CHAPTER FIVE

Contributions of the National Institute of Parasitic Diseases to the control of visceral leishmaniasis in China

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Abstract

Visceral leishmaniasis (VL) caused by *Leishmania* spp. is an important vector-borne disease prevalent in China. VL was rampant in the vast area of China north of the Yangtze River before the founding of the People's Republic of China in 1949. As a result of strenuous interventions, the disease was basically eliminated in most of the former epidemic areas in 1958–60. At present, only sporadic cases occur in the western regions of China. In the process, National Institute of Parasitic Diseases at China CDC and the Chinese Center for Tropical Diseases Research (NIPD-CTDR) have achieved great impact in controlling the diseases as well as in research on *Leishmania* spp. This review summarized the contribution of experts from NIPD-CTDR to the control and elimination of VL in various aspects, such as understanding the epidemiological features of VL, confirmation of VL vectors and their distribution, development of control tools including diagnostics and insecticides, monitoring and evaluation supported by information management, technical supports to the control programmes, as well as analysis of the challenges faced. At the same time, it puts forward constructive suggestions for the ultimate interruption of VL transmission in China.

1. Introduction

Visceral leishmaniasis (VL), also known as Kala-azar, is caused by *Leishmania* spp. and transmitted by sandflies of the genus *Phlebotomus*. VL was one of the five most serious parasitic diseases endangering the human health in the People's Republic of China. It was prevalent in rural areas north of the Yangtze River, affecting more than 600 counties and cities in 16 provinces, municipalities and autonomous regions. Before the founding of the People's Republic of China in 1949, VL was spread continuously owing to the lack of prevention and control measures, resulting in large numbers of deaths. After the founding of the People's Republic of China, China had formulated the work plan to take the control and elimination efforts for a variety of serious diseases as the priority task of health work. This included nine diseases, among which VL were required to be eliminated within the time frame set by the "Framework of the National Agricultural Development Programme". The governments at all levels have attached great importance to the prevention and control of VL and many human and material resources were invested in the national VL control programme. This has led to remarkable achievements, such as the development of a control strategy and measures through pilot research, the establishment of working mechanism on strong governance leadership at all levels and active participation of the people in the effective implementation of control measures, the establishment of an efficient prevention and control network throughout the country, the establishment of professional institutions for prevention and research at all levels, and the understanding of the epidemic situation and epidemic factors of VL in China. Through active efforts in control of VL, the national VL control programme in the country has achieved remarkable results, for instance, VL was basically eliminated in 1958–60 in most of the epidemic areas, and at present, only scattered cases occur in the western region of China. The objectives of this article is to summarize the contribution of experts from the National Institute of Parasitic Diseases at China CDC & Chinese Center for Tropical Diseases Research (NIPD-CTDR) to the control and elimination of VL, analyse the challenges faced, and put forward the constructive suggestions for the ultimate interruption of VL transmission in China.

2. Epidemiological patterns of visceral leishmaniasis

In the early 1950s, in order to strengthen the control work on VL in China, the Eastern-China Branch of the National Institute of Health (the predecessor of the NIPD-CTDR) was authorized by the Ministry of Health to carry out VL investigation in the VL endemic provinces in cooperation with the provincial institutions working on VL control. The results from various investigations indicated that VL was epidemic in more than 680 counties and cities out of 16 provinces, autonomous regions and municipalities, north of the Yangtze River, especially in northern Jiangsu and Anhui, Shandong, Henan, southern Hebei and Shaanxi plains. There were about 530,000 VL cases in 1951 in the endemic areas of China, resulting in high mortality (Ho et al., 1959; Wang and Wu, 1956). At that time, epidemiological characteristics of VL in China were analyzed based on demographic information of cases, such as age distribution, and the relationship with canine visceral leishmaniasis (CVL). It was found that in the northern plains in China, similar to India, the majority of VL cases were in young adult humans, with rare cases of CVL. However, in Gansu and Qinghai provinces, the majority of VL cases were in infants and young children and CVL was more common. The latter picture was similar to the situation which was also consistent with the epidemiologic in the Mediterranean and central Asia.

As the national VL control programme in China progressed, the NIPD-CTDR accumulated abundant of epidemiological data from investigations conducted from 1956 to 1975 in Shanxi, mountain area of the southern

Gansu, northern Sichuan, the Loess Plateau of northern Shaanxi, and the desert zone in Xinjiang and western Inner Mongolia, where VL were still endemic in (Wang et al., 1963, 1964b, 1966; Xiong, 1972; Xiong et al., 1963a, 1963b, 1964a, 1964b, 1964c, 1965, 1974), as well as from 1967 to 1973 in northern Jiangsu, northern Anhui and Shaanxi plains, where VL had been eliminated in 1960s. In 1976, the new perspective of three epidemiological types (Fig. 1) was formulated (Guan et al., 1976; Xiong et al., 1976), providing a scientific reference to the tailoring of the implementation of the national VL control programme to local settings.

