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The Impact of Emerging Infectious Diseases on Chinese Blood Safety☆

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ABSTRACT

Emerging infectious diseases (EIDs) have always been one of the major threats to public health. Although the implementation of mandatory testing for 4 classical transfusion-transmitted infectious—human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis—has reduced the transfusion risk of these pathogens, the potential threat of various EID agents and their constantly evolving variants to blood safety in China is not fully understood. This review presents 9 representative EID agents that are autochthonous and epidemic nationally or regionally in China. The epidemiologic status and distribution of these EID agents among donors and/or healthy populations are summarized. The potential risks of these EID agents to blood safety are discussed. The review also explores strategies to strengthen hemovigilance systems and studies to further evaluate the impact of EID agents on blood safety.

Contents

Emerging infectious diseases (EID) agents are considered as major threats to transfusion safety. The most notorious EID agent that sabotaged blood safety during 1980s was human immunodeficiency virus (HIV). It raised global concerns of EIDs and triggered organized activity to systematically prevent EID agents from threatening transfusion safety. Nowadays, blood donations are screened for various infectious agents in developed countries or regions where EID agents have been well studied. In the United States, the blood supply is routinely screened for Human T-lymphocyte virus (HTLV). West Nile virus (WNV); *Trypanosoma cruzi* [1-3] and *Babesia spp.* [4-7] have been systematically scrutinized to evaluate the value of donor screening [8]; and Zika virus has recently emerged as an EID threat [9]. In China, however, many of the EID agents are rarely investigated among blood donor and evidence for their impact on blood safety is absent. In 2009, the American Association of Blood Banks published a catalog of pathogens relevant to blood

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safety in which 68 EID agents were listed as confirmed or suspected to be associated with transfusion transmissible infection (TTI) [10]. The threat of these EID agents to blood safety varies, due to different spreading patterns, transmission routes, epidemiologic characteristics, and endemic status; therefore, they need to be specifically evaluated in each country or area.

In China, blood donors are routinely tested for only 4 pathogens: HIV-1/2, hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis [11]. With the broad implementation of nucleic acid testing (NAT), the improvement in performance of enzyme immunoassay assays, and the more rigorous policies for donor recruitment and testing, the transfusion risks of the conventional TTIs have been largely reduced in China [11,12]. However, many of the diversely distributed EID agents still pose potential threats to blood safety, yet their risks have never been fully evaluated. Nevertheless, China has witnessed recurrent outbreaks of highly virulent EIDs including severe acute respiratory syndrome (SARS), highly pathogenic avian influenza (H5N1) and *Streptococcus suis*, a zoonotic bacterium mostly carried by pigs or pork products which causes syndromes of streptococcal toxic shock, sepsis and meningitis. [13]. For example, outbreaks of human *Streptococcus suis* infection in China were reported in Sichuan province, resulting in 66 laboratory confirmed cases and 39 deaths from mid-July to the end of August 2005 [14]. Some EID agents with asymptomatic distribution among Chinese general population, such as malaria, hepatitis E virus, and dengue virus may emerge as greater threats to Chinese blood safety and require interventions. In this review, we highlight 9 representative, autochthonous EIDs agents that are nationwide or regionally epidemic. The epidemiology of these EID agents and the investigations among blood donors and/or the general population are reviewed. The geographic distribution for EID agents that are regionally epidemic is summarized, and the prevalence of these EID agents among Chinese donors is summarized.

Nationwide Distribution of EID Agents

Human Parvovirus B19

Human parvovirus B19 (B19V) is a small, non-enveloped, single-strand DNA virus [15], causing various clinical manifestations such as chronic anemia, aplastic crises and arthropathies, and a variety of other syndromes among immune-compromised or immunosuppressed patients [16-19]. B19V has been confirmed to be one of the TTIs transmitted through blood or blood products [20]. The US Food and Drug Administration (FDA) and European Pharmacopeia have proposed a limit of 1×10^4 gEq/mL for pooled-plasma in order to reduce the potential risk of transmission [21,22].

