International Journal of Infectious Diseases 25 (2014) 94–99

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

Prevalence of human T-lymphotropic virus type 1 infection among blood donors in mainland China: a meta-analysis

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ARTICLE INFO

Article history:
Received 21 November 2013
Received in revised form 23 February 2014
Accepted 24 February 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Blood donors
HTLV-1
Prevalence
Genotypes
Chinese mainland
Meta-analysis

SUMMARY

Background: Human T-lymphotropic virus type 1 (HTLV-1) is considered to be the etiological agent of adult T-cell leukemia/lymphoma (ATL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Blood transfusion is a common transmission pathway for HTLV-1. However, no surveys to determine the overall prevalence of HTLV-1 infection and HTLV-1 genotypes among blood donors on the Chinese mainland have yet been conducted.

Methods: A systematic review and meta-analysis of the peer-reviewed literature on this topic was carried out. Data manipulation and statistical analyses were performed using the Comprehensive Meta Analysis Version 2.0 program.

Results: Forty-four eligible articles involving 458 525 blood donors were selected. Analysis revealed the pooled prevalences of HTLV-1 infection among blood donors in Fujian and Guangdong provinces to be 9.9/10 000 (95% confidence interval (CI) 4.4/10 000–22.2/10 000) and 2.9/10 000 (95% CI 1.7/10 000–4.8/10 000), respectively; there were only two cases of HTLV-1 infection among 204 763 donors in other areas of the Chinese mainland. In addition, 40 of 42 (95.2%) HTLV-1 isolates belonged to the Transcontinental subgroup A of the HTLV-1 subtype A (Cosmopolitan subtype).

Conclusions: The prevalence of HTLV-1 infection among blood donors is low and restricted mainly to the provinces of Fujian and Guangdong. Most isolates belong to the Transcontinental subgroup within HTLV-1 subtype A.

1. Introduction

Human T-lymphotropic virus type 1 (HTLV-1) was first isolated from a blood sample of a patient with cutaneous T-cell lymphoma and identified as a retrovirus by Poiesz et al.[1] HTLV-1 is considered to be the etiological agent of adult T-cell leukemia/lymphoma (ATL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[2] Human lymphotropic virus type 2 (HTLV-2), a closely related virus found in 1982, has no clear association with clinical disease.[3,4] HTLV-1/2 can be transmitted by transfusion of infected cellular blood products and sexual contact, as well as mother-to-child transmission.[5–9] Initial screening assays for HTLV-1 antibodies are generally ELISA, particle agglutination (PA), and immunofluorescence (IF) tests. Subsequent immunoblotting and nucleic acid tests (NAT) are used to confirm the presence of HTLV-1 infection.[10] The World Health Organization (WHO) has advised that decisions regarding the screening of blood donations for HTLV be guided by local epidemiological evidence.[11] So far no surveys to determine the overall prevalence of HTLV-1 infection and HTLV-1 genotypes among blood donors have been conducted on the Chinese mainland. Therefore, we conducted a systematic review and meta-analysis of the available data.

2. Methods

2.1. Literature search

The literature on the prevalence and genotypes of HTLV-1 in blood donors on the Chinese mainland was identified through searching electronic databases (PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang) for the period January 1998 to June 2013. To search and include as many related studies as possible, we used combinations of various key words, including human T-lymphotropic virus type I(1) or HTLV-I(1), blood donor or donation, and China or Chinese mainland. A manual search of the reference lists of published articles was also performed. This study

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http://dx.doi.org/10.1016/j.ijid.2014.02.021

was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines issued in 2009.[12]

2.2. Selection and data abstraction

Articles in the literature were identified and data were extracted by two investigators, independently. Disagreements were resolved through discussion. Studies were included if they were: (1) full text articles in the three databases mentioned, with no language restrictions; (2) reported the prevalence or genotypes of HTLV-1 in blood donors on the Chinese mainland; (3) used immunoblot assays or NAT as confirmatory tests of HTLV-1 infection. Studies were excluded if they were: (1) from regions of China other than the mainland (i.e., Hong Kong, Macao, and Taiwan); (2) review papers or dissertations; (3) conference abstracts or presentations. If the same study data were published in both Chinese and English, the articles published in Chinese were excluded from this study. The following information was extracted from the eligible studies on HTLV-1 prevalence: first author's name, year of publication, study location, sample collection period, target population, sample size, testing method, and number of infections.