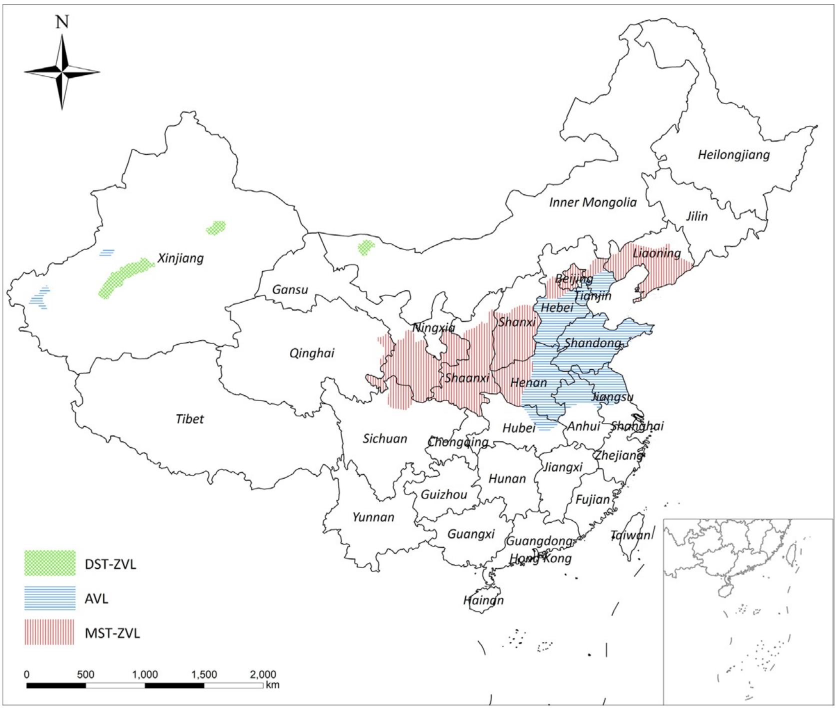

Fig. 1 Geographical distribution of the three sub-types of VL in China. The AVL endemic areas mainly distributed in south-eastern suburbs of Beijing, southern Hebei, Shandong, eastern Henan, northern Jiangsu, northern Anhui, Shaanxi plains, northern Jianghan plain of Hubei and ancient oasis area of southern Xinjiang. The DST-ZVL endemic areas mainly distributed on the edge of Tarim basin and Turpan in Xinjiang as well as Ejina banner in western Inner Mongolia. The MST-ZVL endemic areas mainly distributed in the northern suburbs of Beijing, northern Hebei, Liaoning, western Henan, Shanxi, northern Shaanxi and southern Shaanxi, southern Gansu and northwestern Sichuan, and the eastern part of Qinghai.

2.1 The anthroponotic visceral leishmaniasis (AVL)

The AVL endemic region in China included the south-eastern suburbs of Beijing, southern Hebei, Shandong, eastern Henan, northern Jiangsu, northern Anhui, Shaanxi plains, the northern Jianghan plain of Hubei and ancient oasis area of southern Xinjiang, where majority cases were juveniles, occasionally followed by post kala-azar dermal leishmaniasis (PKDL), and *Phlebotomus chinensis* (endophilic species) and *Ph. longiductus* (peridomestic species) were the vector. Because the patients were the primary reservoir host of AVL, concurrent or consecutive cases often occurred in one household with spatial clusters, sometimes leading to outbreaks. Except for Shaanxi plain, cases of CVL were rare or absent in the AVL endemic area.

2.2 The desert sub-type zoonotic of visceral leishmaniasis (DST-ZVL)

The DST-ZVL region was considered to be a natural nidus of VL, with wild animals presumed to be the source of infection. It had been uncultivated desert for a considerable period of time before it was populated by immigrants who introduced agriculture cultivation and other activities. Consequently, autochthonous infantile VL occurs after immigration. The region can be subdivided into two different sub-type, namely dry desert zone and gravel desert zone.

Dry desert zone. The dry desert zone is distributed on the edge of Tarim basin in Xinjiang and Ejina banner in western Inner Mongolia with vegetation of *Populus diversifolia-Tamarisk* as main vegetation, where *Ph. wui* (an exophilic species) was the primary vector. The incidence of the infection was sporadic and affected mainly infants under 2 years old, usually occurred in autumn and winter, rarely in summer. Lymphoglandular leishmaniasis occurred frequently in adults migrating to the dry desert region.

Gravel desert zone. The gravel desert zone is distributed in the mountain gravel desert area in Turpan, Xinjiang, where *Ph. alexandri* (an exophilic species) was the vector. The incidence of the infection was sporadic, and mainly affecting children under 5 years old, with a few adult cases accounting for about 10%. Typical VL occurs frequently in adults migrating to the gravel desert region.

2.3 The mountainous sub-type of zoonotic VL (MST-ZVL)

The MST-ZVL endemic region in China included the northern suburbs of Beijing, northern Hebei, Liaoning, western Henan, Shanxi, northern

Shaanxi and southern Shaanxi, southern Gansu and northwestern Sichuan, and the eastern part of Qinghai, where a sub-type of *Ph. Chinensis* (a semi-wild species) was the vector and dogs were reservoir with high infection rates. MST-ZVL was hypoendemic in humans and affected mainly infants under 5 years old, rarely followed by PKDL. The human incidence rate is much lower than the canine one, and no obvious correlation relationship was found between cases. In this region, it is highly probable that wild animals also were infected with *L. donovani* or *L. infantum* (Guan and Shen, 1991).

3. Vectors and their distribution

3.1 Confirmation of VL vectors

Before 1950s, investigations and experimental studies had been conducted in Beijing and North Jiangsu, confirming that *Ph. chinensis* was the vector of VL in China. Since then, the NIPD-CTDR has conducted infection experiments on dogs or hamsters using local *Ph. chinensis* in Shandong (1958, 1960), Gansu (1958) and Sichuan (1981) (Institute of Parasitic Diseases and Chinese Academy of Medical Sciences, 1958; Institute of Parasitic Diseases and Chinese Academy of Medical Sciences, 1960; Yin and Yu, 1981). The results showed that once the vector was infected, the promastigotes could multiply in the stomach and enter the anterior of the digestive tract, pharyngeal and proboscis of *Ph. chinensis*, indicating that local *Ph. chinensis* was well suited for the reproduction of *L. donovani* and *L. infantum*, and therefore the transmission of VL. In addition, a natural infection of promastigotes was found in *Ph. chinensis* captured in the wild in VL epidemic county of Jiuzhaigou of Sichuan Province (Xiong et al., 1992), confirmed to be *L. donovani* by ELISA, and further confirming the assertion that *Ph. chinensis* is the main vector of VL in China.

