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RESEARCH ARTICLE

Prevalence of Kaposi's sarcoma-associated herpesvirus among intravenous drug users: a systematic review and meta-analysis

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Intravenous drug users (IDUs) have been demonstrated to be highly vulnerable to HIV/AIDS. Nevertheless, the prevalence of Kaposi's sarcoma associated herpesvirus (KSHV), an important co-infected agent with HIV, among this population remained obscure. We conducted a systematic review on the epidemiological features of KSHV among IDUs worldwide. Eligible studies were retrieved from 6 electronic databases (PubMed, EMBASE, Web of Science, CBM, CNKI and Wanfang). We calculated the pooled prevalence and 95% confidence interval (CI) overall and among subgroups using either random-effects model or fixed-effects model depending on between-study heterogeneity. The potential publication bias was assessed by the Egger's test. A meta-regression analysis was performed to explore the sources of heterogeneity. Finally, twenty-two studies with a total sample of 7881 IDUs were included in the analysis. The pooled prevalence of KSHV was 14.71% (95% CI 11.12%–19.46%) among IDUs. Specifically, KSHV prevalence was 10.86% (95% CI 6.95%–16.96%) in HIV-negative IDUs, and 13.56% (95% CI 10.57%–17.38%) in HIV-positive IDUs. Moreover, prevalence among IDUs from the three continents involved in the current study was similar: 16.10% (95%CI 7.73%–33.54%) in Asia; 14.22% (95%CI 8.96%–22.57%) in Europe and 14.06% (95%CI 11.38%–17.37%) in America. Globally, IDUs are at higher risk of the KSHV infection when compared with the general population, regardless of geographical region or HIV-infection status.

KEYWORDS **Kaposi's sarcoma-associated herpesvirus (KSHV); prevalence; intravenous drug users (IDUs)**

INTRODUCTION

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as Human herpesvirus 8 (HHV8), a member of the gamma herpesvirus family, is the infectious etiological agent associated with all forms of Kaposi's sarcoma (KS), primary effusion lymphoma (PEL) and multicentric Castleman's disease (Razonable, 2011; Zhang et al., 2017). Since its first discovery in 1994(Chang et al., 1994), KSHV has been well studied worldwide (Schwartz et al., 2008; Bagni and Whitby, 2009). Unlike most herpes viruses, KSHV infection is not ubiquitous in the general population. In Asia, North America and West Europe, the prevalence is about 1%–10% (Zhang et al., 2014b; Ahmadi Ghezeldasht et al., 2015). However, previous

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studies have demonstrated that KSHV was endemic in parts of Africa and Mediterranean region, with the prevalence varied from 30% to 50% above (Whitby et al., 1998; Biryahwaho et al., 2010). These studies were of indicative disparities of KSHV prevalence among different geographical regions. Moreover, it has been well documented that HIV was the most important factor associated with KSHV infection (Zhang et al., 2012; Rohner et al., 2016; Liu et al., 2017b), especially in the men who have sex with men (MSM), among whom KSHV has been extensively investigated and some convincible results were obtained. However, among intravenous drug users (IDUs), a population at high risk of HIV infection, results of KSHV infection derived from previous studies were quite diverse. Atkinson et al (Atkinson et al., 2003) reported that KSHV prevalence was 10% in men who practicing intravenous drug use, which was much lower than our previous result (Zhang et al., 2014a). Undoubtedly, the considerable variability of KSHV infection among IDUs (Simpson et al., 1996; Rezza et al., 1998; Wang et al., 2000; Lee et al., 2014) hampered the accurate understanding of KSHV epidemiology in this special population.

Therefore, we, for the first time, performed a comprehensive meta-analysis to obtain the global prevalence of KSHV among IDUs. These results will accelerate the completion of picture depicting the epidemiology of KSHV among IDUs, and assist the better understanding of KSHV transmission route.

MATERIALS AND METHODS

Search strategy

We conducted a comprehensive search of literature in Medline (PubMed), EMBASE, Web of Science, the Chinese Biomedical Literature Database (CBM), the China National Knowledge Infrastructure Database (CNKI) and Wanfang Database. The search strategy was listed in Supplementary Table S1. The references of reviews were also examined to search for additional eligible studies.