The quality of studies on the prevalence of HTLV-1 was assessed using a validated quality assessment tool.[13] Eight items were used to assess the quality of studies: (1) clear definition of the target population; (2) representativeness of probability sampling; (3) sample characteristics matching the overall population; (4) adequate response rate; (5) standardized data collection methods; (6) reliable survey measures; (7) valid survey measures; (8) appropriate statistical methods. Answers were scored 0 and 1 for 'no' and 'yes', respectively. The total score varied between 0 and 8 for each study.

2.3. Statistical analysis

Data manipulation and statistical analyses were carried out using Comprehensive Meta Analysis Version 2.0 (CMA 2.0; Biostat Inc., Englewood, NJ, USA). To normalize the distribution of the prevalence rate, prevalence data were transformed into logit event rate data as follows: logit p = ln [p/(1 − p)], with ln being the natural logarithm and p the prevalence rate. The sampling variance of each logit event rate was called V (logit p) and calculated as $1/(np) + 1/[n(1-p)]$, with n being the sample size. After the statistical analyses, the results were transformed back into prevalence rates using the formula: $p = e^{\text{logit } p}/(e^{\text{logit } p} + 1)$, with e being the base of the natural logarithm.[14] The pooled prevalence estimates and 95% confidence intervals (CI) were determined based on random or fixed effects models, taking into account the possibility of heterogeneity between studies, which was tested using the Q test ($p < 0.10$ was considered indicative of statistically significant heterogeneity) and I^2 test (values of 25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively). Furthermore, meta-regression was used to investigate factors associated with heterogeneity. Publication bias was also assessed by Egger's and Begger's tests ($p < 0.05$ represents statistically significant publication bias). In addition, the HTLV-1 genotypes of blood donors in mainland China were assessed.

3. Results

3.1. Flow of the studies through the selection process

Initially, a total of 407 studies were retrieved from the databases using different combinations of the key search terms: 10 studies from PubMed, 286 studies from CNKI, and 111 from Wanfang. Using the inclusion and exclusion criteria, we excluded 346 studies after title and abstract screening and another 17 articles after reading the full text. Finally, 44 articles were selected, 40 articles[15–54] on the prevalence of HTLV-1 and nine articles[17,27,42,49,51,55–58] on the genotypes. The selection process is illustrated in Figure 1.

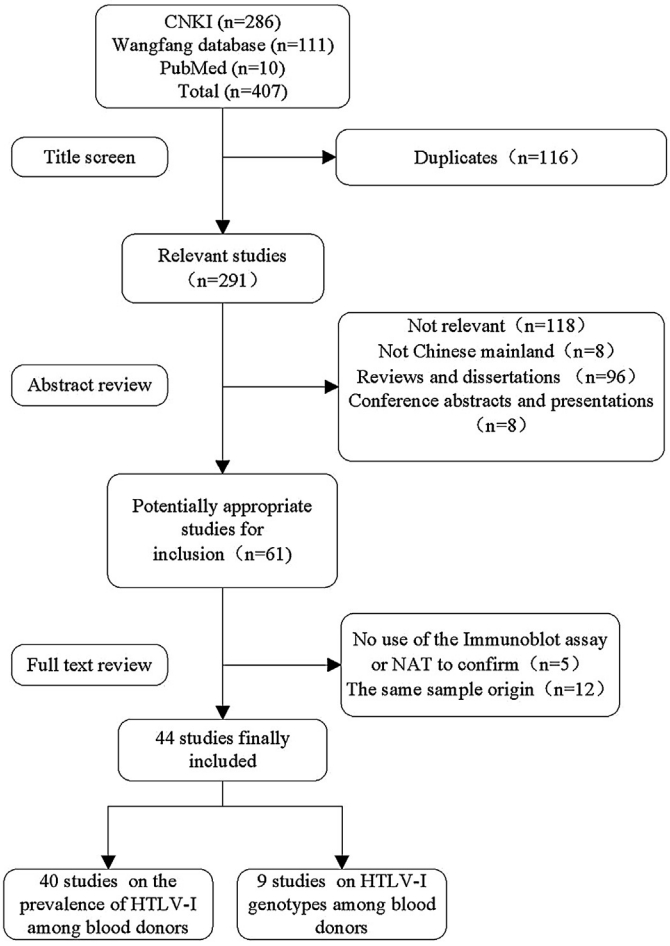

Figure 1. Flow chart of the systematic literature search process.