After 1963, investigations were extended to the western border of China, by NIPD-CTDR in cooperation with the relevant agencies of Gansu, Inner Mongolia and Xinjiang Provinces and autonomous regions. Those investigations have revealed the distribution of *Ph. longiductus*, *Ph. wui* and *Ph. alexandri* in the west of Inner Mongolia and south and north of Tianshan Mountains in Xinjiang (Guan et al., 1986; Jin et al., 2008; Xiong et al., 1974, 1976; Zhao et al., 1985; Zuo et al., 2005). In the endemic areas, the aforementioned three species of sandflies were always the main species, and their geographical distribution was consistent with that of VL. These three kinds of sandflies feed on human, and after engorging the blood of the animal infected with *L. donovani* or *L. infantum*, the promastigotes not only survived in the process of blood digestion, but also flourished and migrated to the front of the stomach, the anterior of the digestive tract, pharyngeal and proboscis. In the endemic area of VL, natural infections of the promastigotes was found in *Ph. wui* and *Ph. alexandri*, which was further confirmed by biochemical or immunological techniques to be the same kind of *Leishmania* species isolated from VL cases; after artificial inoculation with promastigotes isolated from *Ph. wui* and *Ph. alexandri*. Finally, it was found that VL occurred in healthy experimental animals after being bitten by *Ph. alexandri* infected with *L. donovani*.

Studying on the vectors of VL in Xinjiang, scientists from the NIPD-CTDR confirmed that *Leishmania* species isolated from VL cases in Beijing and Shandong could multiply in the stomach of *Ph. longiductus*, and *Leishmania* species isolated from cases in Henan and Gansu Province could flourish and migrate to the pharyngeal and proboscis of *Ph. alexander*, confirming the ability to transmit those types of VL (Guan et al., 1990). Therefore, it is necessary to prevent the entry of exotic infectious sources into Xinjiang to cause local secondary transmission, which is of great significance in epidemiology of VL in Xinjiang Uygur Autonomous Region.

All of these investigations have been of great significance to determine *Ph. longiductus*, *Ph. wui* and *Ph. alexandri* as vectors of VL in China, especially, the confirmation of *Ph. alexandri* as a vector of VL in China, which broke the view of the past that vectors of VL in the old-world were limited to species of major group of Phlebotomus.

3.2 Distribution of sandflies

Research on sandflies has shown for a long time that the species composition of VL vectors varied in different geographic regions in China. Although some sandflies were euryecious species with extensive adaptability to different environment, there werespecies that were typically representative in certain ecological environments. As of 2011, scientists from the NIPD-CTDR have conducted a series of studies on the geographical distribution of 5 important sandflies species in China, to define their geographical scope, distribution characteristics, and map them.

3.2.1 Ph. chinensis

In the 1950s, investigations on the distribution of *Ph. chinensis* have accumulated a wealth of data, which was compiled and summarized by the NIPD-CTDR. The distribution of *Ph. chinensis* sandflies covered 358 counties and cities in 21 provinces, autonomous regions and municipalities

(Guan and Yang, 2012; Ho et al., 1959). As of 2011, the geographical distribution of *Ph. chinensis* was mapped by NIPD-CTDR (Guan et al., 2016) showing that, in terms of latitude, *Ph. chinensis* was present as far north as Changchun of Jilin Province (43°90′N, 125°50′E), as far south as Hekou of Yunnan Province (23°40′N, 104°E), as far west as Zhangye of Gansu Province (38°90′N, 100°40′E), and as far east as Jilin of Jilin Province (43°80′N, 126°60′E). In terms of altitude range, the vector was present in areas varying from 10 meters above the sea level in Jiangsu coastal plain, to 2,750 meters above the sea level in mountains areas of the northwestern Sichuan and southern Gansu Provinces (Guan et al., 2016; Wu et al., 1995; Yin et al., 1990). Even though *Ph. chinensis* is widely distributed, it is mostly encountered in the plains, mountainous, and Loess Plateau area of 32°–43°N, 102°–121°E (see Fig. 2), which is consistent with the geographical distribution of VL (Guan et al., 2016).

The *Ph. chinensis*, distributed in the central and eastern plains of China, is endophilic and highly sensitive to insecticides (Wu et al., 1955), and has

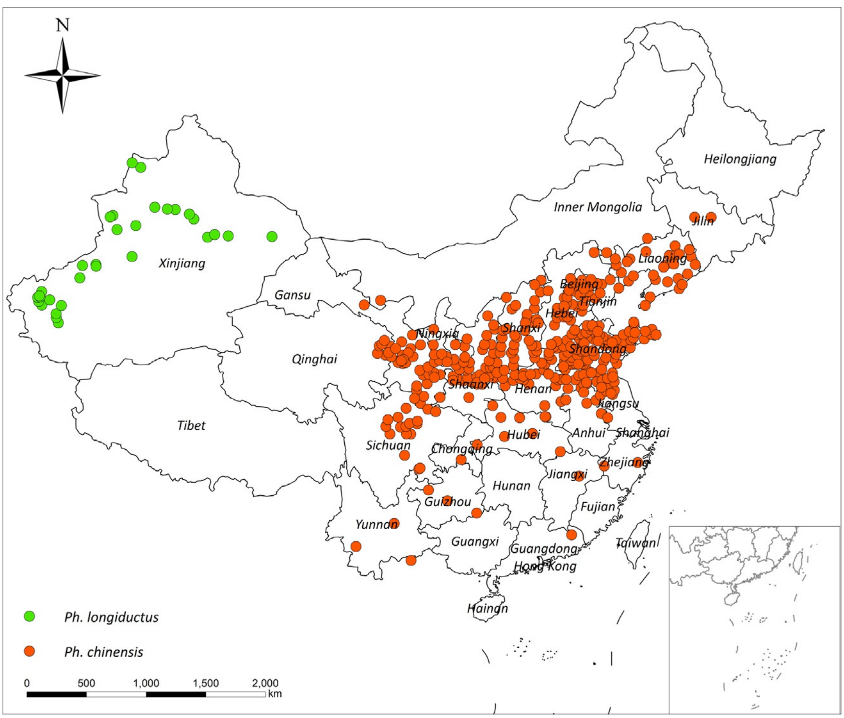

Fig. 2 Distribution of *Ph. chinensis* and *Ph. longiductus* in China.

been effectively got under control by indoor residual spraying (IRS) (Wu, 1957). In the mountainous and Loess Plateau areas, however, *Ph. chinensis* is an exophilic species. Due to a lack of similar effective control measures (Guan, 2010; Guan et al., 1980a), it is still spread widely, with new cases both of VL and CVL frequently emerging (Guan, 2009; Tian et al., 2012).

