

# Prevalence of different HIV-1 subtypes in sexual transmission in China: a systematic review and meta-analysis

R. YUAN<sup>1</sup>†, H. CHENG<sup>2</sup>†, L.-S. CHEN<sup>1</sup>, X. ZHANG<sup>2</sup> AND B. WANG<sup>1</sup>\*

<sup>1</sup> Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing, China

<sup>2</sup> Wuxi Center for Disease Control and Prevention, Wuxi, Jiangsu, China

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## SUMMARY

Sexual transmission has become the primary route of HIV transmission in China. Therefore, a comprehensive overview of HIV-1 subtype distribution is necessary for the prevention and control of the HIV epidemic. The present study aimed to provide a comprehensive prevalence estimate of different HIV-1 subtypes in sexual transmission in China. We conducted a systematic literature review for studies of HIV-1 subtypes in English and Chinese through several databases. Eligible articles were screened and selected by two authors independently. Random-effects model were applied to calculate the pooled prevalence of different HIV-1 subtypes, and subgroup analyses examined prevalence estimates across time, locations, and populations. A total of 130 eligible studies were identified, including 18 752 successfully genotyped samples. The pooled prevalence of CRF01\_AE, subtype B, CRF07\_BC, CRF08\_BC, and subtype C were 44·54% (95% CI 40·81–48·30), 18·31% (95% CI 14·71–22·17), 16·45% (95% CI 13·82–19·25), 2·55% (95% CI 1·56–3·73), 0·37% (95% CI 0·11–0·72), respectively. The prevalence of subtype B in sexual transmission decreased, while the prevalence of CRF01\_AE and CRF07\_BC in sexual transmission, and CRF08\_BC in heterosexual transmission increased. There is significant variation in HIV-1 subtype distribution between regions. The distribution of HIV-1 subtypes and circulating recombinant forms have changed significantly. The high genetic variability of HIV-1 poses a significant challenge for disease control and surveillance in China.

**Key words:** China, HIV-1, sexual transmission, subtype.

## INTRODUCTION

The HIV and AIDS epidemic in China remains very serious. Incidence of HIV/AIDS continues to increase annually, from 21 700 in 2003 to 90 100 in 2013 [1]. In 2011, an estimate of 780 000 (range 620 000–940 000) individuals had HIV/AIDS in China [2]. By the end of July 2015, 554602 people were reported to be infected

with HIV/AIDS and 171 186 died from AIDS-related illnesses [3]. In the last 10 years, the main drivers of the HIV epidemic in China have shifted, from primarily blood-borne spreading to sexual contact. Of the new cases diagnosed annually, the percentage of sexually transmitted cases increased from 33·1% in 2006 to 90·8% in 2013, with the male homosexual transmission rate increasing from 2·5% in 2006 to 21·4% in 2013 [4].

HIV is characterized by a high genetic diversity and extensive heterogeneity. This characteristic is due to multiple factors including multiple zoonotic transmissions into human populations, high rates of viral

\* Author for correspondence: Professor B. Wang, Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing 210009, China.  
(Email: wangbeilxb@163.com)

† These authors contributed equally to this work.

evolution, and recombination. HIV has two major types, HIV-1 and HIV-2, which are further divided into groups, subtypes, and recombinant forms [5]. Globally, over 90% of the HIV infections belong to HIV-1 group M viruses, which have been further classified into nine subtypes (A–D, F–H, J, K) and more than 72 circulating recombinant forms (CRFs). Additionally, there are many unique recombinant forms (URFs) that are globally distributed [6, 7]. The spread of HIV-1 variants has implications for disease diagnosis, treatment, and vaccine development [8].

In China, the distribution of HIV-1 subtypes is complex and diverse. Previous studies have shown that HIV-1 prevalent strains include at least 30 subtypes, including nine subtypes and more than 21 CRFs [6, 8–10]. Of these, CRF01\_AE, CRF07\_BC, CRF08\_BC, and subtype B are the predominant circulating HIV-1 subtypes [9–11]. This diversity presents a serious challenge for HIV prevention and treatment strategies. However, HIV strains often show specific associations with geographical regions and modes of transmission [12, 13]. Nevertheless, HIV-1 subtypes are possibly related to disease progression and drug resistance [14, 15]. Through surveillance of the dynamic changes of HIV-1 genetic variability, we can track the source of infection and develop public health strategies in a timely manner in order to effectively prevent the virus spreading. This will also benefit HIV-1 diagnosis, treatment, and vaccine development [16]. Currently, sexual transmission has become the primary mode of HIV-1 spread in China, but little is known about HIV-1 subtype distribution in sexual transmission and this should be the primary focus.