Inclusion and exclusion criteria

Studies were eligible if they fulfilled the following criteria: 1) reporting data on prevalence of KSHV infection (a positive result for antigens or virus DNA) among IDUs (drug users who ever had an injecting history) from any region in the world; 2) testing KSHV antibodies or DNA for virus detection; 3) cohort studies, case-control studies, cross-sectional surveys, or randomized controlled trials documenting the prevalence of KSHV infection with a minimum sample size of 50 participants in total. We excluded publications that were: 1) of which study population covered by other articles from the same research group; 2) non-original studies (including commentaries, reviews, meta-analyses, correspondence, editorials); 3) lacking of sufficient information.

The titles retrieved from this research were reviewed independently by two researchers (QWF and ZQL). The third researcher was involved in the decision-making in case of any disagreement. At least three authors (including first author) further reviewed the abstracts and full texts of the included papers before making a final decision on which studies to be included in this meta-analysis. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement was followed as a guideline for conducting this systematic review and meta-analysis.

Data extraction

The following information was extracted from each study: first author, year of publication, study location (country, continent), testing method of KSHV, age range and gender distribution of the participants, number of KSHV-positive cases and sample size of the IDUs (total and stratified by HIV-infected status). If any data essential to the analysis were not available for a study, best efforts were made to contact the authors to obtain the missing data. Two researchers extracted the information independently. Inconsistencies were resolved by examining the original paper and discussing the discrepancy until a consensus was reached.

Statistical analysis

The number of KSHV infected cases and all participants in each study were combined to obtain a pooled proportion and 95% confidence interval (CI). Subgroup analysis was conducted to aggregate the prevalence among IDUs with different HIV-infection status and from different continents. The overall prevalence was presented via forest plots. Considering the variance stabilization, 0.5 was added to event number and sample size of studies with an event probability of either 0 or 1 and log-transformation of the original prevalence was implemented to calculate an overall prevalence according to the Shapiro-Wilk normality test (Luo et al., 2013). Heterogeneity across the included studies was tested using the Q-test, and the results were considered statistically significant when $P < 0.1$. I^2 metric was also used to quantify heterogeneity. When the effects were assumed to be homogeneous ($P > 0.1$, $I^2 < 25\%$), the fixed-effects model was used; otherwise, the random-effects model was applied. Between-study heterogeneity, if existed, was further explored using meta-regression analysis, in which we evaluated the effect of variables included in the data extraction form. Dummy variables were created for the categorical variables. Publication bias was examined with funnels plots, which showed a scatter plot of studies included in the meta-analysis. An asymmetrical appearance

of dots in the funnel plots can be regarded as a proof of publication bias. Egger weighted regression methods (Egger's test) were used to statistically assess publication bias. All analyses were performed using R package *Meta* (Version 4.8-2) and *Metafor* (version 2.0-0). A two tailed $P < 0.05$ was considered statistically significant, unless otherwise specified.

RESULTS

Studies included in the meta-analysis

A total of 193 abstracts were retrieved after duplicates were removed. Through preliminary screening of their titles and abstracts, we excluded 149 studies due to irrelevance and undesirable study design. After further full-text reading, additional 22 studies were excluded. A full PRISMA record management flow chart was presented in Figure 1. Finally, twenty-two studies were eligible for this meta-analysis according to the inclusion and exclusion criteria. A total of 7881 IDUs, involving 3611 HIV-uninfected and 2504 HIV-infected individuals, were included (Table 1). Variables, such as age and gender, were not shown in Table 1 or subsequently analyzed in the meta-regression due to the scarcity of original data.

Prevalence estimates

The pooled prevalence of KSHV among IDUs was 14.71% (95% CI 11.12%– 19.46%), varied from 3.17% to 58.88% across included studies. Random-effects model was applied because of the significant between-study heterogeneity ($I^2 = 96\%$; $P < 0.01$) (Figure 2). In those free of HIV, the pooled KSHV prevalence was 10.86% (95% CI, 6.95%–16.96%; $I^2 = 94\%$; $P < 0.01$), varied from1.14% to 44.62% (Supplementary Figure S1A), while in those infected HIV, the pooled KSHV prevalence was 13.56% (95% CI, 10.57%–17.38%; $I^2 = 83\%$; $P < 0.01$), varied from 6.63% to 23.61% (Supplementary Figure S1B).