3.2.2 *Ph. mongoliensis*

Ph. mongoliensis was distributed in 240 counties/cities in 17 provinces, autonomous regions or municipalities (Chen et al., 2003; Ho et al., 1959; Zuo et al., 1998). In terms of latitude it was present as far north as Hebukesaier of Xinjiang Uygur Autonomous Region (46°80′N, 85°70′E), as far south as Jingmen of Hubei Province (31°N, 112°10′E), as far west as Huocheng of Xinjiang Uygur Autonomous Region (44°N, 80°80′E), and as far east as Suizhong of Liaoning Province (40°30′N, 120°30′E) (see Fig. 3). It was present at an altitude range of 10 meters above the sea level (in the Northern Jiangsu Coastal Plain) to 1,900 meters above the sea level (in

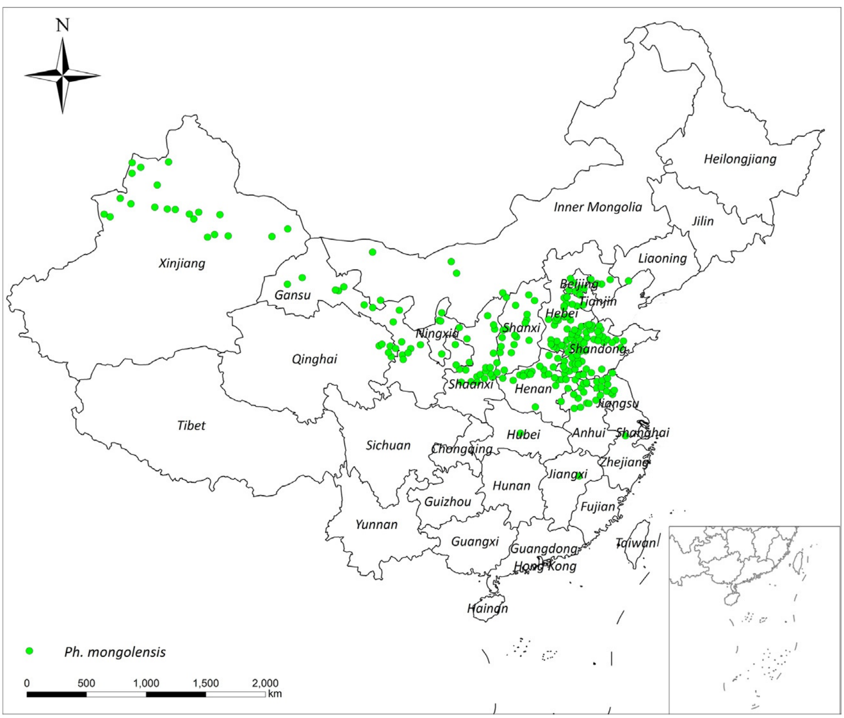

Fig. 3 Distribution of *Ph. mongoliensis* in China.

Dongxiang of Gansu Province), with the highest density observed in the northern China plain region (32°–40°N, 114°–120°′E), as well as desert areas covered with Chenopodiaceae plants in Western Inner Mongolia, the Hexi Corridor of Gansu Province, and the Zhungeer basin north of Mt. Tianshan in Xinjiang Uygur Autonomous Region (Guan et al., 2016). *Ph. mongoliensis* has been proven the vector for *L. gerbilli* and *L. turanica*, rather than for human VL (Feng, 1951), since it has been found in the subcutaneous tissue of the gerbils in some desert areas in western China (Liu et al., 1982; Wang et al., 1963, 1964a; Xu et al., 1991).

3.2.3 *Ph. longiductus*

The distribution of *Ph. longiductus* sandflies in China was limited to 30 counties and cities inside Xinjiang Uygur Autonomous Region (Zuo et al., 1998), as far north as Tacheng (46°45′N, 83°E), as far south as Yecheng (37°52′N, 77°24′E), as far west as Kashgar (37°50′N, 76°E), and as far east as Shanshan (42°90′N, 90°13′E) (see Fig. 2). Compatible altitude ranged from 90 meters (Turfan) to 2,100 meters, vertically at an altitude ranging from 90 (Turfan) to 2100 above the sea level (Wensu) (Guan et al., 2016), with the highest density found in ancient oases, at altitudes from 1,000 to 1,500 meters above the sea level in the western and northern rims of the Tarim Basin, followed by the mountainous regions. It was not found in desert areas (Guan and Yang, 2012; Guan et al., 2016).

3.2.4 *Ph. wui*

Ph. wui sandflies were present in 37 counties (banners) in Xinjiang, Gansu, and Inner Mongolia, as far north as Tacheng of Xinjiang Uygur Autonomous Region (46°45′N, 83°E), as far south as Minfeng, Xinjiang Uygur Autonomous Region (37°04′N, 82°41′E), as far west as Shufu of Xinjiang Uygur Autonomous Region (39°50′N, 75°85′E), and as far east as Eji'naqi of Inner Mongolia Autonomous Region (41°57′N, 77°50′E) (see Fig. 4). It was present at an altitude from 90 to 1,500 meters, and vertically at an altitude from 90 to 1500, mainly in desert areas covered with vegetation of *Poplar diversifolia* and *Tamarix taklamakanensis* at the edge of the Tarim Basin in south Xinjiang and western Inner Mongolia (Guan et al., 2016), followed by the ancient oasis with less than 16.8% of the local sandfly population, and occasionally in the mountainous landscape (Guan and Chai, 1996).