The main objective of this review was to provide a comprehensive overview and pooled prevalence estimate of different HIV-1 subtypes in sexual transmission in China. In addition, we also analysed the temporal and geographical variation from the data to provide more detailed information for the effective prevention and control of HIV-1 in China.

## METHOD

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform and report this meta-analysis [17].

### Search strategy

We conducted a literature search in English and Chinese using the following databases: PubMed,

Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Wanfang, from inception to 10 December 2015. Using the following search items: (HIV OR human immunodeficiency virus OR AIDS OR acquired immunodeficiency syndrome) AND (genotype OR subtype OR molecular epidemiology) AND China. Additionally, we reviewed the reference lists of the retrieved articles for additional relevant studies.

### Selection criteria

Two authors (R.Y. and H.C.) independently assessed the eligibility of the articles, and a third reviewer (B.W.) supervised this process when opinions were divergent. The following criteria were applied: (1) studies based on HIV-1 subtypes in China; (2) modes of transmission must contain sexual transmission, such as bisexual, heterosexual (HST), or men who have sex with men (MSM) transmission; (3) provide primary data of the frequency of each subtype; (4) provide available information on study time and location; and (5) sample size of more than 10. Exclusion criteria included studies on a single specific subtype or the assessment of articles on detection techniques. To avoid duplication, if the same study data were reported repeatedly, the one that provided more detailed information and/or a larger sample size was chosen.

### Data extraction

According to the selection criteria, two authors (R.Y. and H.C.) independently extracted study data, including first-named author, year of publication, study period, study locations, study populations (or modes of transmission), study method of classification of HIV-1 subtypes, sample size, number of successfully genotyped samples and the frequency of each subtype. Any differences were resolved by consensus. As for the method of HIV-1 classification, sequence-based typing was viewed as the 'gold standard' [18]. In particular, manual phylogenetic analysis of the *pol*, *gag* and *env* regions was widely applied to HIV subtyping in China because automated subtyping tools do not provide accurate subtype assignment for complex strains such as CRF07\_BC, CRF08\_BC, etc. Therefore, all of the included studies determined HIV-1 subtypes based on *pol*, *gag* and/or *env* gene amplification and sequencing.

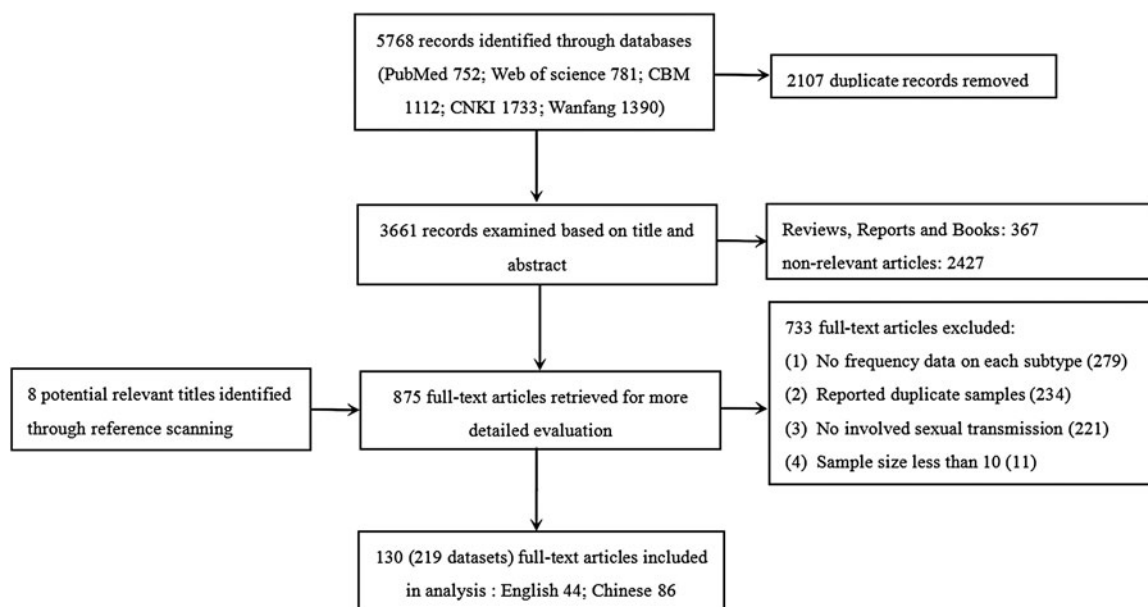


Fig. 1. Summary of literature search and selection procedure.

