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LETTER

Seroprevalence of Dengue Virus among Young Adults in Beijing, China, 2019

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Dear editor,

Dengue is one of the major mosquito-borne diseases and prevalent across tropical and subtropical regions (Carod-Artal *et al.* 2013; Ferguson 2018). Infection with four serotypes of dengue virus (DENV1–4) individually or multiply may cause severe clinical manifestations and complications. In the mainland of China, dengue had been usually characterized as an imported epidemic disease in the past. The first confirmed outbreak of dengue caused by DENV4 occurred in 1978 in Guangdong, a province in south China (Sang *et al.* 2016). Since then, dengue occurred predominantly in south China, and expanded gradually to east and southwest China (Wu *et al.* 2010). Currently, each serotype of DENV circulates and distributes throughout China (Wu *et al.* 2010; Lai *et al.* 2015). Moreover, the retrospective researches suggested that the regions reporting indigenous dengue cases had incessantly traversed its geographic limits from southeast coastal provinces to central or western provinces within China (Sang *et al.* 2016), due to the change of vectorial capacity of mosquitoes and global climate (Misslin *et al.* 2016). Thus, the increasing prevalence of dengue has posed a serious threat to public health in China.

Currently, epidemiologic researches in China mainly focus on imported dengue cases and genetic analysis of the isolated DENV strains, whereas the investigation of seroprevalence of anti-DENV antibody among populations in some non-endemic regions, such as Beijing, is limited. Generally, DENV seroprevalence is more reliable for prediction of transmission and outbreak than analysis of imported and indigenous cases alone. Since the vast majority (~ 80%) of DENV infections result in no perceptible symptoms (Yacoub and Wills 2014), actual DENV infection and transmission might be underestimated if an analysis was performed only in those virologically verified patients. Thus, asymptomatically imported individuals could well evolve into an indigenous transmission when a compatible vector exists in certain areas of China. Therefore, active surveillance for DENV seroprevalence at entry-exit ports and certain local regions, in the non-endemic areas, is helpful to timely identify epidemic dengue and to prevent local DENV transmission.

Beijing, the capital of China, is still characterized to be a non-endemic city but imported dengue cases were reported annually since the first case was described in 2001 (Lai *et al.* 2015). 4.4% of all imported dengue cases of China were happened in Beijing (Lai *et al.* 2015). Increased outbound travel and huge population movements may have contributed to the explosion of imported dengue cases. Besides, *Aedes* (*A.*) *albopictus*, one of two main vector mosquitoes of DENV transmission, is existing in Beijing. The above-mentioned factors highlight the potential risk for a dengue outbreak in Beijing. As aforementioned,

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seroprevalence of anti-DENV antibody has been proposed as a useful marker of endemicity. Moreover, there are currently no related studies because of the lack of indigenous dengue outbreak in Beijing. Thus, to provide the baseline data on DENV seroprevalence among young adults in Beijing, a cross-sectional study was performed at Capital Medical University.

In the present study, a total of 961 healthy students, lived in Beijing, were recruited and their serum specimens were collected in 2019. Socio-demographics of individuals, including gender, birth year and travel history, were recorded and analyzed anonymously (Supplementary Table 1). Of 961 enrolled subjects, 344 were male and 617 were female, with male to female ratio of 1:1.79. The age (years of birth) of subjects were grouped into the two categories, 21-year-old (1998) with 236 individuals (24.6%) and 20-year-old (1999) with 725 individuals (75.4%).

First of all, we verified the seroprevalence of anti-DENV antibodies by ELISA (The details of the experiment were shown in Supplementary Materials and Methods). Overall, 1.5% (14/961) of serum samples were seropositive for anti-DENV IgG. Similarly, there were 1.2% (4/344) and 1.6% (10/617) of anti-DENV IgG seropositivity for male and female subjects, respectively, and they were not significantly different with each other ($P = 0.570$). In addition, there was no association between seroprevalence of anti-DENV IgG and years of birth ($P = 0.784$, Supplementary Table 1). Theoretically, individuals with anti-DENV IgG had experienced at least one DENV infection since there is currently no dengue vaccine available in China. As expected, all 14 IgG seropositive individuals had ever traveled to southern China (SC, including Guangdong, Yunnan, Guangxi or Fujian) or Southeast Asia (SEA), implying a history of DENV exposure (data not shown).