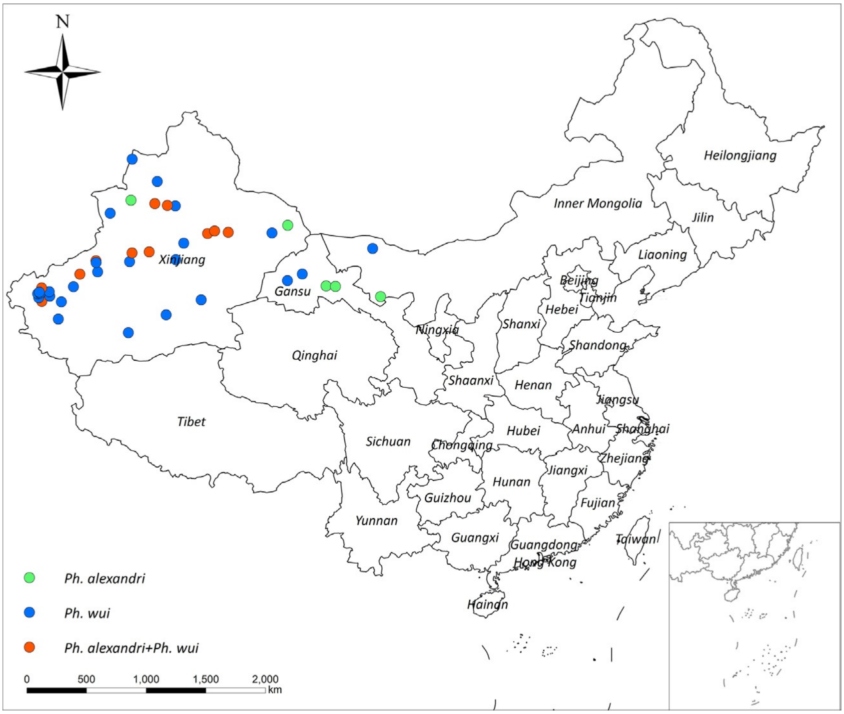

Fig. 4 Distribution of *Ph. wui* and *Ph. alexandri* in China.

3.2.5 *Ph. alexandri*

Ph. alexandri sandfly were present in 17 counties in Xinjiang, Gansu, and Inner Mongolia, as far north as Guertu in Wusu of Xinjiang Uygur Autonomous Region (44°50′N, 76°10′E), as far south as Yingjisha of Xinjiang Uygur Autonomous Region (39°10′N, 76°10′E), as far west as Atushi of Xinjiang Uygur Autonomous Region (39°70′N, 76°10′E), and as far east as Yabulai Mountains in Alxa Youqi of Inner Mongolia Autonomous Region (39°40′N, 103°10′E) (see Fig. 4) (Guan et al., 2016). *Ph. alexandri* is primarily present in areas of piedmont and stony desert, at an altitude from 500 to 1,750 meters above the sea level (Guan et al., 2016), where there is no other natural vegetation than small shrubs and various kinds of burrows can serve as the habitat of *Ph. alexandri* sandflies (Guan, 2009).

Acquired knowledge about the vector distribution and their favoured ecological environments have revealed that these four vectors, namely *Ph. chinensis*, *Ph. Longiductus*, *Ph. wui* and *Ph. alexandri*, have different requirement of ecological environment, which provides a reference for further studies on the geographical distribution of leishmaniasis and the environmental factors influencing it, as well as on the planning of national VL control programme

4. Visceral leishmaniasis in China: Then and now

Since the early 1950s, the national VL control programme has been initiated with comprehensive measures to eliminate infectious sources and control sandflies. As a result, the incidence of VL in the 16 historically endemic provinces, autonomous regions and municipalities declined rapidly. In the North China Plain and Shaanxi Plain regions, AVL had been controlled by 1958, and the standard of elimination was met in the early 1980s (Wang et al., 2000). However, VL has never totally disappeared from six provinces and autonomous regions including Xinjiang, Gansu, Sichuan, Shaanxi, Shanxi and Inner Mongolia, where sporadic cases and small-scale epidemics have been reported. Imported cases have also been notified in 51 non-endemic districts and cities nationwide (Guan et al., 2000). After entering the 21st century, case information was collected and analyzed by NIPD-CTDR through the infectious disease network reporting system in China. From 2004 to 2018, a total of 4,793 cases of VL were reported in China, with 306, 311, 270, 355, 518, 523, 375, 300, 219, 158, 293, 510, 310, 183 and 162 annual cases reported respectively, an annual average number of reported cases of 320 (Table 1), showing a decline trend. The epidemic area of VL has expanded to 82 counties and cities in 8 provinces and autonomous regions, namely Xinjiang, Gansu, Sichuan, Shaanxi, Shanxi, Inner Mongolia, Henan, Hebei Province (Table 2, Fig. 5). Generally, cases are scattered, with some concentration of cases seen in Jiashi County in Xinjiang, Zhouqu County, Dangchang County and Wudu District in Gansu Province. An annual incidence rate of over 1/10,000, and even periodic outbreaks with an interval of 7–8 years, were even reported in Jiashi County in Xinjiang in 2008 and 2015 with 202 and 356 cases reported respectively. The number of imported cases has also increased in non-endemic areas of the country (Han et al., 2019; Wang et al., 2012).

4.1 Control efforts—What was done

Establishment of professional institutions and training professionals for VL control in major endemic areas. After the founding of the People's Republic of China, the central people's government began to set up professional institutions for VL control at the provincial level in major endemic areas. Between 1950 and 1953, anti-VL stations were established in

Table 1 Distribution of VL endemic areas in China from 2004 to 2016.

Province	City (state, union)	Endemic county (district, county)
Xinjiang Autonomous Region	Bayingolin Mongol Autonomous Prefecture	Yuli, Korla, Luntai, Muchi, Ruoqiang, Yanqi hui Autonomous County, Hejing, Heshu, Bohu
	Aksu Prefecture	Wushi, Kuqa, Shaya, Aksu, Wensu, Xinhe, Baicheng, Awati, Keping
	Kizilsu Kirgiz	Acto, Artosh, Aheqi, Ucha
	Kashgar Prefecture	Kashgar, Shufu, Shule, Jiashi, Yingjisha, Megeti, Zepu, Yuepuhu, Shaka, Bachu, Yecheng
	Hotan Prefecture	Hetian city, Hetian, Moyu, Pishan, Lopu, Cele, Yutian, Minfeng
	Turpan	Gaochang, Toksun
	Hami	Yizhou
	Municipality directly under the jurisdiction of prefecture-level city	Tumushuk
Subtotal	8	45
Gansu Province	Longnan	Wudu, Wenxian, Tanchang, Kangxian, Lixian, Xihe
	Gannan state	Zhouqu, Diebu
	Jiuquan	Guazhou
	Pingliang	Kongtong, Jingning
	Dingxi	Tongwei
	Qingyang	Huanxian, Qingcheng
Subtotal	6	14
Sichuan Province	Aba state	Jiuzhaigou, Maoxian, Heishui, Wenchuan, Lixian
	Mianyang	Beichuan, Pingwu
Subtotal	2	7