3.2. Study characteristics

All forty studies on the prevalence of HTLV-1 infection were cross-sectional; they involved 17 provinces, one autonomous region, and three municipalities. The present analysis included 458 525 participants (198 448 from Fujian, 55 314 from Guangdong, and 204 763 from other areas). The blood samples mainly came from blood banks, the Centers for Disease Control and Prevention (CDC), and hospitals. The sample size of the selected studies ranged from 80 to 131 823 (median 3404, interquartile range 1402–8813). ELISA was used for laboratory screening in all except a few studies, which also used PA (particle agglutination) or IF (immunofluorescence).[15,23–25] Immunoblot assays or NAT were used for confirmation in all studies. The details of each study on the prevalence of HTLV-1 are presented in Table 1.

3.3. Prevalence of HTLV-1 among blood donors in mainland China

A pooled estimate of HTLV-1 prevalence was obtained from an analysis of 12 studies involving blood donors in Fujian Province.[15,17,26–28,33,39,42–44,48,49] The heterogeneity (I^2 = 90.7%,

Table 1
Summary of data from selected articles on HTLV-1 prevalence among blood donors in mainland China.

First author and year of publication	Language	Study location	Screening tests	Confirmatory tests	Sample collection year(s)	Target population	Sample size	Number of HTLV-1 infections	Quality assessment score
Cao F, 1998[15]	English	Fujian	PA/ELISA	Immunoblot	NA	Blood donor	1299	2	6
		Sichuan	PA/ELISA	Immunoblot	NA	Blood donor	2614	0	
Cao Y, 2008[16]	Chinese	Jiangsu	ELISA	Immunoblot	2004	Blood donor	3608	0	6
Chen CR, 2012[17]	Chinese	Fujian	ELISA	Immunoblot/NAT	2004–2009	Blood donor	131 823	24	7
Chen ZW, 2009[18]	Chinese	Guangdong	ELISA	Immunoblot	2004–2005	Blood donor	1008	0	6
Du Y, 2008[19]	Chinese	Zhejiang	ELISA	Immunoblot	2006–2007	Blood donor	5556	0	6
Fan WA, 2002[20]	Chinese	Anhui	ELISA	Immunoblot	NA	Blood donor	880	0	3
Fang CF, 2004[21]	Chinese	Jiangxi	ELISA	NT	NA	Blood donor	8850	0	6
Feng GJ, 2005[22]	Chinese	Shandong	ELISA	Immunoblot	NA	Blood donor	6160	0	6
Geng L, 1998[23]	English	Liaoning	PA/ELISA/IF	Immunoblot	1995–1997	Blood donor	1645	0	7
Guan SF, 2001[24]	Chinese	Beijing	PA	NT	1996	Blood donor	749	0	4
Hu J, 2003[25]	Chinese	Chongqing	PA/ELISA	Immunoblot	NA	Blood donor	1462	0	6
Huang RX, 1998[26]	Chinese	Fujian	ELISA	Immunoblot	NA	Blood donor	2100	3	6
Huang RX, 2002[27]	Chinese	Fujian	ELISA	Immunoblot/NAT	2000	Blood donor	10 512	1	6
Ji Y, 2000[28]	Chinese	Fujian	ELISA	Immunoblot	1997–1998	Blood donor	2399	3	6
		Hubei	ELISA	Immunoblot	1997–1998	Blood donor	578	0	
		Shandong	ELISA	Immunoblot	1997–1998	Blood donor	1994	0	
		Xinjiang	ELISA	Immunoblot	1997–1998	Blood donor	1572	0	
		Zhejiang	ELISA	Immunoblot	1997–1998	Blood donor	1029	0	
Jia W, 2004[29]	Chinese	Qinhai	ELISA	NT	NA	Blood donor	4529	0	5
Li J, 2008[30]	Chinese	Guangdong	ELISA	Immunoblot	2006–2007	Blood donor	26 608	9	6