There is limited data on B19V prevalence among blood donors or the general population in China. According to several reports, the estimated prevalence rate could be as high as 3.5% in the general Chinese population [23] and 4.5% in HIV co-infected individuals [24]. In the Tibetan area, the B19V DNA positivity rate was 4.8% among the general population [23]. Among Chinese blood donors, the B19V DNA prevalence rate was 0.58%, which is much lower than that in the general population [25]. The same study also reported that different geographic locations demonstrated different prevalence rates for B19V, and that the DNA sequences in Xinjiang Province showed a different genetic lineage than in other places of China [25]. In another study, B19V DNA was detected in 54.2% (77/142) of plasma pools from 2 Chinese blood product manufacturers of intravenous immunoglobulin (IVIG), factor VIII, fibrinogen and prothrombin complex concentrates, with levels of B19V-DNA varying from 1×10^2gEq/mL to 1×10^7 gEq/mL [26]. The viral load in one donation sample was 1.09×10^{10}gEq/mL, which was significantly higher than the threshold recommended by the US FDA and European Pharmacopeia (1×10^4 gEq/mL). While further investigation is necessary to determine whether B19V NAT screening should be implemented as a routine in Chinese blood centers, the current B19V contamination in plasma products is a serious concern.

Malaria

Malaria is caused by infection with the parasites of *Plasmodia spp.* and the current distribution covers the tropics and large parts of the subtropics [27]. Infection with *Plasmodia spp.* often resembles a common viral infection which may lead to a delay in diagnosis [28]. Malaria is considered a transfusion risk since asymptomatic immigrants who reside in and travelers who visit endemic areas might import malaria to non-endemic areas [10]. Therefore, US FDA has initiated a donor deferral policy that temporarily defers donors who travel to endemic areas. As a result, about 1% of US donors are deferred for that reason [29].

Malaria was once highly endemic in China with an estimated 30 million cases per year [30]. The Chinese government began a tremendous effort to eliminate malaria in 1955 when the National Malaria Control Program was launched [31]. The main species that causes malaria in China is *P vivax* and has been found in many regions; however, other species of *Plasmodia* have also been reported [32]. Although malaria has been well controlled in the last 2 decades, sporadic outbreaks are frequently reported [31], and malaria remains a reportable infectious disease in China [13]. Several cases of malaria transmission by transfusion were recently reported (Table 1) [33-49]. Meanwhile, the DNA of *P knowlesi* was also found in pooled plasma from a manufacturer in Guizhou [50]. However, currently Chinese blood centers do not have a policy to defer donors who have traveled to malaria endemic areas or malaria infected countries during epidemic seasons. The actual prevalence of malaria and its residual risks among voluntary blood donors is unknown. Further studies on malaria infected blood donors in China, such as a survey on the risks of infection and demographic characteristics of *Plasmodium* infected donors, are crucial to better understand the transfusion risks of malaria in China.

Hepatitis E Virus

Hepatitis E virus (HEV) is an enterically transmitted, positive-sense, single-stranded non-enveloped RNA icosahedral virus [51]. It usually causes an acute and self-limiting infection. HEV has a worldwide distribution and substantial morbidity and mortality in some developing countries [52]. Many cases of HEV transmission by blood transfusion have been documented all over the world [53-59]. Routine screening of donors for HEV RNA was suggested by some studies [60].