Continued

Table 1 Distribution of VL endemic areas in China from 2004 to 2016.—cont'd

Province	City (state, union)	Endemic county (district, county)
Inner Mongolia Autonomous Region	Alxa League	Ejin Banner
Subtotal	1	1
Henan Province	Anyang	Linzhou
Subtotal	1	1
Shaanxi Province	Weinan	Hancheng
	Yanan	Baota, Yichuan
Subtotal	2	3
Shanxi Province	Jiuquan	Urban area, Suburb, Mengxian, Pingding
	Changzhi	Wuxiang, Suburb, Xiangyuan, Tunliu
	Jinzhong	Yushe
	Linfen	Yaodu, Daning
Subtotal	4	11
Total	24	82

Shandong, Jiangsu, Anhui, Henan, Hebei, Shaanxi and Gansu province to take responsibility to determine local epidemic situation and epidemiological factors of VL, train technical personnel at different levels and establish network from county to village levels for VL control, and provide technical guidance and supervise for VL control (Guan and Wu, 2014). In order to strengthen technical guidance, in 1951, the NIPD-CTDR was authorized to work in cooperation with Shandong provincial institutes to develop the standard manuals and embarked on 3–6 months multidisciplinary training courses for health personnel, via which, thousands of trainees were trained to become proficient in dealing with patient diagnosis, clinical treatment and case management and chemotherapy, as well as collection, identification, and control of vectors and reservoirs (Guan and Yang, 2012; Lun et al., 2015), which laid solid foundation for VL control in the endemic areas.

Table 2 Distribution of the reported VL cases in China from 2004 to 2018.

Endemic regions			Non-endemic regions		
Province	**The cumulative cases**	**Composition ratio/%**	**Province**	**The cumulative cases**	**Composition ratio/%**
Xinjiang Autonomous Region	2,347	48.97	Chongqing	19	0.40
Gansu Province	1,557	32.48	Zhejiang Province	9	0.19
Sichuan Province	583	12.16	Hubei Province	10	0.21
Shaanxi Province	97	2.02	Hunan Province	10	0.21
Shanxi Province	86	1.79	Yunnan Province	7	0.15
Inner Mongolia Autonomous Region	10	0.21	Tianjing	7	0.15
Henan Province	13	0.27	Heilongjiang Province	5	0.10
			Guangxi Zhuang Autonomous Region	5	0.10
			Beijing	4	0.08
			Hebei Province	6	0.13
			Jiangxi Province	3	0.06
			Qinghai Province	3	0.06
			Jilin Province	3	0.06
			Jiangsu Province	2	0.04
			Anhui Province	3	0.06
			Shandong Province	2	0.04
			Tibet Autonomous Region	1	0.02
			Fujian Province	1	0.02
Subtotal	4,693	97.91	Subtotal	100	2.09

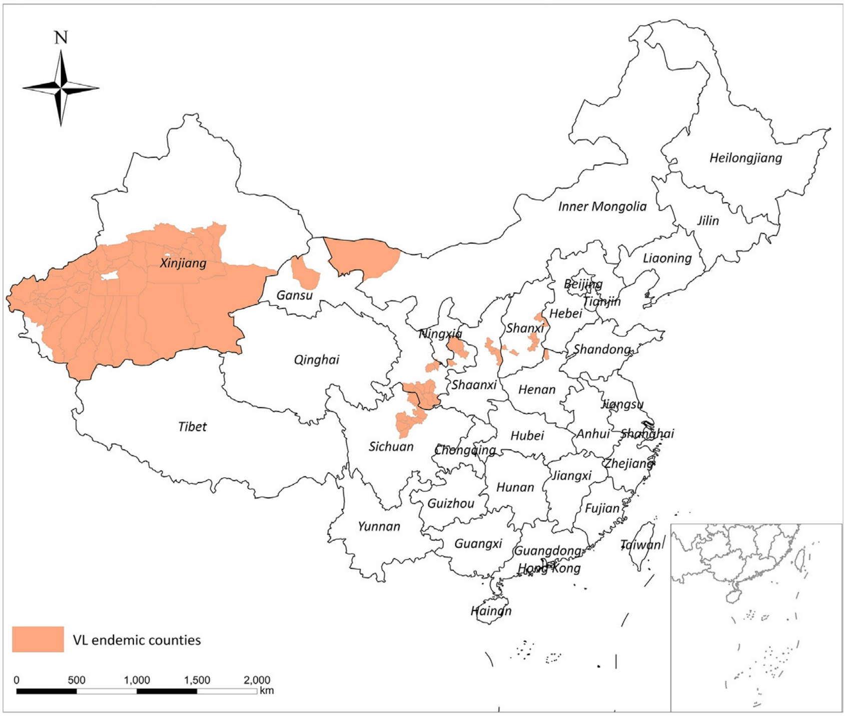

Fig. 5 Distribution of VL endemic counties and cities in China from 2004 to 2016.

Setting up control pilot sites and conducting control technology research. Although in the 1930s, pentavalent antimony, such as Neostibosan, Urea Stibamine, Solustibosan, and Pentostam have been used to treat VL in China (Guan and Wu, 2014), it was still too expensive to be used extensively for most people in China, because all of them had to be imported from abroad. In 1950, the Shandong Xinhua Pharmaceutical Factory successfully synthesized pentavalent sodium antimony gluconate which was suitable for rural medical staff to use it either for intravenous or intramuscular injection, fully meeting the needs for VL treatment in China. Before large-scale use of homemade pentavalent sodium antimony gluconate, pilot site was firstly set up in Shandong province to conduct clinical trials to determine its therapeutic effect and the method suitable for its application in rural areas. As a result, the "six-day therapy" was recommended as the therapeutic scheme of choice in the endemic areas. Besides, the "three-day therapy" was suitable for patients in good health and without complications, and "three-week therapy" was suitable for those in poor health or with serious illness (Guan and Yang, 2012).