Li RL, 2005[31]	Chinese	Tianjing	ELISA	Immunoblot	2002–2003	Blood donor	11 757	0	6
Li YF, 2008[32]	Chinese	Guangdong	ELISA	Immunoblot	2006	Blood donor	6112	0	6
Lin YS, 2004[33]	Chinese	Fujian	ELISA	Immunoblot/NAT	2002	Blood donor	5000	4	6
Ma Y, 2013[34]	English	Henan, Hubei	ELISA	Immunoblot	2008–2011	Blood donor	3548	2	7
Sun SJ, 2013[35]	Chinese	Guangdong	ELISA	Immunoblot	2012	Blood donor	2500	1	6
Tang Q, 2002[36]	Chinese	Jiangsu	ELISA	Immunoblot	2000	Blood donor	1436	0	6
Tang QP, 2007[37]	Chinese	Hainan	ELISA	Immunoblot	NA	Blood donor	11 000	0	6
Tang RC, 2003[38]	Chinese	Jiangsu	ELISA	NAT	2002	Blood donor	9500	0	5
Wang HR, 2004[39]	Chinese	Fujian	ELISA	Immunoblot	1999–2002	Blood donor	1643	1	6
Wang JQ, 2001[40]	Chinese	Zhejiang	ELISA	NT	NA	Blood donor	892	0	5
Wang WL, 1999[41]	Chinese	Beijing	ELISA	Immunoblot	NA	Blood donor	1929	0	6
Wang YC, 2005[42]	English	Fujian	ELISA	Immunoblot	NA	Blood donor	34 800	19	6
		Guangdong	ELISA	Immunoblot	NA	Blood donor	5073	0	
		Hainan	ELISA	Immunoblot	2004–2005	Blood donor	12 084	0	
		Henan	ELISA	Immunoblot	2004–2005	Blood donor	14 266	0	
		Hubei	ELISA	Immunoblot	2004–2005	Blood donor	8800	0	
		Jiangsu	ELISA	Immunoblot	2004–2005	Blood donor	9500	0	
		Jiangxi	ELISA	Immunoblot	2004–2005	Blood donor	8500	0	
		Jilin	ELISA	Immunoblot	2004–2005	Blood donor	8900	0	
		Liaoning	ELISA	Immunoblot	2004–2005	Blood donor	18 300	0	
		Shandong	ELISA	Immunoblot	2004–2005	Blood donor	13 769	0	
		Tianjing	ELISA	Immunoblot	2004–2005	Blood donor	4635	0	
		Xinjiang	ELISA	Immunoblot	2004–2005	Blood donor	1820	0	
		Zhejiang	ELISA	Immunoblot	2004–2005	Blood donor	4846	0	
Xue GZ, 2001[43]	Chinese	Fujian	ELISA	Immunoblot	1997–1998	Blood donor	252	2	5
Yin HZ, 2000[44]	Chinese	Beijing	ELISA	Immunoblot	NA	Blood donor	920	0	6
		Fujian	ELISA	Immunoblot	NA	Blood donor	1056	4	
		Guangxi	ELISA	Immunoblot	NA	Blood donor	592	0	
		Jiangxi	ELISA	Immunoblot	NA	Blood donor	845	0	
Yue XQ, 2005[45]	Chinese	Jilin, Liaoning, Heilongjiang	ELISA	Immunoblot	2000	Blood donor	80	0	4
Zeng JF, 2004[46]	Chinese	Guangdong	ELISA	Immunoblot	2002	Blood donor	3260	0	7
Zhang BW, 2003[47]	Chinese	Henan	ELISA	Immunoblot	NA	Blood donor	9074	0	6
Zhang GZ, 2002[48]	Chinese	Fujian	ELISA	Immunoblot/NAT	1998–2000	Blood donor	4564	16	6
Zhang QW, 2007[49]	Chinese	Fujian	ELISA	Immunoblot	2006	Blood donor	3000	1	6
Zhang SB, 2009[50]	Chinese	Hunan	ELISA	Immunoblot	2008	Blood donor	830	0	6
Zhou P, 2009[51]	Chinese	Guangdong	ELISA	NAT	2006–2007	Blood donor	7630	1	6
Zhou ZM, 1999[52]	Chinese	Guangxi	ELISA	Immunoblot	NA	Blood donor	868	0	6
Zhu H, 2004[53]	Chinese	Zhejiang	ELISA	Immunoblot	2002	Blood donor	4846	0	6
Zhuang W, 2001[54]	Chinese	Guangdong	ELISA	Immunoblot	NA	Blood donor	3123	1	6

HTLV-1, human T-lymphotropic virus type 1; ELISA, enzyme-linked immunosorbent assays; IF, immunofluorescence tests; NA, not available; NAT, nucleic acid tests; NT, not tested; PA, particle agglutination tests.