In China, the anti-HEV seroprevalence is about 40% in the general population and increases with age by 1% per year [61]. Approximately 2.7% of individuals are IgM positive (indicating acute infection) and 0.3% are asymptomatic with viremia [62]. In the early 1990s, due to the frequent occurrence of illegal blood donation in central China, the anti-HEV IgG prevalence spiked to 22.7% and anti-HEV IgM prevalence was 1.8% among illegal blood donors [63]. In a recent study using test results from routine donations collected at 6 urban blood centers, investigators reported a prevalence of 32.6% for anti-HEV IgG, 0.94% for anti-HEV IgM, and 0.07% for HEV RNA among 44 816 donations. In addition, they found that prevalence rates varied by blood center locations [64]. In a comparative study [63], where samples from both qualified blood donors and donors deferred due to elevation of alanine aminotransferase (ALT) were examined, the prevalence rates of anti-HEV IgM and anti-HEV IgG in ALT-elevated donors (2.76% and 40.02%, respectively) were significantly higher than those in qualified donors (1.02% and 27.42%, respectively). Meanwhile, the prevalence of HEV antigen among the ALT-elevated donors (0.25%) was also higher than that among qualified donors (0.06%), but not at a statistically significant level. These data suggest that routine pre-screening and post-donation ALT tests can reduce, but not eliminate the potential risks of HEV infection from otherwise qualified donations in China.

Table 1
Parts of the transfusion-transmitted malaria infections in China.

Malarial species	Location (province)	Number of cases	Reasons for transfusion	Outcomes	Ref
P vivax	Sichuan	1	Orthopedic surgery	Acute renal failure and death	[31]
P vivax	Sichuan	1	Orthopedic surgery, anemia	Chills and fever	[31]
P falciparum	Zhejiang	1	Brain trauma	Fever and headache and diarrhea	[32]
P vivax	Sichuan	2	Primary thrombocytopenic	Chills and fever	[33]
P sp.	Liaoning	1	Uterine bleeding	Fever	[34]
P sp.	Liaoning	1	Extrauterine pregnancy	Chills, fever and icteric sclera	[34]
P sp.	Liaoning	1	Splenectomy	Chills and fever	[34]
P sp.	Beijing	5	NA	Chills and fever	[35]
P sp.	Jilin	4	NA	Chills and fever	[38]
P malariae	Shanghai	1	Hip replacement	Fever	[42]
P vivax	Jiangsu	69	NA	Chills, fever and splenomegaly	[43]

EID Agents with Distributions Concentrated in Different Regions of China

Dengue Viruses (DENV)

DENV causes dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome. DENV is a life-threatening mosquito-borne disease with global spread [65]. DENV was shown to be capable of transmission by transfusion [66]. Transfusion of red blood cells which tested DENV seronegative but were RNA positive with high viral load ($>10^7$ copies/mL) can lead to DENV infections in transfusion recipients [67]. Several countries and regions with a high prevalence of DENV have investigated DENV among blood donors and recipients to evaluate its impact on blood safety, as well as to develop a proper donor enrollment strategy to reduce the transfusion-transmission risk [68-70].

In China, early outbreaks of DHF in 1980s were reported mostly in Guangdong, Guangxi, Yunnan, Hainan, Fujian, and Zhejiang provinces located in the southeast coastal regions or border areas next to Southeast Asia [71]. More than 80% of the documented DHF cases were from Guangdong province, one of the most developed provinces located in the South coastal area [72]. Since dengue fever first reemerged in Guangdong province in 1978 [73], the epidemic of DENV spread to 26 Chinese provinces by 2014 [74]. From 1990 to 2013, the epidemic status of DHF gradually changed from sporadic imported to autochthonous endemic cases [75]. In 2013, there was a large DHF outbreak from July to November in Foshan city, Guangdong province with 5173 suspected febrile cases [76]. Among them, 641 DENV infections were confirmed by laboratory testing (436 RNA positive and 205 IgM positive) [76]. The following year, the third historically largest DHF outbreak spread throughout Guangdong province (20 of 21 cities with reported cases) with 45 236 febrile cases (6024 DENV infections confirmed) resulting in 6 deaths [77]. Partly in response to the outbreaks in 2013 and 2014, the Chinese Center for Disease Control and Prevention (CDC) amended the guidelines for DHF prevention and control to strengthen the implementation of mosquito control [78]. In 2015, the DHF cases in Guangdong province dropped sharply to 739 cases by the end of September [79], reflecting the effectiveness of DENV control measures in this area. DENV sentinel monitoring by sero–surveillance has been in operation in DHF epidemic regions in China since 1990s. The DENV seroprevalence rate varied (IgG: 0.25%-14.49%; IgM: 0.56%-5.2%) in the DENV endemic areas in Guangdong [80,81], Guangxi [82], Yunnan [83,84], Hainan [85], and Fujian [86] provinces. A pilot study of DENV serology and viremia among asymptomatic donors in Guangzhou city (Guangdong province) in September and October 2014 found that the DENV IgM prevalence rate was 2.4% (n = 3000). The study also identified one DENV RNA positive donor with viral load of 944 copies/mL [87]. Another post-outbreak serological investigation among healthy populations in Foshan city (next to Guangzhou city) found significantly higher DENV seroprevalence rates in the 4 towns that experienced DHF outbreaks in 2013 (IgG rate: 2.7%, n = 817) compared with the 2 towns without autochthonous cases (IgG rate: 0.6%) [76]. A blood product with DENV RNA viremia can potentially lead to transfusion-transmitted infection. However, to date, there are no published studies on DENV transmission via transfusion in China.