To explore geographical diversity of KSHV distribution, the variability across different regions was assessed as well (Figure 3). Overall, the pooled KSHV prevalence among IDUs in the three continents involved in the present meta-analysis was 16.10% (95%CI 7.73%–33.54%) in Asia, 14.22% (95%CI 8.96%–22.57%) in Europe, 18.24% (95%CI 11.63%–28.61%) in the Mediterranean part and 14.06% (95%CI 11.38%–17.37%) in America, respectively. There is no significant difference in the KSHV prevalence amongst these geographical regions.

Publication bias and meta-regression analysis

No publication bias was detected in terms of Egger's test ($t = -1.37$, $P = 0.18$), and the shape of the funnel plots did not reveal any evidence of asymmetry (Figure 4).

The variables including publication year, study regions and testing assays were fitted in the multivariate model of meta-regression. None of the three variables proved to be statistically significant (Table 2).

DISCUSSION

In the present meta-analysis, we found a moderately higher KSHV prevalence (14.71%, 95% CI, 11.12%–19.46%) among IDUs in contrast to the general population (Moore, 2000) and no significant difference was detected among

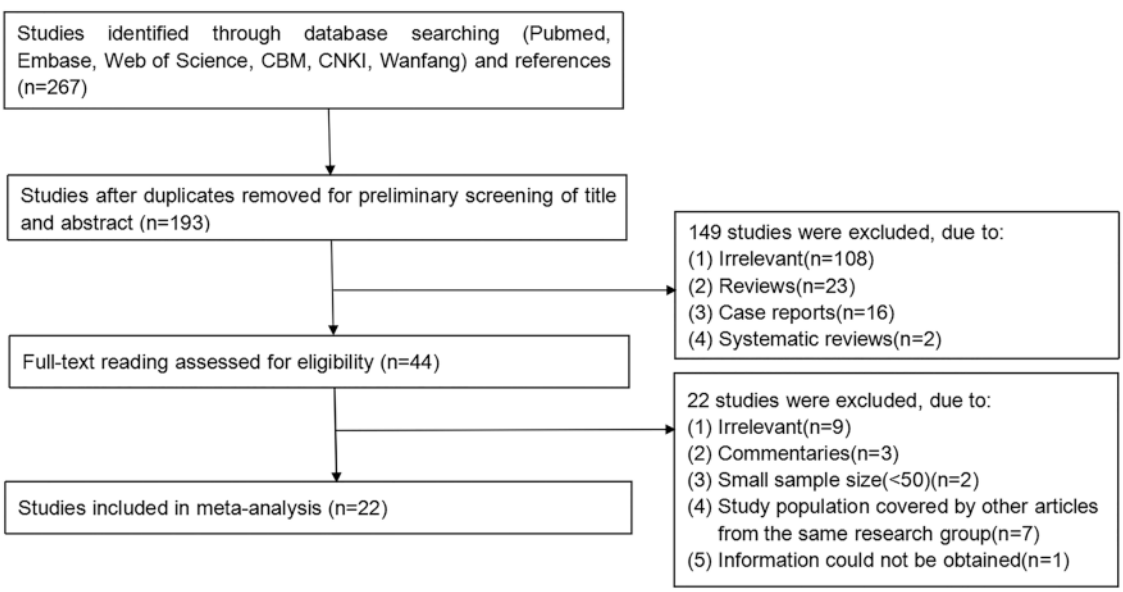

Figure 1. Flow chart of the study selection process and specific reasons for exclusion from meta-analysis.