Simultaneous efforts were devoted by the NIPD-CTDR and provincial institutes to control vectors. Between 1951 and 1953 (Wu et al., 1955), vector control pilot sites were set up in Shandong, Jiangsu, and Anhui Province, to conduct sandflies bionomics investigation and elimination approach. The results demonstrated the following bionomical characteristics of *Ph. chinensis* in the plain region: The breeding sites of the larvae were widely scattered; hence it was difficult to control effectively. However, the adult is endophilic and susceptible to insecticide, with their activity season as short as 3.5 months. The obtained information led to the implementation of vector control by indoor DDT spraying of human dwellings and animal shelters (Guan et al., 2000; Wang et al., 2000; Wu et al., 1955). The insecticides, dichlorodiphenyltrichloroethane (DDT) 1.5 g pure insecticide/m^2 and hexachlorocyclohexane (HCH) 0.15 g/m^2, were used to spray whole villages in the endemic areas. No new cases were found in the sprayed area of the whole village, while new cases were found in the control village (where patients were only treated) every year. It fully showed that the combination of killing sandflies and treatment of VL patients in the whole village had significant effects on the control of AVL in the central and eastern plain of China. According to the successful experience of vector control with insecticide, Wu and others (Wu and Wang, 1956) extended the experimental process and specific measures to the whole country, which significantly promoted the AVL control process in endemic areas of eastern and central plain in China.

The control outcomes in different types of endemic area. Since 1950, the government provided homemade pentavalent sodium antimony gluconate for free to all VL patients. If they could afford it, the patients in principle should pay for the treatment of complications. Otherwise, the government would provide relevant subsidies for them (Guan and Wu, 2014). Since 1955, free insecticides were provided for vector control by the VL control institutions, and village doctors responsible for VL treatment would get a service subsidy from governments based on the number of cases treated (Guan and Yang, 2012).The massive mobilization of the general public was conducted by a top-down approach from the provincial to the village level for education of the population about VL by trained health personnel to actively engage in the control programmes (Lun et al., 2015). In the process of VL control, NIPD-CTDR played a key role as technical guidance.

AVL endemic area. From 1950 to 1958, in the endemic areas, professional VL control institutions as the mainstay, with participation from rural health workers, carried out massive screening to identify patients through spleen palpation and inquiry of disease history. Then necessary serological or parasitological examination was performed on suspected VL cases. Later, free treatment was provided for confirmed cases in the township clinics, and treatment for severe patients in the county hospital or competent institutions at the higher level (Guan and Wu, 2014). During the period, a total of 248,427, 53,820, and 110,999 cases were treated in Shandong, Shaanxi, and Jiangsu, respectively (Guan and Yang, 2012). Since 1955, massive and thorough screening and treatment, combining vector control with insecticide spraying was conducted to eliminate the source of infection and kill the sandflies. At the end of the 1950s, the seriously epidemic areas of VL had been controlled in Southern Hebei, Northern Jiangsu, Northern Anhui, Eastern Henan, Northern Hubei and central Shaanxi and reached the elimination standard in the early 1980s (Guan and Yang, 2012).

Since 1977, annually one–two times massive screening to identify VL patients for treatment was carried out in eight AVL endemic counties and cities in the Kashgar ancient oasis in southern Xinjiang. Simultaneously, the wh1ole village with patients last year was sprayed with BHC or deltamethrin once a year. The number of VL cases in these eight counties had dropped from 222 cases in 1979 to 14 cases in 1988 (Chai and Guan, 2006). However, once the aforementioned measures were halted, the number of cases rebounded year by year, with a vengeance from 1996 to 2002 (Chai and Guan, 2006). The reason maybe that even after IRS, a large number of *Ph. Longiductus* with peridomestic bionomic characteristic still exist in AVL endemic areas. Meanwhile, asymptomatic patients cannot be identified and eliminated in campaign of massive screening (Burza et al., 2018), which could develop into new source of infection (Hasker et al., 2014). As infection source begin to accumulate, VL would rebound, even outbreak again (Medley et al., 2015).

MST-ZVL endemic area. Before 1958, comprehensive interventions were implemented in MST-ZVL endemic area, including provision of free VL treatment services for patients, IRS killing sandflies and dogs culling campaign which led to domestic dogs were once all but extinct there, thus, the prevalence of VL constantly decline. For example, the number of cases in Gansu province dropped from 3698 cases in 1953 to 33 cases in 1961 (Guan and Yang, 2012). No new autochthonic case was reported from Qinghai, Ningxia and Liaoning province after 1959, 1973 and 1975, respectively (Guan and Yang, 2012). However, different from that in plain areas, the local *Ph. chinesis* is an exophilic sandfly species, which lead to poor effectiveness of IRS. Since the mid-1960s, as the number of domestic dogs in rural areas gradually increased in the areas of southern Gansu, northwestern Sichuan, northern Shaanxi and southern Shanxi, both CVL and human VL rebounded significantly.

From 1980s, the interventions integrated IRS of patient and their neighbour's household with deltamethrin, timely treatment of patients and culling infected dogs confirmed by bone marrow aspiration have constricted MST-ZVL at a low incidence in China, whereas, the endemic area is extending gradually (Guan and Yang, 2012). In 1994, scientists from the NIPD-CTDR (Xiong et al., 1994) reported that domestic dogs bathed with 25 ppm water solution of 2.5% deltamethrin wettable powder in Jiuzhaigou County of Sichuan Province could prevent *Ph. chinensis* sandflies for the first time. The experimental dogs were exposed to wild *Ph. chinensis* sandflies in mosquito nets for five times within 30 to 104 days after a medicated bath. The blood absorption rate of sandflies was 2.7–4.9% for 8 h of exposure each time, and then the blood-sucking and non-blood-sucking sandflies were reared in the laboratory. The mortality rate of sandflies was 98% in 24 h. Under the same conditions, the blood absorption rate and blood-sucking mortality rate of sandflies to healthy dogs were 61.5% and 5.4–14.9% respectively. The results showed that the use of deltamethrin in bathing dogs could prevent the bite of *Ph. chinensis* sandflies, and subsequently can block the transmission of CVL, and thus effectively reduce the incidence of VL in the population. However, it is a challenge to promote this technology with sporadic VL cases scattered in remote mountain villages, for close corporation from dog owners are required. If the number of domesticated dogs can be contained after large-scale culling of infected dogs, it will have a more significant effectiveness on control the epidemic of VL, but it is still difficult in practice for lacking of sufficiently sensitive and specific diagnostics to identify CVL and ethical issues.