Brucella

Human brucellosis caused by *Brucella spp*. is one of the most severe zoonotic diseases worldwide [88]. Transfusion-transmitted brucellosis cases have been reported since the 1950s [89-92], and *Brucella spp.* are considered a potential risk for blood safety [10]. Human brucellosis is one of the leading threats to public health in farming areas with livestock in China [93]. More than 90% of brucellosis cases in China were found in north China and were concentrated in Inner Mongolia, Shaanxi, Heilongjiang, Jilin, and Hebei provinces [94]. A total of 141 604 brucellosis cases were confirmed in these areas. In addition, a rapidly increasing trend was observed in brucellosis incidence, from 0.92 cases per 100 000 people in 2004 to 2.62 clinical cases per 100 000 people in 2010 [94,95]. An epidemiological investigation in Inner Mongolia reported the incidence rate as high as 12.94% among people who had close contact with livestock [96].

In China, most of *Brucella* surveillance has focused on risk factors for infections [97,98], prevalence in dairy cattle [99] and local animals [100,101] with the goal of providing information for brucellosis prevention and control. The DNA prevalence rate of *Brucella* in raw whole milk samples was found to be 1.07% in 15 provinces [102]. The low-risk population in urban areas is at increasing risk of Brucellosis from contaminated milk or raw meat [103]. Limited data showed the seroprevalence rate of *Brucella* among the healthy human population to be 9.82% in endemic areas [104]. Recently, a *Brucella spp.* investigation based on enzyme immunoassay testing among blood donors in an endemic area (Kashi, Xinjiang province) showed that the reactive rate was 1% (39/3896), in which 0.64% (25/3896) samples were further confirmed by western blot (WB) testing, and the *Brucella* DNA prevalence rate was 0.39% (15/3896) [105]. Although no infection cases transmitted by transfusion have been reported, the existence of *Brucella* DNA in donors' plasma samples indicates potential risk of transfusion-transmitted brucellosis in endemic areas and warrants future investigation.

Human T-cell lymphotropic virus

As the first retrovirus discovered in humans [106], HTLV is one of the important TTIs that may lead to various human diseases such as adult T-cell leukemia/lymphoma, myelopathy/tropical spastic paraparesis, opportunistic infections, and inflammatory disorders [107]. The implementation of mandatory testing on donors has been in effect since mid-1980s in many countries to reduce the risk of transfusion transmission.