$p < 0.001$, by test for heterogeneity) among the 12 studies included was substantial. Therefore, a random-effects model was used to estimate the pooled prevalence of HTLV-1 among blood donors in Fujian. The estimate was 9.9/10 000 (95% CI 4.4/10 000–22.2/10 000). Begger's and Egger's tests found no significant publication bias ($p_{\text{Begger's test}} = 0.95$, and $p_{\text{Egger's test}} = 0.40$) and therefore no effect of publication bias on this estimate. In addition, meta-regression was used to estimate the effect of study factors (publication period, sample size, and language) on the log prevalence of the outcome. The year of publication and sample size, but not the language of publication, contributed significantly to heterogeneity. The pooled prevalence of HTLV-1 was also significantly lower for studies published after 2005 than before 2005 (i.e., 3.2/10 000 and 16.0/10 000, respectively). Studies with

Table 2
Results of univariable meta-regression analysis of the Fujian Province data[a]

Study factors	No. of studies (n)	Heterogeneity		Pooled estimate, per 10 000, (95% CI)	Meta-regression
		I^2 (%)	p-Value		β, p-value
Total	12	90.7	0	9.9 (4.4–22.2)	
Period of publication					
January 1998–December 2004	9	68.5	$p < 0.01$[b]	16.0 (8.2–31.1)	β = −1.67
January 2005–June 2013	3	84.4	$p < 0.01$[b]	3.2 (1.3–8.0)	$p < 0.01$[b]
Sample size					
<5000	8	50.3	$p = 0.05$[b]	20.9 (11.7–37.1)	β = −1.82
≥5000	4	83.2	$p < 0.01$[b]	3.4 (1.5–7.9)	$p < 0.01$[b]
Language of article					
Chinese	10	92.2	$p < 0.01$[b]	10.0 (3.5–28.4)	β = −0.21
English	2	48.6	$p = 0.16$	7.4 (2.9–18.6)	$p = 0.82$

[a] The pooled estimate (per 10 000), 95% confidence interval (CI), number of studies (n), meta-regression coefficient (β), and significance of β (p-value) are shown.
[b] p-Values represent significant associations ($p < 0.10$).

sampling sizes greater than 5000 tended to report lower prevalence than otherwise (Table 2).

With no significant heterogeneities ($I^2 = 0\%$, $p = 0.91$) among eight studies, a meta-analysis (fixed-effects model) was use to calculate the pooled estimate of HTLV-1 prevalence among blood donors in Guangdong Province.[18,30,32,35,42,46,51,54] The estimate was 2.9/10 000 (95% CI 1.7/10 000–4.8/10 000). No significant publication bias was detected by Begger's and Egger's tests ($p_{\text{Begger's test}} = 1.0$, and $p_{\text{Egger's test}} = 0.12$).

Only two cases of HTLV-1 infection among 204 763 donors, one from Henan and the other from Hubei Province, were reported in all other areas of mainland China.[34]

3.4. Genotypes of HTLV-1 among infected blood donors

Nine of the studies included used phylogenetic analyses of *env* and LTR (the long terminal repeat) regions to genotype 42 HTLV-1 isolates from confirmed positive samples.[17,27,42,49,51,55–58] The genetic analyses showed that 40 of the 42 (95.2%) isolates belonged to the Transcontinental subgroup A of the HTLV-1 subtype A (Cosmopolitan subtype) and two isolates (4.8%) clustered within the Japanese subgroup B.

4. Discussion

Like several other blood-borne infectious agents (hepatitis B virus, hepatitis C virus, and HIV), HTLV-1 has a worldwide prevalence. It is estimated that 15 to 20 million individuals are HTLV-1-infected.[9,59] HTLV-1 prevalence is relatively high in southwestern Japan (up to 10%),[60,61] several countries in the Caribbean area, for example Jamaica and Trinidad (up to 6%),[62,63] some countries of Sub-Saharan Africa including Benin, Cameroon, and Guinea-Bissau (up to 5%),[64–67] and localized areas of Australo-Melanesia and Iran (less than 5%),[68,69] and it is somewhat lower in several countries of South America.[70–74] For blood donors in North America and Europe, HTLV-1 prevalence is very low, i.e., 1–3/10 000 in the USA and Canada, 0.2/10 000 in Norway, and 0.56/10 000 in Greece.[75–78] In Asia, except for some important endemic areas including mainly Iran and Japan, the prevalence of HTLV-1 appears low.[79] However, in most areas of Asia, particularly the Chinese mainland, HTLV-1 prevalence among blood donors remains unknown due to the lack of large and representative studies. In addition, screening of blood donors is an effective strategy for preventing HTLV-1 transmission. Given the high cost of testing, a relatively accurate prevalence rate is needed for an appropriate strategy of blood donation screening in various areas. Hence the prevalence of HTLV-1 infection among blood donors on the Chinese mainland was evaluated in this study.