Table 1. The detailed characteristics of all eligible studies

Authors	Year	Continent (Country)	Testing Method	KSHV positivity (No. of positive sera/No. of tested sera)		
				Total	HIV-positive	HIV-negative
Khajedaluee *et al*.	2016	Asia (Iran)	ELISA	8/111	–	–
Kakavand-Ghalehnoei *et al*.	2016	Asia (Iran)	PCR	8/60	–	–
Lee *et al*.	2014	Asia (China)	ELISA	27/553	25/377	2/176
Zhang *et al*.	2014	Asia (China)	IFA	56/296	–	–
Zavitsanou *et al*.	2010	Europe (Greece)	ELISA	70/288	–	67/286
Yang *et al*.	2010	Asia (China)	ELISA	58/203	–	–
Larocca *et al*.	2005	Europe (Italy)	IFA	14/134	8/32	6/102
Bernstein *et al*.	2003	America (US)	IFA	45/390	38/294	7/96
Atkinson *et al*.	2003	America (US)	ELISA	218/1905	55/233	163/1672
Goedert *et al*.	2003	America (US)	ELISA	14/137	14/137	–
Parisi *et al*.	2002	Europe (Italy)	IFA	13/155	13/155	–
	2002	Europe (Italy)	IFA	18/85	18/85	–
Sosa *et al*.	2001	America (Argentina)	IFA	26/153	25/144	1/9
Greenblatt *et al*.	2001	America (US)	IFA	40/237	35/178	5/59
Gambus *et al*.	2001	Europe (Spain)	IFA	44/382	29/254	15/128
Cannon *et al*.	2001	America (US)	ELISA	141/771	–	–
Diamond *et al*.	2001	America (US)	IFA	9/65	–	–
Perna *et al*.	2000	Europe (Italy)	IFA	62/374	32/163	30/211
Wang *et al*.	2000	Asia (China)	ELISA	63/107	–	–
Rezza *et al*.	1999	Europe (Italy)	IFA	20/133	20/133	–
Renwick *et al*.	1998	Europe (The Netherlands)	ELISA	89/1167	26/351	63/816
Rezza *et al*.	1998	Europe (Italy)	IFA	55/112	26/47	29/65
Simpson *et al*.	1996	Europe (UK)	ELISA	2/63	2/38	0/25

subgroups, thereby highlighting the vulnerability of KSHV infection in IDUs regardless of the HIV status and geographical region.

A previous systematic review reported that the KSHV seroprevalence was 47% in HIV-positive population and 24% in HIV-negative population which suggested an increased risk of KSHV seropositivity was associated with HIV-infection (Rohner et al., 2016). In the current study, higher KSHV prevalence was found in HIV positive IDUs than those free of HIV, albeit the difference was not statistically significant. This result might partly be explained by the between-study heterogeneity and also to some extent imply the absolute risk of intravenous drug use for KSHV infection. However, IDUs seem to have a lower KSHV prevalence when compared with MSM (Liu et al., 2017a). According to our pre-published results, KSHV prevalence was approximately double fold in MSM than that in IDUs. This discrepancy might suggest KSHV is much more likely to be transmitted via sexual behaviors while not blood, though controversy remains (Kedes et al., 1996; Vitale et al., 2000; Minhas and Wood, 2014). Since it is difficult to synthesize information on behavior-associated risk factors quantitatively due to the lack of data, the current meta-analysis could not resolve the perplexity precisely. Further studies focusing on more restricted target population, for example, blood donors, transfusion recipients or children without high-risk sexual practice, are warranted.

Moreover, no significant disparity of KSHV prevalence was detected across geographical regions included in this analysis, while according to previous studies, the KSHV infection were deemed to be low in Asia, Europe