In China, sero-surveillance of HTLV among the general population started in 1980s when an early study in Beijing and other 28 provinces found a 0.08% positive rate in 9303 samples—all connected to the endemic country Japan [108]. In 2005 and 2012, 2 nationwide investigations reported the prevalence of HTLV among blood donors to be 0.05% (n = 145 293) [109] and 0.03% (n = 122 468) [110] respectively. A meta-analysis of 40 studies among 458 525 donors in 21 provinces and regions found that the pooled estimates of HTLV-1 prevalence in Fujian and Guangdong were 9.9/10 000 (95% 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. Most isolates belonged to the transcontinental subgroup A whereas only 2 cases of HTLV-1 infection were found among 204 763 donors in other provinces and regions [111]. Data from these studies indicate that while HTLV prevalence is low in China, the infection has expanded from concentrated coastal regions in Fujian and Guangdong to the neighboring provinces where seroprevalence remains low (ranging from 0.02% in Shanghai and 0.12% in Jiangxi) [108,110]. Although no transfusion-transmitted HTLV infections have been reported, the surveillance of HTLV among blood donors and the evaluation of its impact on blood safety continue to be studied in China.

Severe Fever with Thrombocytopenia Syndrome Virus

Severe fever with thrombocytopenia syndrome virus (SFTSV), a novel tick-borne bunyavirus, was first identified in China to be the etiologic agent of severe fever with thrombocytopenia syndromes (SFTS) with initial fatality rates between 12% and 30% in 2009 [112]. SFTSV is concentrated in the mountainous rural areas in central and eastern China [112-114]. The epidemic seasons of SFTS are mainly from spring to autumn and peak in May to July [113]. Farmers are at high risk for SFTS due to more exposure to ticks [115]. The molecular characteristics, epidemiologic distribution, risk factors and clinical symptoms have been well summarized in several reviews [116,117]. By the end of 2013, SFTSV had spread from 6 provinces in 2009 [113] to 14 provinces with a growing incidence but a decreasing fatality rate [118]. The increasing epidemic of SFTS was reported and annual incidence was estimated to be 3 cases per 100 000 populations in autochthonous endemic area [118]. Meanwhile, increasing numbers of SFTS cases were reported in Japan [119-121] and South Korea [122,123]. Migratory birds are suspected to have played an important role in promoting the spread of SFTSV in East Asia [124].

Although there is no recorded transfusion-transmitted SFTS case at present, SFTSV has the potential to become a transfusion-transmitted infectious agent due to several considerations: (1) nosocomial transmissions caused by direct exposure to SFTS patients' blood have demonstrated that SFTSV is a blood-borne pathogen [125-128]. (2) The incubation period from infection to onset of the disease is one or 2 weeks on average [129], and in some cases up to thirty days [130]. Viremic asymptomatic blood donors within the incubation period may therefore potentially transmit SFTSV to recipients leading to SFTs. In a study launched by the National Heart, Lung, and Blood Institute, Johns Hopkins University, the Chinese Institute of Blood Transfusion, and 3 Chinese blood centers (one located in an endemic and 2 in non-endemic regions), antibody screening and follow-up SFTSV RNA detections were performed on 17 208 blood donor plasma samples collected between April and October 2012. The seroprevalence rates were 0.54% (80/14 752), 0.27% (3/1130) and 0.28% (3/1326) in an endemic area (Xinyang) and non-endemic regions (Mianyang and Luoyang) respectively, with no significant difference observed ($P > .1$). Among 9964 donors screened by 4-sample minipool SFTSV RNA testing, 2 suspected viremic samples were detected each with a viral load less than 20 plaque-forming units (PFU)/mL [131]. Other regional SFTSV among the healthy individuals reported seroprevalence rates varying between 0.44% and 7.2% [132-134] in epidemic areas, with finding asymptomatic viremic cases. Continued investigation is needed to evaluate whether SFTSV presents a risk to transfusion recipients in China.