### Statistical analysis

The Freeman–Tukey double arcsine transformation of proportions was used to estimate the pooled proportion of different HIV-1 subtypes [19, 20]. Heterogeneity between the studies was examined using Cochran’s  $Q$  statistic and the  $I^2$  statistic [21, 22]. Depending on the heterogeneity, A mixed-effects model was chosen to calculate the pooled point estimate: random-effects models were selected when the  $P$  value of Cochran’s  $Q$  statistic was  $<0.1$  or  $I^2$  was  $>50\%$ , or fixed-effects models were used. Subgroup analyses were conducted based on the time period, study location, and study population to further assess heterogeneity. The funnel plot and Egger’s test were used to assess publication bias, which found no evidence of bias (Supplementary Fig. S1). All analyses were performed using R software (version 3.2.1) [23] and SAS (version 9.3, SAS Institute Inc., USA).

## RESULTS

### Study selection and characteristics

Figure 1 summarizes the literature search results and selection procedure. Of the 5768 abstracts (4234 in Chinese, 1533 in English) initially identified, 130 unique articles were finally included. Most articles were identified through database searching, and only three (out of eight potentially relevant titles) additional eligible articles were identified through bibliography

scanning. The 130 studies were divided into 219 datasets based on different study times, locations, or populations. The study period ranged from 1988 to 2014. Five studies were from the national survey of HIV-1 subtypes. Of the remainder, study sites were distributed throughout 28 different provinces or regions. Eventually, 18 752 successfully genotyped samples were included in the analysis which comprised 6759 heterosexuals, 10 516 MSM, 198 bisexuals, and 1279 uncertain unprotected sexual contact individuals. More detailed information is included in Supplementary Table S1.

### Proportion of different HIV-1 subtypes

The prevalent HIV-1 strains in sexual transmission were commonly CRF01\_AE, CRF07\_BC, CRF08\_BC, and subtype B (including US-European B and Thailand B). Comprehensive analysis of the pooled proportion of different HIV-1 subtypes to CRF01\_AE, CRF07\_BC, CRF08\_BC, B/B’, C, and others was 44.54% [95% confidence interval (CI) 40.81–48.30], 16.45% (95% CI 13.82–19.25), 2.55% (95% CI 1.56–3.73), 18.31% (95% CI 14.71–22.17), 0.37% (95% CI 0.11–0.72), and 2.01% (95% CI 1.36–2.75), respectively.

### Subgroup analysis

As shown in Table 1, the proportion of different HIV-1 subtypes was further explored within identifiable

Table 1. Pooled prevalence of different HIV-1 subtypes stratified by time period, study region and risk group