Forty articles on HTLV-1 prevalence among blood donors were identified for this study.[15–54] Most HTLV-1-infected blood donors were reported in the provinces of Fujian and Guangdong, and only two cases were reported in other areas of mainland China. Hence, meta-analyses were conducted to estimate the prevalence of HTLV-1 among blood donors in Fujian and Guangdong provinces. The prevalence was 9.9/10 000 (95% CI 4.4/10 000–22.2/10 000) in Fujian and 2.9/10 000 (95% CI 1.7/10 000–4.8/10 000) in Guangdong. These are much lower than those in southern Japan, Sub-Saharan Africa, and the Caribbean area, and higher than those in North America and Europe. In addition, our results suggest that the distribution of HTLV-1-infected blood donors in mainland China is similar to that in the rest of the world, which means clusters of endemicity (Fujian and Guangdong) tend to occur near provinces where the virus has not been reported previously. Generally, a low prevalence of HTLV-1 is defined as less than 1% in a specific population.[9,10] The present study found the prevalence of HTLV-1 infection among blood donors to be low in Fujian and Guangdong provinces, and that HTLV-1 is not endemic throughout mainland China.

Furthermore, meta-regression analysis identified publication period and sample size to be contributors to the heterogeneity between studies on prevalence in Fujian Province. Pooled prevalence estimates of HTLV-1 among blood donors decreased between the earlier (January 1998–December 2004) and later (January 2005–June 2013) periods. Possible explanations for this decrease include improvements in laboratory technology, improvements in research designs, lifestyle changes, improvements in sanitary conditions, etc. Our results also showed that the prevalence of HTLV-1 among blood donors was lower in studies with large sample sizes (≥5000) than in those with small sample sizes.

Phylogenetic analysis of the *env* and LTR genes has detected four main genotypes of HTLV-1: HTLV-1 subtype A (Cosmopolitan subtype), which is distributed worldwide; HTLV-1 subtype B and subtype D, found in Central Africa; and HTLV-1 subtype C, found in Australo-Melanesia. Furthermore, four subgroups are distinguished within HTLV-1 subtype A, namely, the Transcontinental, Japanese, West African, and North African subgroups.[80] Our results showed that the genotypes of most HTLV-1 isolates from blood donors belonged to the Transcontinental subgroup within HTLV-1 subtype A. It would be helpful to understand the origins and dissemination of HTLV-1 infection throughout the Chinese mainland.

The strategies for HTLV-1 prevention and control should be based on local epidemiological evidence. To date, however, there are no public health policies for the prevention of HTLV-1 transmission via blood transfusions on the Chinese mainland. It is advised that blood donors in Fujian and Guangdong provinces be

screened for HTLV. Considering the cost of testing, more cost-effective strategies for HTLV screening of donated blood need to be designed and evaluated. Moreover, a surveillance system of HTLV-1 infection should be implemented in endemic or non-endemic areas, especially in the high population mobility areas of mainland China.

This meta-analysis has several limitations. Of the 31 provinces on the Chinese mainland, only 21 provinces (i.e., 17 provinces, one autonomous region, and three municipalities) were included. No data on the prevalence of HTLV-1 infection among blood donors were available for all other regions. Secondly, our ability to assess study quality was limited because many of the selected studies failed to provide detailed information on subjects or valid data on important factors. Thirdly, the studies included were observational and blood donors were not chosen randomly. So confounding and selection bias appears inevitable. Considering that the publication of negative trials is sometimes less likely, this study also has the potential limitation of publication bias. Additionally, most of our data were extracted from studies written in Chinese, which makes it difficult for non-Chinese readers to refer back to the original materials. However, we have confidence in our results since most of the articles included were from multiple sources, and pooling of data for 458 525 blood donors provided us with a large sample size.

In summary, our study reveals that the prevalence of HTLV-1 infection among blood donors is low and restricted mainly to Fujian and Guangdong provinces on the Chinese mainland, and the genotypes of most HTLV-1 isolates belong to the Transcontinental subgroup within HTLV-1 subtype A.

Acknowledgements

The authors gratefully acknowledge the financial support of the National and Fujian Provincial Key Clinical Specialty Discipline Construction Program, P.R. China.

Ethical approval: No ethical approval was needed for this study.

Conflict of interest: No conflict of interest to declare.

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