Leishmania

Leishmania infection is responsible for cutaneous and visceral leishmaniasis (kala-azar). *Leishmania spp.* are usually transmitted to people through the Phlebotomine sandfly [135]. The infected individual may harbor a persistent infection up to 30 years before recovery [136]. The transmissibility of *Leishmania* infection via blood has been demonstrated in animals [137,138] as well as human beings [139-142]. *Leishmania* in human red blood cells (RBCs) can survive for as long as 15 days under blood bank storage conditions [143]. It has been reported to cause cutaneous or visceral leishmaniasis in infants and immunocompromised patients [139-142]. Asymptomatic infections are usually found in healthy blood donors from endemic areas [144-148]. US military blood banks enforce permanent deferral for individuals with any history of leishmaniasis, but there is no existing regulation or standard for *Leishmania* testing in civilian donor screening [10]. During the 1950s, there were more than 500 000 documented kala-azar cases in China, mainly in rural areas in the north [149]. With the efforts of a national control program, kala-azar was almost eliminated in 1960s [150]. Currently, more than 300 cases of kala-azar are reported each year, mainly from Xinjiang Province and other provinces in Western China [150]. Recently, a retrospective study of visceral leishmaniasis by the Chinese CDC reported an increase in the number of visceral leishmaniasis cases in endemic areas between 2005 and 2010 [149], indicating that prevention and control strategies must be taken to restrain the increasing incidence and spread of leishmaniasis. Otherwise, frequent population migration, tourism, and a rapidly growing public transportation may lead to further spread of the infection and push it up on the list of transfusion-transmitted infectious diseases in China. To date, there are still no survey studies of infection among donors and no documented transfusion-transmitted cases for *Leishmania* infection in China.

Q Fever

Q fever is a zoonosis due to *Coxiella burnetii* infection. *C burnetii* usually causes asymptomatic clinical manifestations such as a flu-like disease or atypical pneumonia in humans [151]; however, acute [152,153] and fatal chronic infections [154-157] have been reported. In 2007, there was a large outbreak of Q fever in the Netherlands [158]. Hogema et al initiated a surveillance of *C burnetii* DNA and antibodies in local blood donations and found that the *C burnetii* DNA positive rate was 0.3%, while the IgG seropositive rate was 12.2% [159]. Furthermore, 10 seroconversions were detected in donors with an incidence rate of 5.7% per year during the outbreaks from 2007 to 2009 [159]. After the great outbreaks of Q fever, Slot et al. started to investigate if chronically infected donors posed a threat to blood safety in the Netherlands. The serological results from 2490 serum samples collected in the most affected area during August 2012 to January 2013 showed that chronic *C burnetii* infection was absent in the epidemic blood donors, which led to the donor re-entry policy that had already been initiated elsewhere in Europe [160].

In China, most *C burnetii* infections have been observed in Tibet, Yunnan, Xinjiang and Inner Mongolia [161]. The *C burnetii* DNA positivity rate was about 10% in ticks and 7% in humans in Western China [162]. As Q fever is mainly an airborne disease, the individuals with exposure to livestock bear a higher risk. Some epidemiological studies show that more than 50% of rural farmers had antibodies to *C burnetii* [163,164]. Although blood donor screening of *C burnetii* has not been initiated in China, the DNA of *C burnetii* was found in pooled plasma from a manufacturer in Guizhou [50]. A cross-sectional study of the seroprevalence and viremia status of *C burnetii* among blood donors, especially in nomadic herding and livestock regions, would provide a more comprehensive assessment of its impact on blood safety in China.

Discussion

Due to its biological and geographic diversity, China will always be at high risk for various EID agents. As a populous country, a dramatic ramp-up in the number of blood donations was reported recently, with more than 21 million donations collected in 2012 at the donation index of 8.5 donations per 1000 people [165]. However, monitoring of the classical TTIs such as HIV, HBV, HCV and syphilis, as well as EID agents has only been implemented by the Chinese CDC and mostly based on sentinel investigations and clinical case report systems. The monitoring systems have demonstrated effectiveness in establishing proper guidelines for disease prevention and control based on epidemiological analysis of transmission routes and infection risk factors. The fatality rates and clinical symptoms from the documented cases are periodically summarized and analyzed to help with diagnosis and therapy of these pathogens, as well as with the development and improvement of laboratory diagnostic assays. Effort towards disease control has benefitted from the system in the face of several outbreaks of EID epidemics, such as: SARS [166], H5N1 [167], SFTSV [113], and DENV [76].