Category	N	CRF01_AE			CRF07_BC			CRF08_BC		
		Proportion % (95% CI)	P*, I <sup>2</sup>	P†	Proportion % (95% CI)	P*, I <sup>2</sup>	P†	Proportion % (95% CI)	P*, I <sup>2</sup>	P†
Region‡				0.001			<0.01			<0.01
Northeastern	22	57.80 (45.74–69.44)	<0.01, 94.0%		4.63 (2.57–7.13)	<0.01, 58.2%		0.00 (0.00–0.00)	0.757, 0.0%	
Eastern	115	48.95 (44.17–53.74)	<0.01, 95.7%		12.47 (9.84–15.35)	<0.01, 93.8%		1.33 (0.64–2.19)	<0.01, 85.3%	
Central	27	34.41 (24.75–44.72)	<0.01, 94.2%		19.52 (11.78–28.51)	<0.01, 94.1%		0.14 (0.00–0.84)	0.004, 46.8%	
Northwestern	7	22.68 (4.31–48.76)	<0.01, 96.7%		65.89 (35.98–90.41)	<0.01, 97.3%		0.00 (0.00–0.39)	0.153, 36.1%	
Southwestern	45	36.16 (28.16–44.55)	<0.01, 96.1%		25.94 (18.20–34.46)	<0.01, 96.7%		13.93 (7.93–21.13)	<0.01, 96.7%	
Time period§				0.001			<0.01			0.164
Before 2000	9	29.11 (15.37–44.92)	<0.01, 95.5%		0.59 (0.00–3.92)	<0.01, 85.3%		0.44 (0.00–3.34)	<0.01, 82.8%	
2001–2004	14	28.73 (17.30–41.61)	<0.01, 89.8%		6.44 (1.74–13.18)	<0.01, 84.2%		6.72 (1.39–14.72)	<0.01, 88.1%	
2005–2007	34	33.30 (22.76–44.69)	<0.01, 97.5%		10.53 (6.04–15.93)	<0.01, 94.0%		4.67 (1.60–8.86)	<0.01, 94.1%	
2008–2010	86	49.92 (43.96–55.88)	<0.01, 95.6%		15.04 (11.50–18.92)	<0.01, 93.8%		2.06 (0.62–4.06)	<0.01, 93.8%	
2011–2014	76	48.25 (42.68–53.83)	<0.01, 94.9%		26.02 (20.90–31.47)	<0.01, 95.6%		1.96 (0.75–3.57)	<0.01, 91.4%	
Risk group				<0.01			0.083			<0.01
MSM	121	51.28 (46.15–56.40)	<0.01, 96.1%		19.98 (16.17–24.07)	<0.01, 95.7%		0.00 (0.00–0.00)	0.577, 0.00%	
HST	76	38.78 (33.08–44.63)	<0.01, 95.4%		14.88 (10.96–19.23)	<0.01, 95.0%		9.81 (6.44–13.70)	<0.01, 95.3%	
Total	219	44.54 (40.81–48.30)	<0.01, 96.0%		16.45 (13.82–19.25)	<0.01, 95.5%		2.55(1.56–3.73)	<0.01, 93.3%	
		B/B'			C			Others#		
Category	N	Proportion % (95% CI)	P*, I <sup>2</sup>	P†	Proportion % (95% CI)	P*, I <sup>2</sup>	P†	Proportion % (95% CI)	P*, I <sup>2</sup>	P†
Region‡				<0.01			0.123			0.007
Northeastern	22	26.15 (16.83–36.60)	<0.01, 93.0%		0.00 (0.00–0.06)	0.105, 28.5%		2.40 (1.45–3.51)	<0.01, 77.8%	
Eastern	115	24.99 (19.38–31.03)	<0.01, 97.8%		0.21 (0.03–0.49)	<0.01, 55.8%		1.17 (0.65–1.78)	<0.01, 73.3%	
Central	27	28.90 (15.78–43.96)	<0.01, 97.4%		0.06 (0.00–0.39)	0.363, 6.8%		3.22 (1.39–5.57)	<0.01, 73.8%	
Northwestern	7	5.07 (0.64–12.23)	<0.01, 82.4%		0.00 (0.00–0.07)	0.982, 0.0%		0.16 (0.00–1.12)	0.082, 46.4%	
Southwestern	45	1.82 (1.01–2.81)	<0.01, 57.5%		1.12 (0.01–3.27)	<0.01, 92.6%		3.33 (1.05–6.50)	<0.01, 93.6%	
Time period§				<0.01			0.768			0.114
Before 2000	9	52.40 (32.41–72.03)	<0.01, 97.2%		0.10 (0.00–1.89)	<0.01, 73.1%		1.00 (0.00–4.56)	<0.01, 84.3%	
2001–2004	14	44.23 (24.99–64.36)	<0.01, 95.6%		0.69 (0.03–1.89)	0.045, 42.9%		0.48 (0.00–2.34)	0.007, 54.5%	
2005–2007	34	34.69 (22.05–48.46)	<0.01, 98.2%		0.45 (0.01–1.29)	<0.01, 64.7%		1.65 (0.59–3.06)	<0.01, 73.7%	
2008–2010	86	17.77 (12.65–23.47)	<0.01, 96.8%		0.36 (0.01–1.02)	<0.01, 80.0%		1.46 (0.45–2.86)	<0.01, 90.0%	
2011–2014	76	7.17 (4.51–10.32)	<0.01, 94.5%		0.29 (0.00–0.93)	<0.01, 82.0%		3.35 (2.25–4.62)	<0.01, 80.1%	

Table 1 (cont.)

Category	B/B'			C			Others#			
	N	Proportion % (95% CI)		P†	Proportion % (95% CI)		P†	Proportion % (95% CI)		P†
		P*	I²		P*	I²		P*	I²	
Risk group				0.508			<0.01			0.2109
MSM	121	17.74 (12.78–23.26)	<0.01, 97.8%		0.00 (0.00–0.00)	0.999, 0.0%		1.56 (0.98–2.24)	<0.01, 72.0%	
HST	76	15.41 (11.15–20.16)	<0.01, 95.9%		1.89 (0.81–3.28)	<0.01, 88.2%		2.39 (1.33–3.66)	<0.01, 83.5%	
Total	219	18.31 (14.71–22.17)	<0.01, 97.5%		0.37 (0.11–0.72)	<0.01, 78.5%		2.01 (1.36–2.75)	<0.01, 85.4%	

N, Number of estimates; CI, confidence interval; MSM, men who have sex with men; HST, heterosexual transmission.