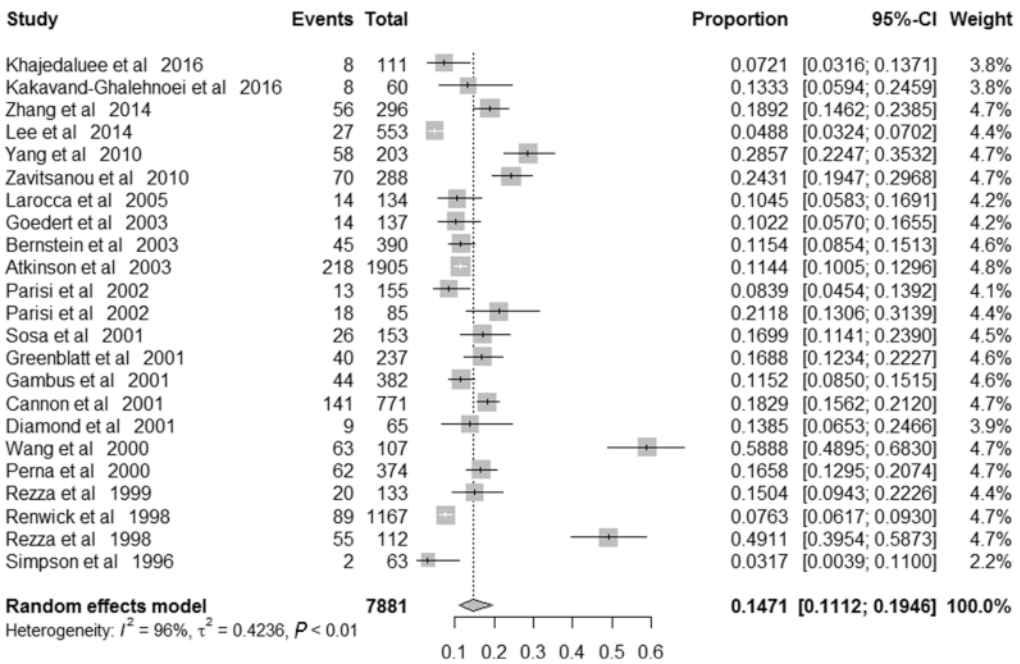

Figure 2. Pooled prevalence of KSHV infection among intravenous drug users.

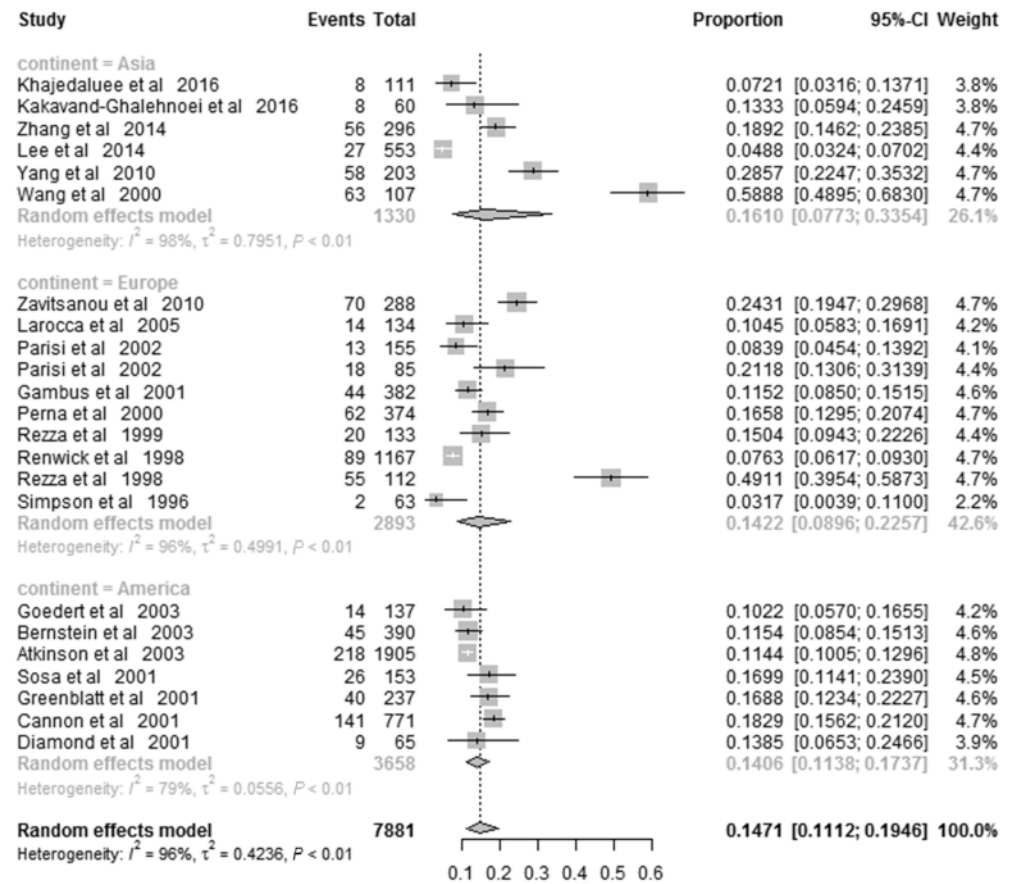

Figure 3. Subgroup analysis of the pooled prevalence of KSHV infection according to study location.