The regional spread of infection is an important aspect to consider when evaluating the transfusion risk for EID agents. Among the 9 EID agents listed above, all of them have been proven to result in pathological and autochthonous epidemics in China. B19V, HEV and *Plasmodium spp.* have nationwide distribution. Three insect-borne EID agents (DENV, SFTSV, and *Leishmania spp.*) and 2 zoonoses (*Brucella spp.* and *C burnetii*) display significant geographic diversity due to their patterns of transmission. HTLV is clustered in one coastal region. The regional distribution of 6 EID agents is shown in Fig. 1. Not surprisingly, the regional distribution of insect-borne pathogens matches that of disease vectors (mosquitos, sand-flies and ticks). DENV, a well-described mosquito-borne virus, has a global distribution in tropical and subtropical areas, the location of recent outbreaks of DHF. The infections of SFTSV, the novel tick-borne bunyavirus, were identified from SFTS patients in rural mountainous areas in central and eastern China, mainly because of the higher risk of tick exposure. In a similar way, most of the infections of zoonotic diseases (Q-fever and Brucellosis) were found in rural livestock farming areas in northern and western China. By compiling the distribution of reported clinical cases and the prevalence of EID agents in donors and/or general population, we provide estimates of the frequency of EID agents among Chinese blood donor populations. See Fig. 2. HEV and B19V are estimated to have national distribution among donors and general population in China based on previous cross-sectional studies. Spread of *Brucella spp.* depends on transmission routes from contaminated milk and raw meat produced from endemic regions. Considering the current DNA prevalence rate (0.39%) of *Brucella* spp. among blood donors in endemic regions and its potential high frequency in the general donor population, this EID is a matter for concern. In the shadows of recent global outbreaks and the fast expanding trends of DHF, DENV should also be highlighted for its potential risks in endemic areas in China. The other 3 regionally concentrated EID agents: Q-fever, *Leishmania spp.*, and SFTSV are estimated to have moderate or low frequency among the blood donor population. However, ongoing surveillance on these EID agents in donors is prudent in order to provide sound evidence regarding their impact on blood safety in China.

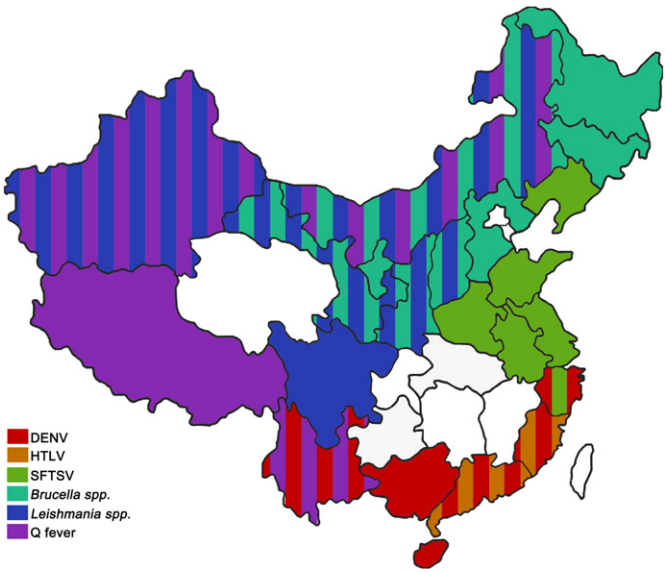

Fig. 1. The distribution of 6 major regional EID agents in China.