\* P value was calculated by examining Cochran's Q statistic ( $P < 0.1$  was considered statistically significant).

† P value stand for the differences between groups ( $P < 0.05$  was considered statistically significant).

‡ For time period subgroup analysis, 219 datasets from 129 articles were used.

§ For study region subgroup analysis, 216 datasets from 126 articles were used.

|| For risk group subgroup analysis, 197 datasets from 120 articles were used.

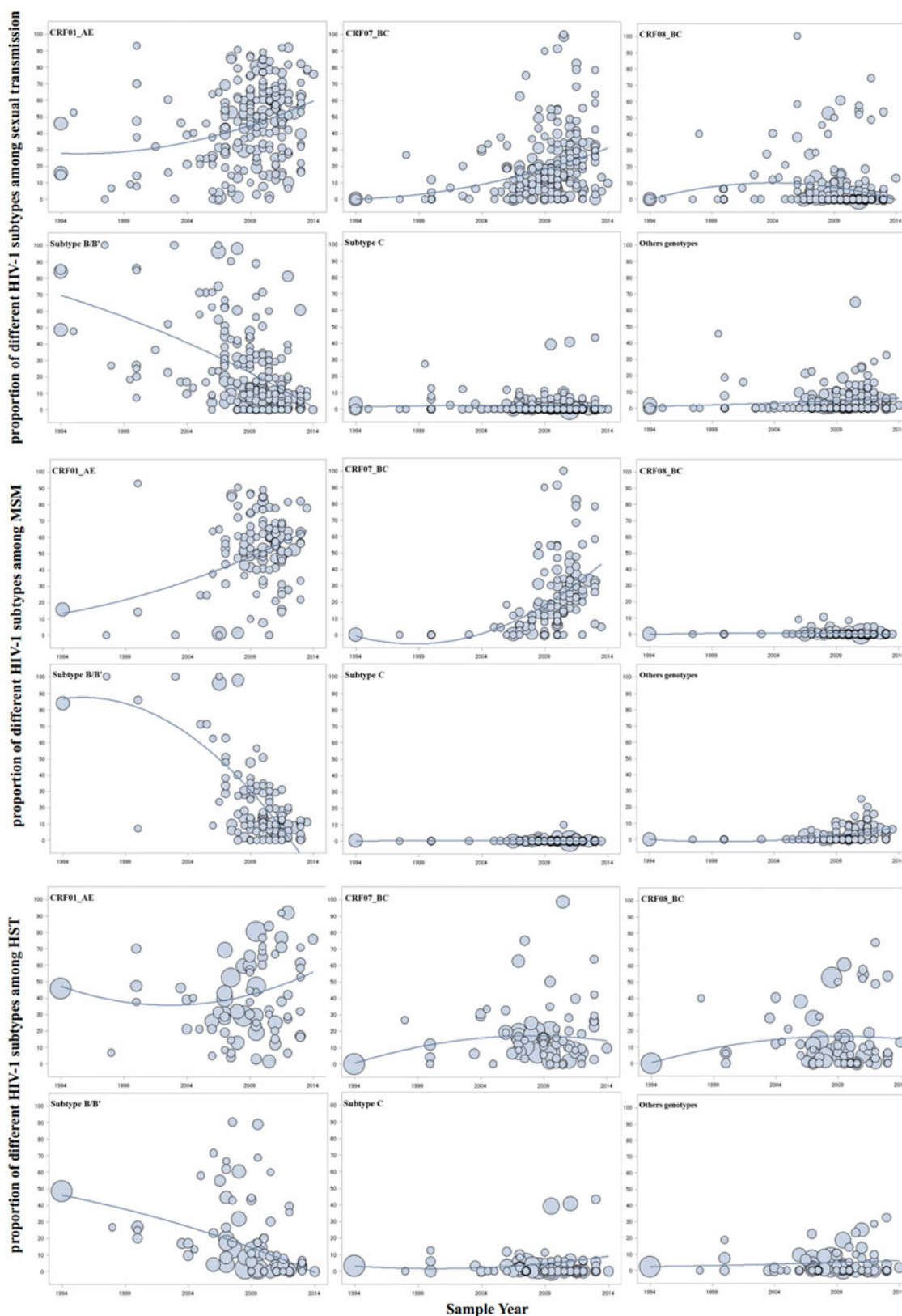
# Others included unique recombinant forms (URFs) and other subtypes.

