need for an HTLV-1 vaccine[9]. The estimate was based on two main data sources. The first was the incidence of the two most common HTLV-1-associated diseases, HAM/TSP and ATLL, in the Caribbean and Japan, together with the life-time risks of HTLV-1-infected persons developing either of these diseases[34-36]. The second was estimates of the prevalence of HTLV-1 infection in

Figure 2. *Location of countries which have reported HTLV-1 prevalence in the general population. It should be noted that the general population studies indicated here do not correspond exactly to the country boundaries shown in the map. For example, in Japan it is limited to certain islands of the country.*

inter-tropical Africa, Central and South Africa, derived from Mueller's 1990s review of seroprevalence studies from 1984-89[34-37]. There are, therefore, four problems in using these figures to address the current situation. The data for the original estimate are now 25 years old. The assays used were generally of low specificity. The studies were not necessarily representative of the general population. The global population has grown from 5.7 billion in 1996 to 6.7 billion in 2009.

Most existing data on this important epidemiological problem do not focus on the general population but on selected groups. Data from blood donors may underestimate the true population prevalence as "high-risk" groups are generally excluded and ethnic minorities may also be underrepresented. Hospital-based studies are more likely to include a biased selection of patients with severe diseases such as lymphomas.

This is the first systematic summary of the epidemiology of HTLV-1 infection that focuses on general populations. This review only included studies that reported a confirmatory HTLV-1 test and were conducted in the general population. Despite methodological and reporting limitations, the prevalence of HTLV-1 infection varied considerably and there were differences between and within geographic regions. In Japan, Okinawa reported a prevalence of 17%, while in another part of the country, Tsushima Island, rates were as high as 36.4%. Differences were also noted in Africa, with a prevalence of up to 8.5 vs. 1.0% in Gabon and Guinea, respectively. The comparison of prevalence data between regions is hampered by differences in the availability of published data, especially from endemic regions. Only three studies came from West Africa and none from Southern Africa; the only Indian study was from the north, whilst cases of HTLV-1-associated disease have been reported from the south of India[38]. Information in many of the reports is insufficient to provide valid data on prevalence rates and cannot therefore be generalized or used to draw conclusions from comparison with other studies. This emphasizes the need for further studies on the general population. Inadequate standardization of assays in some earlier studies may also have contributed to significant differences in prevalence.

Table 3. Characteristics of the included studies

Author	(n)	Date of study	Country	Age (years)
1. Grant, et al. 1992[17]	340	Jun-Aug 1988	Haiti, West Indies	15-76
2. Roy, et al. 1994[18]	946	Jan 1992-Feb 1993	Uttar Pradesh, West Bengal, India	16-80
3. Bastuuri, et al. 1993[19]	1,100	NS	Mongolia	16-87
4. Yap, et al. 1992[20]	626	NS	Malaysia	NS
5. Kinoshita, et al. 1993[21]	209	NS	Tsushima Island, Japan	35-83
6. Morofuji-Hirata, et al. 1993[22]	3,486	1980,1989+1990	Okinawa Island, Japan	0- ≥ 80
7. Betherat, et al. 1998[23]	456	Jan 1996	Gabon	14-55
8. LeHesran, et al. 1994[24]	1,240	Mar 1988	Gabon	
9. Jeannel, et al. 1995[25]	2,285	Jan-Feb 1992	Guinea	22.1, 24.3, 23.4
10. Sanders, et al. 1993[26]	2,907	1972-1991	Papua New Guinea	> 18
11. Takao, et al. 2000[27]	1,221	NS	Papua New Guinea and Indonesia	0-69
12. Vallinoto, et al. 2006[28]	259	NS	Amazon Island, Brazil	3-80
13. Dourado, et al, 2003[29]	1,385	May-Jul 1998	Salvador, Brazil	1-89
14. Arango, et al. 1999[30]	1,014	1988,1990, 1992	Columbia	< 10 - > 60
15. Duenas-Barajas, et al. 1993[31]	1,250	1990-1992	Columbia	1-89
16. Inostroza, et al. 1991[32]	405	NS	Chile	NS
17. Bouzas, et al. 1994[33]	454	1987-1992	Argentina	1 > 50

The 17 papers reviewed are listed, ordered by first author and then by date of publication. The diagnostic and confirmatory tests performed in the different studies are shown. Population studied in each paper and prevalence rates with their confidence intervals (95% CI) are all shown.