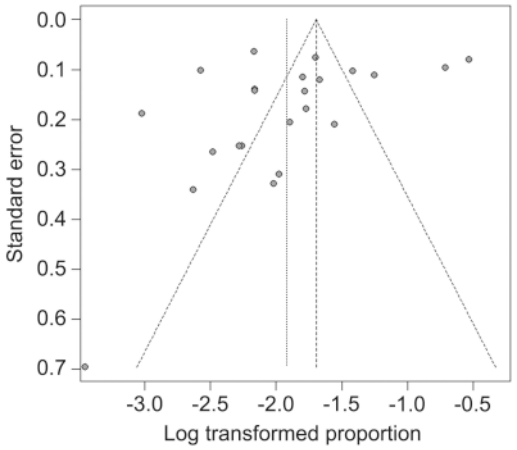

Figure 4. Funnel plot of the KSHV prevalence in the overall population

except Mediterranean regions, and America (Tornesello et al., 2010; Stiller et al., 2014; Zhang and Wang, 2017). An elevated KSHV prevalence was observed within IDUs compared with general population. In the current study, seven studies were from either Italy or Greece, where were endemic of KSHV(Schwartz, 2004). Nevertheless, the KSHV prevalence in Europe was not significantly higher than that in other regions among IDUs. This result may partly ascribe to the between-study heterogeneity, as regional differences have been documented by Whitby *et al.* in Italy: a low prevalence was reported for the northern part, whereas a prevalence of 35% was detected in Sicily (Whitby et al., 1998). Moreover, since no publication bias was detected in our study, the shrunken gap of KSHV infection among IDUs from different geographical regions compared with general population may also serve as a reminder of the role intravenous drug abuse played in the transmission of KSHV.

Unfortunately, limited information on the KSHV seroprevalence among IDUs in Africa is available, though comprehensive literature research has been performed. Generally, in Africa, particularly the sub-Saharan part, both HIV and KSHV are endemic (Butler et al., 2009). Therefore, it is not hard to expect an appallingly high KSHV seroprevalence among IDUs, because injection drug use is increasingly contributing to the HIV epidemic across sub-Saharan Africa (Syvertsen et al., 2015). This fact of missing information on the KSHV prevalence among IDUs in Africa highlights the unmet study for KSHV in Africa and calls for wider range of KSHV investigations.

Some limitations of this study should be mentioned. First, significantly higher between-study heterogeneity was noted. A meta-regression was conducted to identify the potential sources, but no significant variable was detected. Second, data from Africa, South America and Australia were not available, thereby undermining the accuracy and representativeness of overall KSHV prevalence. Finally, some variables such as age and sex have not been evaluated in our study due to the dearth of data. Therefore, the pooled results should be interpreted with caution.

In conclusion, the prevalence of KSHV among IDUs was higher compared to general population, regardless of geographical location and HIV-infected status. To our best knowledge, this is the first systematic analysis on the epidemiologic characteristics of KSHV infection among IDUs. It can be used as an important supplement to the existing KSHV data, elucidate the gaps in the epidemiologic characteristics of this virus, as well as provide evidence for changing KSHV prevention practice in the marginalized population. Given the paucity and some limitations of the available studies, more well-designed researches should be performed in the future to depict

Table 2. Meta-regression analysis showing influence of variables on the heterogeneity of prevalence (N = 7881)

	Standard error	Z value	*P* value	Regression coefficient (95%CI)
Constant	73.62	1.55	0.12	113.88 (–30.40, 258.17)
Year	0.04	–1.58	0.12	–0.06 (–0.13, 0.01)
Continent				
America (reference)	–	–	–	–
Asia	0.51	1.57	0.12	0.79 (–0.20, 1.79)
Europe	0.33	–0.12	0.91	–0.04 (–0.68, 0.60)
Testing method				
ELISA (reference)	–	–	–	–
IFA	0.31	0.82	0.41	0.25 (–0.35, 0.86)
PCR	0.79	0.16	0.88	0.12 (–1.43, 1.67)

the epidemiology of KSHV and to enrich the present findings, especially in Africa.

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COMPLIANCE WITH ETHICS GUIDELINES

The author declares no conflict of interest. This article does not contain any studies with human or animal subjects performed by the author.

AUTHOR CONTRIBUTIONS

QWF, ZQL and TJZ designed the experiments. QWF, ZQL and YZ searched literature, collected and summed up the data. QWF, YZ and ZJZ analyzed the data. QWF, ZQL wrote the paper. All authors read and approved the final manuscript.

Supplementary figures/tables are available on the websites of *Virologica Sinica*: www.virosin.org; link.springer.com/journal/12250.

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