subgroups where relevant information was provided. Study time was further categorized roughly into five time periods to analyse the trends of different HIV-1 subtype distributions in sexual transmission. Figure 2 shows chronological trends of different HIV-1 subtypes in sexual transmission, MSM, and HST according to the midpoint of the year in which study participants were recruited. There was an upward trend in the proportion of CRF01\_AE and CRF07\_BC, especially among MSM. However, the proportion of subtype B/B' showed a linearly downward trend. The proportion of CRF08\_BC rose in the early stages and then decreased after about 2004, while it showed an upward trend in HST. Furthermore, CRF08\_BC (9.81%, 95% CI 6.44–13.70) and subtype C (1.89%, 95% CI 0.81–3.28) mainly existed in HST (Table 1). The prevalence of subtype C and other subtypes in sexual transmission maintained a stable trend at a low level. Markedly, the proportion of URFs and other subtypes in MSM showed an upward trend.

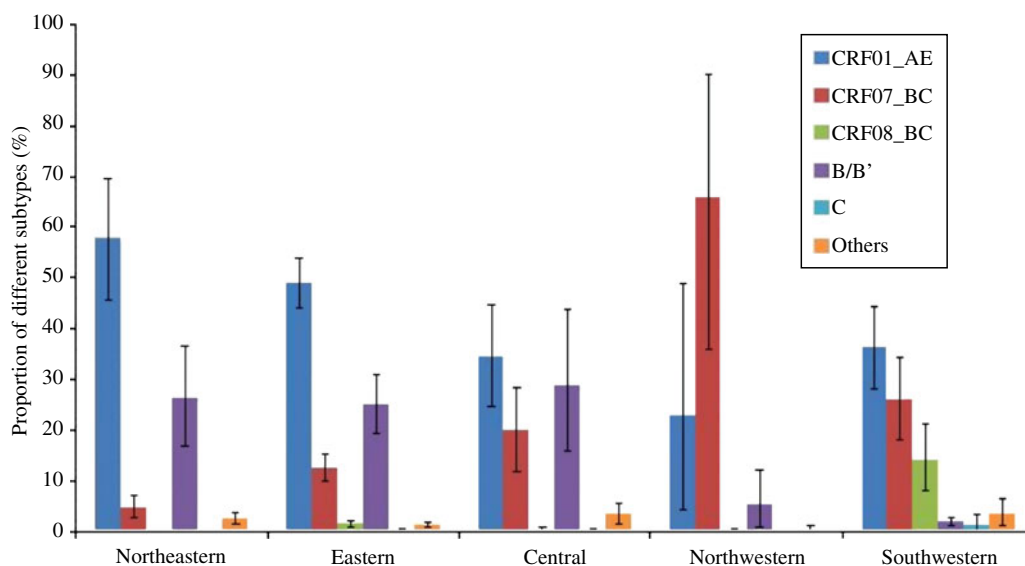
Study location was also categorized roughly into five regions to further analyse the geographical distribution characteristics of HIV-1 subtypes. Figure 3 shows a diversity of HIV-1 subtype distributions in sexual transmission in different geographical regions. In the northeastern region, CRF01\_AE (57.80%, 95% CI 45.74–69.44) and subtype B/B' (26.15%, 95% CI 16.83–36.60) were the predominant circulating strains. In the eastern region, CRF01\_AE (48.95%, 95% CI 44.17–53.74), subtype B/B' (24.99%, 95% CI 19.38–31.03), and CRF07\_BC (12.47%, 95% CI 9.84–15.35) were the predominant circulating strains. Furthermore, CRF01\_AE (34.41%, 95% CI 24.75–44.72), subtype B/B' (28.90%, 95% CI 15.78–43.96), and CRF07\_BC (19.52%, 95% CI 11.78–28.51) were also the three predominant circulating strains in the central region. In the northwestern region, HIV-1 prevalent strains were relatively simple, where CRF07\_BC (65.89%, 95% CI 35.98–90.41) was the predominant circulating strain and CRF01\_AE (22.68%, 95% CI 4.31–48.76) ranked second. In the southwestern region, CRF01\_AE (36.16%, 95% CI 28.16–44.55), CRF07\_BC (25.94%, 95% CI 18.20–34.46), and CRF08\_BC (13.93%, 95% CI 7.93–21.13) were the three major circulating strains. Of note, URFs and other subtypes (3.33%, 95% CI 1.05–6.50) were detected in significant proportions. This is the region where HIV-1 prevalent strains showed the highest diversity after the eastern and central regions.