We therefore compared data from these specific populations with the general population in the same regions to see how comparable and useful they could be (Table 5)[39-51]. As expected, where targeted populations are studied, e.g. injecting drug users, prevalence was higher than in the general population. Conversely, our data suggest that blood donors and pregnant women in South America and the Caribbean may be more representative of the general population and suitable for estimating prevalence in these regions. This was an unexpected finding since in Europe HTLV-1 prevalence in blood donors consistently tends to be ten-times less than that of pregnant women[11]; in some regions there were no data for comparison.

Target population/sampling frame	Measurements		Prevalence % (95% CI)
	Screening	Confirmation	
Healthy individuals accompanying others to hospital	ELISA	WB[d] RIPA	3.8
Different ethnic groups, population-based survey for genetic study	PA	WB[b]	0
General population, genetic study	PA	IF	0
Ethnic non-patient Malays	ELISA[g]	WB[e] RIPA	0
Healthy subjects, Tsushima Island	ELISA[d] PA	WB PCR	36.4
General population	ELISA[d]	WB	17.8 (1980) 17.1 (1989-1990
Various ethnic groups/clusters	ELISA[f]	WB[a]	6.6 (4.0-9.9)
Bateke, Kota-Obamba plus other ethnic groups, house-to-house survey	ELISA[b]	WB[c]	8.5 (overall) 3.4 (Bateke) 11 (Kota-Obamba)
Samoé, Boulivel, Koumbia, house-to-house survey	PA ELISA[e]	WB[e]	0.7 Boulivel, 0.2 Koumbia 1.9 Samoé
Populations from 3 geographic zones	PA	WB[g,h]	1.9 (overall); 0-12.2 (coastal & island); 1.1-6.4 (highland fringe); 0 (highland)
Different ethnic populations, (general population)	PA	WB[b]	3.7
General population	ELISA[e]	WB[a]	1.15
General population	ELISA[a]	WB[a]	1.7 (1.1-2.5)
Columbian Amerindian tribes	ELISA[a,b]	WB[g]	1 (0.5-1.8) Embera 0.8 (.3-1.8) Paez 1.2 (0.2-4.6) Inga
Columbian Indian tribes, random collection	ELISA[a]	WB[f]	2.1
Healthy Mapuches	ELISA[b,c]	WB[d] , RIPA	0.7
Indians and Natives from different regions, immunogenetic study	PA	IFA, PCR	0.45

ELISA assays used: Cambridge Biotech Hopkinton, MA, USA[a]; Abbott Laboratories, Chicago, IL[b]; DuPont Wilmington, DE, USA[c]; EiTest-ATL, Eisai K.K, Tokyo, Japan[d]; Ortho-Diagnostic Systems Inc US[e]; Genelabs Diagnostics, Singapore, Singapore[f]; Diagnostic Biotechnology, Singapore[g]. Western Blot assays used: HTLV 2.4 Genelabs Laboratories[a]; Problot HTLV, Fujirebio, Tokyo, Japan[b]; Ortho Diagnostic System, Raritan, NJ[c]; Dupont[d]; HTLV Blot 2.2 Diagnostic Biotechnology, Singapore[e]; Cambridge Biotech, USA[f]; Diagnostic Biotechnology Ltd, Singapore[g], Biotech Research Laboratories[h]; NS: not specified; PA: Serodia-ATLA, Fujirebio Inc, Tokyo.

It is difficult to give a global estimate of the prevalence of HTLV-1 infection as the data to inform this are very minimal. African data mostly come from hospital populations. European data have been limited to pregnant women and blood donors. There are large gaps in information from Asia and Africa where more than half the world's population live. Africa has been considered to be the largest reservoir for HTLV-1 infection[52], but the few studies identified were restricted to West Africa. It was not possible to calculate summary statistics of the global burden of HTLV-1 infection because of study heterogeneity. The latter also limited a comparison of prevalence data between studies.