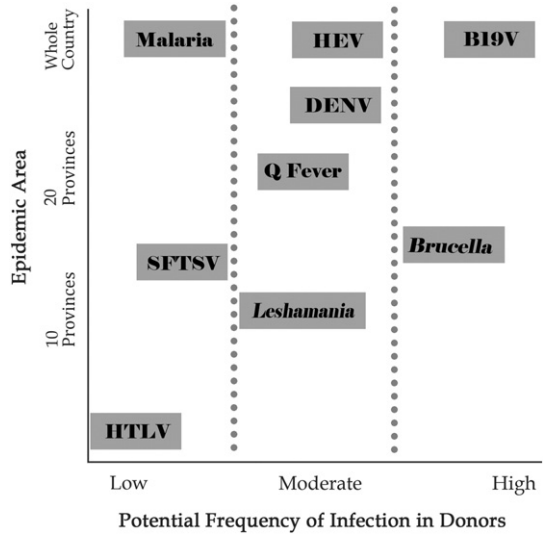

Fig. 2. The distribution and potential prevalence of EID agents in blood donors in China.

In order to evaluate the impact of EIDs on blood safety, a practical and feasible approach is to monitor the existence of EID agents among asymptomatic blood donors and obtain direct evidence from transfusion-transmitted cases confirmed by molecular analysis. Firstly, the surveillance among blood donors through sero-markers and nucleic acid of pathogens provides data for estimating transfusion risk. Among the 9 EIDs discussed in this review, only HTLV has been continuously investigated at blood centers since 1980s. There are a few investigations and case reports on B19V, HEV and *Plasmodium spp.* among blood donors, but no systematic and continuous investigation on these EIDs. Data on SFTSV, DENV and *Brucella spp.* in China are very limited with only one documented donor surveillance study available for each agent. *C burnetii* (Q fever) and *Leishmania spp.* have not been investigated. In addition, well-organized and appropriately designed donor-recipient linkage studies may directly confirm transmission by transfusion, facilitate further evaluation of the post-transfusion outcomes, and yield more convincing evidence to support strategies for screening donors for EID agents. Although China has not performed such linkage studies, Brazil examined donor-recipient linkage for dengue virus using a large, nationally representative database [168]. This study may serve as an example to follow in order to evaluate transfusion risk of EIDs in China.

Collaborative efforts from global surveillance programs may prove useful to mitigate the transfusion risk of EIDs. Although most EID agents in China were historically imported, some agents, such as SARS and SFTSV, originated in China and are expanding to other adjacent countries. Also, non-endemic EID agents such as West Nile Virus (WNV), Chikungunya virus, variant Creutzfeldt-Jacob disease (vCJD) and Zika virus (ZIKV) should be immediately addressed due to their worldwide distribution and severity of clinical outcomes. Recently, transfusion-transmitted ZIKV has been documented [169-170]. Several cases of ZIKV infection among travelers from epidemic areas have been reported in China[171-172]. Currently immigration authorities recommend oral

declaration of infection at entry-exit inspection and quarantine of symptomatic travelers from ZIKV epidemic areas upon entry into China. Travelers from countries epidemic for vCJD are deferred from donation by health questionnaire in Chinese blood centers. However, whether WNV, Chikungunya virus and ZIKV should also be added to the deferral list remains a matter of controversy that needs evidence from further investigation.

Pathogen reduction of blood products is an alternative defense against EID agents. Several studies described effective inactivation of EID agents such as DENV [173] and WNV [174]. Currently the only pathogen reduction technology in use in China is the methylene blue-photochemical technology applied to plasma products [175]. The technology is not mandatory and only performed at a few blood centers. More efforts should be made to evaluate whether and how pathogen reduction can be used to safeguard the blood supply in China. The cost-effectiveness of screening strategies is a key factor to consider. Currently there is a lack of cost-effectiveness studies on the existing screening strategies for the 4 classical TTIs in China. Such studies are needed to enhance the development and improvement of additional EID screening strategies in blood donations. In conclusion, the threats to blood safety posed by EID agents in China require further evaluation. With the support of the substantial evidence from such studies, China can implement more effective blood screening strategies on EID agents and further reduce transfusion risk to patients.

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