In the different risk groups, the proportion of CRF01\_AE, CRF07\_BC, and subtype B/B' in MSM





**Fig. 2.** Temporal trends in the yearly proportion of different HIV-1 subtypes in sexual transmission, men who have sex with men (MSM) and heterosexual transmission (HST) in China. The x-axis represents the midpoint of the year in which study samples were collected and analysed. The diameter of each bubble is proportional to the sample size of each study. The fitted line was plotted using a generalized linear mixed model regression.



**Fig. 3.** Proportion of different HIV-1 subtypes in sexual transmission in different regions. The northeastern region includes Heilongjiang, Jilin and Liaoning provinces. The eastern region includes Beijing, Fujian, Guangdong, Hainan, Hebei, Hongkong, Jiangsu, Shandong, Shanghai, Taiwan, Tianjin, and Zhejiang provinces. The central region includes Anhui, Henan, Hubei, Hunan, Jiangxi, and Shanxi provinces. The northwestern region includes Gansu, Shaanxi, and Xinjiang provinces. The southwestern region includes Chongqing, Guangxi, Guizhou, Sichuan, and Yunnan, provinces.

were relatively higher than those in HST, while CRF08\_BC and subtype C showed the opposite trend.

## DISCUSSION

To our knowledge, this current meta-analysis is the largest to investigate the distribution of HIV-1 subtypes in sexual transmission in China [11, 18, 24]. The present study was also the first to provide a quantitative synthesis of the proportion of different HIV-1 subtype and subgroup analysis in sexual transmission in China with the use of proper statistical software. Through comprehensive searching of the literature, 130 eligible articles published from 2000 to 2015 and 18 752 samples that were amplified successfully and genotyped were included in the analysis. The results showed that CRF01\_AE, CRF07\_BC, CRF08\_BC, and subtype B were the four predominant subtypes in sexual transmission in China. The pooled proportion of different HIV-1 subtypes was similar to the national survey of HIV molecular epidemiology in China [11, 24]. It partially verified that sexual transmission was the major pathway for the spread of HIV-1 in China [4, 25, 26].

The results showed that CRF01\_AE represented the highest proportion both in MSM and HST. CRF01\_AE, mainly through HST, was the only globally distributed non-B clade that originated in

Thailand but not Africa [27, 28]. It was first identified from female sex workers in northern Thailand in 1989 and later spread throughout Southeast Asia [29–31]. In China, CRF01\_AE was originally detected in Yunnan Province in 1989 in intravenous drug users (IDUs) who were infected through commercial sex workers from Thailand [32]. It then rapidly spread across the country. Currently, there are seven distinct phylogenetic clusters of CRF01\_AE in China, which mainly exist in heterosexuals, homosexuals, and IDUs [33]. Previous studies revealed that CRF01\_AE strains with high frequencies of CXCR4 tropism were possibly related to the cause of a severe loss of CD4+ T cell counts and rapid disease progression [34, 35]. CRF01\_AE had the highest proportion in different regions except for northwestern China. Moreover, it showed an upward trend, especially in MSM. Therefore, regular surveillance of HIV-1 subtypes is necessary to effectively prevent and control the HIV epidemic.

CRF07\_BC and CRF08\_BC, two major CRF strains in China, were first described in IDUs in Yunnan and Guangxi provinces [36, 37]. Through phylogenetic analysis, previous studies speculated that CRF07\_BC possibly originated in China through recombination between subtype B from Thailand and subtype C from India [38–40]. Phylogeographic analysis suggested CRF07\_BC had two phylogenetic clusters. One originated from Xinjiang in the 1990s and

spread to Liaoning, Jiangsu, Heilongjiang, Beijing and Guangdong through IDUs. Another one from Yunnan spread to Taiwan. However, CRF08\_BC was first confirmed in Yunnan and later spread to Guangxi and Liaoning in the mid-1990s [41]. The proportion of CRF07/08\_BC gradually increased in IDUs and later spread to other risk groups through cross-infection and transmission between IDUs and unprotected sexual behaviour [42, 43]. Our meta-analysis showed CRF07\_BC in sexual transmission and CRF08\_BC in HST were increasing, due to a high correlation between unprotected sexual intercourse and drug use increasing HIV transmission in China [42–44]. Thus, novel and effective prevention strategies are necessary for drug use in unprotected sexual behaviours.