Then, we further detected serotype-specific neutralizing antibody (nAb) titers by $PRNT_{50}$ (The details of the experiment were shown in Supplementary Materials and Methods). Of the 14 anti-DENV IgG seropositive subjects, 92.9% (13/14) had at least one detectable serotype-specific nAb. Anti-DENV1, -DENV2, -DENV3, and -DENV4 nAb seropositivity was found in 50.0% (7/14), 35.7% (5/14), 57.1% (8/14), and 7.1% (1/14) of them, respectively (Fig. 1A, Table 1). As a matter of fact, four closely-related DENV serotypes had been isolated from both large-scale and sporadic dengue outbreaks in China (Qiu *et al.* 1993; Lai *et al.* 2015), and the possibility of DENV1–4 prevalence in China shows no significant difference. Moreover, most nAb titers against any serotype of DENV were just 1:20, implying the previous infection had likely occurred quite a while ago. Only two subjects (No. 3072 and No. 3107) had titers of 1:40 and 1:160 against DENV1, respectively (Table 1).

Additionally, 42.9% (6/14), 42.9% (6/14) and 7.1% (1/14) of serum samples were nAb positive for one, two or three serotypes, respectively (Fig. 1B). Half of the seropositive subjects were detected neutralized for at least two serotypes, suggesting that the detectable cross-neutralization may exist between serotypes, or they had probably experienced infections with multiple DENV serotypes. Interestingly, nAb was not detected in one anti-DENV IgG seropositive sample, suggesting a better specificity of $PRNT_{50}$ than ELISA.

Taken together, the overall low seroprevalence displayed in our study presented an average weak force of infection in Beijing, and seropositive individuals probably resulted from travel in endemic regions. Moreover, the low DENV seroprevalence among adults reveals that there are adequate preconditions for DENV reservations and potential indigenous transmission in Beijing. First, according to the data released from Beijing Center for Disease Control and Prevention, *Culex*, the vector of Japanese encephalitis virus, is still a predominant vector species in Beijing, but meanwhile, the proportion of *A. albopictus*, in Beijing has increased from 7% in 2013 to 14% in 2017, implying the increased risk of dengue transmission. Second, imported cases have been reported annually in Beijing since 2001 (Lai *et al.* 2015), and epidemiological data indicate that the average probability of dengue importation from SEA into Beijing increased from 0.38 in 2005 to 0.77 in 2015 (Lai *et al.* 2018). Third, asymptomatic dengue accounted for the most proportion of dengue, and the subclinical individuals can be the main source of infection (Duong *et al.* 2015; Ten Bosch *et al.* 2018). Fourth, the susceptibility in the Beijing population is relatively high because the vast majority of people lack pre-existing immunity against DENV. Therefore, constant surveillance of imported and indigenous dengue cases and serosurvey is necessary in Beijing due to the continuous spread of dengue.

In addition, in this study, owing to the lack of age-stratification during sampling, we only focus on young adults. For a comprehensive serosurvey, further investigation needs to expand as follows in the future, (1) for disease alarm and tracking, the asymptomatic carriers from DENV-endemic areas should be closely monitored through detection of DENV specific IgM as well as IgG, especially when coinciding with the high season of outbound travel or the grand international events that is hosted in Beijing; (2) mosquitoes that can carry DENV need to be controlled during the monsoon season or summer; (3) our results cannot be representative of a broader setting since the present study was limited to young adults in Beijing, thus systematic serological surveillance for DENV with an enlarged sample size and with age-stratification must be conducted at multiple study sites to provide more comprehensive and reliable data for future prevention.