Table 4. Results of quality assessment for distinct HTLV-1 studies

Author	Year of publication	External Validity				Internal Validity					Total	Grade*
		a	b	c	Sum	d	e	f	g	Sum		
Takao, et al.	2000	–	–	+	1	+	+	–	+	3	4	B
Roy, et al.	1994	+	+	+	3	+	+	–	+	3	6	B
LeHesran, et al.	1994	+	+	+	3	+	+	+	–	4	6	B
Inostroza, et al.	1991	+	–	–	1	+	+	–	–	2	3	C
Grant, et al.	1992	+	–	+	2	+	+	+	+	4	6	B
Morofuji-Hirata, et al.	1993	–	+	+	2	+	+	+	+	4	6	B
Jeannel, et al.	1995	+	+	+	3	+	+	+	–	3	6	B
Betheral, et al	1998	+	+	+	3	+	+	+	–	3	6	B
Bastuuri, et al.	1993	–	+	+	2	+	+	–	+	3	5	B
Dourado et al.	2003	+	+	+	3	+	+	+	+	4	7	A
Duenas-Brajas, et al.	1993	+	+	+	3	+	+	–	+	3	6	B
Arango, et al.	1999	+	–	–	1	+	+	+	–	3	4	B
Sanders, et al.	1993	+	–	+	2	+	+	–	+	3	5	B
Vallinoto, et al.	2006	+	–	+	2	+	+	–	–	2	4	B
Yap, et al.	1992	–	–	–	0	+	+	–	+	3	3	C
Bouzas, et al.	1994	+	+	–	2	+	+	+	–	3	5	B
Kinoshita, et al.	1993	–	–	+	1	+	+	–	+	3	4	B

Using a list of criteria stipulated in table 2, items were given positive and/or negative points. All positive scores were summed. Studies that contained all seven positive features of the criteria were deemed of high quality and were graded A. Studies with less than four positive points of the criteria were regarded as of low quality and graded C. Studies of moderate quality had between four and six positive points, graded B. One study was graded A (high quality). Two studies were graded C, indicating low quality, while the majority of the studies fell between four and six positive scores and were graded B.
*Grade score: A = 7, B = > 6 to ≥ 4, C = < 4.

Conclusions

There are currently insufficient published data to estimate the global burden of HTLV-1 infection from data on general populations. More data are required before the results of specific populations that are generally more accessible, e.g. pregnant women or blood donors, can be extrapolated to the general population. Most importantly, much of the data relates to small samples and between-study heterogeneity prevents calculation of a summary statistic of the global burden of HTLV-1 infection. The historical estimate of 10-20 million HTLV-1-infected people worldwide should be reviewed. General population studies are clearly needed to assess, and therefore address the implications of, HTLV-1 infection so as to inform public health policies, especially in HTLV-1 endemic countries that also have an increasing burden of HIV. The findings of this review reveal that the prevalence of HTLV-1 in general populations remains unknown. This therefore underlines

Table 5. Comparison of general and specific populations in distinct HTLV-1 epidemiological studies

Country	Population prevalence (%)	Population studied	Specific prevalence (%)
Salvador, Brazil	1.7	Injecting drug users[39] Pregnant women[40]	22 0.78
Uttar Pradesh, West Bengal, India	0		No result
Gabon, Africa	8.4 (overall) 3.4 (Bateke) 11 (Kota-Obamba)	Pregnant women[41]	0-5 (overall) 5 (Haut Ougoué region) 0-2 (other 4 regions)
Argentina	0.45	Blood donors[42] Blood donors[42] Pregnant women[43] Blood donors[43]	0.6-1 (North Argentina) 0.005-0.046 (South Argentina) 0.19* Cordoba 0.019 Cordoba
Chile	0.7	Blood donors[44] Prostitutes[45]	0.73 0.84
Guinea	0.2-1.9	Pregnant women[46]	2.6
Mongolia	0		No result
Colombia	2.1		No result
Amazon Island, Brazil	1.15	Blood donors[47] Japanese immigrants in Brazil[48]	0.46 1.8
Tsushima, Japan	36.4		No result
Haiti, West Indies	3.8	Blood donors[49]	3.1
Okinawa, Japan	17.1-17.8	Pregnant women[50]	Average 3.9 7.3-1.9 (serial measurements from 1989-2002)
Papua New Guinea	3.7	Combination of healthy persons, persons with various hematological diseases and blood donors[51]	0.15

Comparison of the different published prevalence estimates obtained by studying the select populations as opposed to the estimates derived from general population studies. Data on prevalence estimates based on specific populations could not be obtained for some of the countries that published general population prevalence.

the need for further general population studies to investigate the extent of infection and disease worldwide so as to inform the epidemiology of HTLV infections globally.

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