Our results indicated that the proportion of subtype B rapidly decreased, especially in MSM. This is consistent with other studies where CRF01\_AE became the predominant circulating strain, replacing subtype B, in MSM [16, 45]. In China, subtype B has four distinct subgroups, namely B (Thai-B), BJ-B (Beijing-B), Pan-B (Pandemic-B), and TW-B (Taiwan-B) [46]. Thai-B was transmitted from IDUs in Yunnan to former plasma donors (FPDs) in central China in the 1990s. Then it rapidly spread across the country through sexual transmission [11, 47, 48]. However, BJ-B, TW-B, and Pan-B (circulating in the United States and Europe) lineages were restricted to particular regions. Although subtype B showed a rapid downward trend in sexual transmission, it still represented a large proportion. Furthermore, the recombinant virus of subtype B and other subtypes were constantly emerging in China, such as CRF\_01B, CRF\_BC, CRF65\_cpx, etc. [7, 49]. These results significantly impact HIV therapeutics and vaccine development in China.

Geographical sub-analysis showed the diverse distribution of HIV-1 subtypes in different regions. The distribution of HIV-1 subtypes was relatively simple in the northeastern and northwestern regions, comparatively diverse in the eastern and central regions, with the highest diversity in the southwestern region. This is relevant to the differences in the drivers of HIV-1 transmission. In the northeast, CRF01\_AE and subtype B became the two predominant circulating strains owing to heterosexuals and MSM dominating HIV-1 transmission [11, 50]. In the east, there were multiple risk groups due to the booming economy attracting large numbers of migrants from all over the country. The coexistence of multiple risk groups

lead to a diversity of the HIV-1 virus [49, 51, 52]. In the central region, FPD dominated the spread of HIV-1 in the early stage, and later was gradually replaced by sexual transmission [4, 53]. Furthermore, the central and eastern regions have maintained close contacts due to their adjacent location and economic exchanges. Therefore, the distributions of HIV-1 subtypes were similar in these two regions. In the northwestern region, the overall prevalence of CRF07\_BC was higher mainly due to it originating from IDUs in Xinjiang [41]. The proportion of CRF01\_AE, higher than in previous studies [11], suggested that sexual transmission was shifting the major pathway of the spread of HIV-1 in this region. The southwestern region included Yunnan, Guizhou, Guangxi and Sichuan provinces, which was the region worst affected by HIV due to cross-infection from different strains and spread in multiple risk groups. In particular, Yunnan was the first location where the HIV epidemic was identified in China [54]. Furthermore, previous studies revealed that almost all of the HIV-1 subtypes from other regions originated in Yunnan [54–56]. Our results also suggested that HIV-1 prevalent strains had the highest diversity in this region. The diverse distribution of HIV-1 subtypes poses a significant challenge to disease control and surveillance in the different regions of China.

Additionally, our meta-analysis found the proportions of CRF01\_AE, CRF07\_BC, and subtype B in MSM were relatively higher than those in HST, while CRF08\_BC and subtype C showed the opposite trend. Additionally, the prevalence of CRF08\_BC was restricted to the southwestern region. Subtype C and other subtypes in sexual transmission were consistently low. However, the proportion of URFs and other subtypes in MSM showed an upward trend. These results provide important information to effectively guide the prevention and control of HIV-1 in China.

Our study also faced several important limitations. First, significant heterogeneity was observed and in the subgroup analysis. It might be attributed to the small sample size of some of the studies included in this analysis, or that a high diversity of HIV-1 subtype distribution existed in different regions, time periods, and risk groups. Second, as most studies included in the analysis did not provide detailed categorical data on subtypes B and B', we merged and analysed them together. Finally, even though the funnel plot and Egger's test suggests an overall low risk of publication bias, we cannot avoid the other biases, such as language bias, database bias, multiple publication bias, etc.



Despite these limitations, the present study represents the first comprehensive investigation of HIV-1 subtypes in sexual transmission in China. These HIV-1 prevalent strains have evolved into complicated subtypes, and major subtypes include CRF01\_AE, CRF07\_BC, CRF08\_BC, and subtype B. In addition, the proportion of different HIV-1 subtypes has changed constantly over time. New recombinant strains are also constantly emerging in China. The high genetic variability of HIV-1 poses a significant challenge for disease diagnosis, treatment, and vaccine development in China.

## SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0950268816000212>.

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## DECLARATION OF INTEREST

None.

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