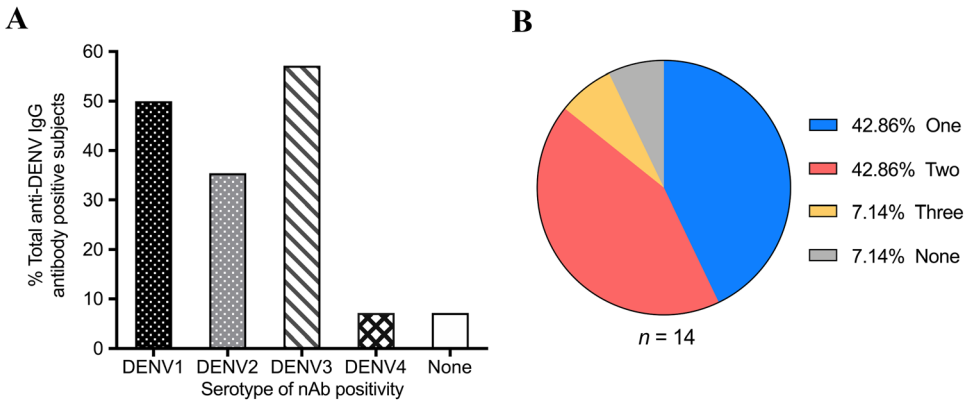

Fig. 1 Identification for serotype specificity in anti-DENV nAb seropositive participants (n = 14). **A** Bar chart displayed the percentages of each serotype in anti-DENV nAb seropositivity, the serum samples were from participants with anti-DENV IgG seropositivity. Anti-DENV nAb seropositivity was defined as having a $PRNT_{50}$ titer $\geq$ 1:10. **B** Pie chart represented summarized results of the number of positive serotypes in anti-DENV IgG positive subjects.

Table 1 Seroprevalence of anti-DENV nAb among all anti-DENV IgG antibody positive participants (n = 14).

Participant no.	Age (year of birth)	Gender	Seroprevalence of anti-DENV nAb				Positive serotype of DENV
			Titers of anti-DENV nAb				
			DENV1	DENV2	DENV3	DENV4	
3052	20 (1999)	Female	< 1:10	< 1:10	1:20	< 1:10	DENV3
3072	20 (1999)	Female	1:40	< 1:10	< 1:10	< 1:10	DENV1
3099	20 (1999)	Male	< 1:10	1:20	< 1:10	< 1:10	DENV2
3103	20 (1999)	Female	1:20	< 1:10	< 1:10	< 1:10	DENV1
3107	20 (1999)	Female	1:160	< 1:10	1:10	< 1:10	DENV1, DENV3
3150	20 (1999)	Male	< 1:10	1:10	1:20	< 1:10	DENV2, DENV3
3461	20 (1999)	Female	< 1:10	< 1:10	< 1:10	< 1:10	None
3482	20 (1999)	Female	1:10	1:20	< 1:10	< 1:10	DENV1, DENV2
3505	20 (1999)	Female	< 1:10	< 1:10	1:20	< 1:10	DENV3
3591	20 (1999)	Male	< 1:10	1:20	1:20	< 1:10	DENV2, DENV3
3616	21 (1998)	Male	< 1:10	1:20	1:20	< 1:10	DENV2, DENV3
3631	20 (1999)	Female	1:20	< 1:10	1:10	< 1:10	DENV1, DENV3
4404	20 (1999)	Female	1:20	1:10	< 1:10	1:10	DENV1, DENV2, DENV4
4468	21 (1998)	Female	1:20	< 1:10	< 1:10	< 1:10	DENV1

In summary, more active monitoring of the DENV seroprevalence is necessary to evaluate the risk of dengue outbreak in Beijing, due to a sizeable proportion of asymptotic cases. The present cross-sectional study provides the first baseline data on DENV seroprevalence among young adults in Beijing. This will benefit to put the transmission dynamics of DENV into perspective, so as to stop or postpone the potential indigenous outbreak in Beijing.

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Authors contribution RW designed and performed the experiments, analyzed the data and wrote the manuscript; DY collected serum samples, demographic information from the study population and informed consent; LW and YL helped with the experiments; HZ designed the research; NG analyzed the data and revised the manuscript; JA principally designed the experiments and directed the project. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and Human Rights Statement This work was approved by the Ethical Committee of Capital Medical University. This study adhered to the tenets of the Declaration of Helsinki. The purpose and procedures used in the study were explained to all participants, and written consent was obtained from all participants before the conduct of the study.

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