DST-ZVL endemic area. Due to the DST-ZVL cases is scattered, IRS is inefficient for controlling *Philebotomus wui*, an exophilic sandfly (Chai and Guan, 2006; Guan and Shen, 1991), and reservoir hosts are yet unconfirmed wild animals (Liao et al., 2009), the local health department has no other intervention measures except to identify VL patients for treatment timely (Chai and Guan, 2006). Evidences have shown that large-scale reclamation of desert to change the original ecological environment, or continuous spraying of insecticides in the *Populus diversifolia-Tamarisk* forest belt to reduce the density of sandflies, can greatly decrease the DST-ZVL incidence, but the former is contrary to the policy of the ecological environment conservation, and the latter is also uneconomical (Guan and Yang, 2012).

4.2 Supportive research from NIPD-CTDR

4.2.1 Research on immunoassay

4.2.1.1 Antibody detection

Indirect immunofluorescent antibody test (IFAT). IFAT was used to detect antibodies in the body infected with *Leishmania* spp. Serum of patients was once used as the test sample, but collecting blood from infants and young children was inconvenient. In 1979, scientists from the NIPD-CTDR tried to replace serum with "filter paper dried blood droplets". IFAT was performed on 23 patients with VL and 13 mice infected with *Leishmania donovani*. The results showed that the dried blood droplets and serum had equal efficiency, with similar results after two to four times of repeated tests (Guan et al., 1980b).

Counterimmunoelectrophoresis (CIEP). In 1981, the soluble antigen of leishmanial promastigotes was used to test the serum of 30 patients with VL confirmed by pathogenic examination. The positive rate of the test by the methods of counterimmunoelectrophoresis (CIEP) was 96.7%. The serum of 26 patients for post-cure 23–28 months was still able to be detected by CIEP. Only two cases showed weak positive reaction and the rest were negative. No positive reaction with sera of tuberculosis, hepatitis and healthy people was noticed (Wang et al., 1981).

Enzyme-linked immunosorbent assay (ELISA). ELISA was used to detect specific antibodies in serum of VL patients with soluble crude antigen of leishmanial promastigotes, intact leishmanial promastigotes or recombinant antigen. Intact leishmanial promastigotes was used as coating antigen in ELISA to detect 16 sera of VL patients confirmed by pathogenic examination, which showed positive results in ELISA by using leishmanial promastigotes soluble antigen as coating antigen and negative in 9 sera of healthy persons. The results showed that all sera of patients were positive and all sera of healthy persons were negative, thus proving that intact leishmanial promastigotes antigen and soluble crude antigen had the same diagnostic efficiency (Wang and Chen, 1987). The rK39 was used as coating antigen in ELISA for immunodiagnosis, and sera of 107 VL cases from Western China was detected. The positive rate was 96.2%, and 1 was found as seropositive in 31 cases of cutaneous leishmaniasis in Karamay of Xinjiang Uygur Autonomous Region (Qu et al., 1996a).

Immunochromatographic strip test. Immunochromatographic strip test is a rapid diagnostic method developed in recent years. It combines immune molecule affinity principle with Western blot and classic thin layer chromatography. Because of its high sensitivity, simple operation and fast reporting, it has been widely used in diagnosis. Scientists from the NIPD-CTDR successfully developed immunochromatographic strip test for detection of specific antibodies in VL patients using colloidal gold method with leishmania promastigotes crude antigen as coating antigen (Yang et al., 2014). The sensitivity and specificity of the strip were 96.1% and 95.6%, respectively, in 129 sera of VL patients diagnosed and confirmed by pathogen examination in the laboratory. The field evaluation in different VL endemic areas in China also showed high sensitivity and specificity, and the results had no statistical difference with parallel detection of rK39 (Feng et al., 2016). The strip is also suitable for detecting specific antibody in dog blood samples from zoonotic visceral leishmaniasis (ZVL) endemic areas (Feng et al., 2015).

4.2.1.2 Detection of circulating antigen

Monoclonal antibody labelled with peroxidase dot—ELISA. Scientists from the NIPD-CTDR used monoclonal antibody against the target antigen of *L. donovani* promastigotes labelled horseradish peroxidase in dot-ELISA test for detecting circulating antigen in serum of patients with VL, and the positive rate was 88.9–90.6% (Qu et al., 1990, 1991, 1996b). Positive correlation was exhibited between the titre of circulating antigen in the sera and the number of protozoa in the bone marrow smear. No positive result was obtained from patients who had been recovered from the disease. The sera of healthy people tested were all negative, and no cross reaction was found with the sera of patients with malaria, leprosy, brucellosis and schistosomiasis. It was suggested that McAb dot-ELISA method could be used not only for the diagnosis of current VL, but also for field evaluation of therapeutic effectiveness for VL.

Monoclonal antibody-enzyme linked immunotransfer blot technique (McAb-EITB). In 1991, scientists from the NIPD-CTDR (Wang et al., 1991) first used monoclonal antibody (HRP-L12H4) against *L. donovani* labelled horseradish peroxidase and enzyme-linked immunotransfer blot technique (EITB) to detect circulating antigen in sera of VL patients, and results showed that McAb-EITB was a sensitive, specific and practical diagnosis method for VL.

Immunochromatographic test (ICT). Scientists from the NIPD-CTDR (Gao et al., 2015c) prepared monoclonal antibodies (mAbs) against *L. donovani* promastigotes soluble crude antigen. Two secreted mAbs recognizing the same leishmanial protein were used to produce an ICT for the detection of circulating antigen in serum and blood of patients diagnosed with VL. Sensitivity, specificity and diagnostic efficiency of the new ICT was 95.8%, 98.7% and 97.3%, respectively. There was no significant difference in sensitivity or specificity between the test strips prepared in this study and the rK39 test strips. As the ICT detecting a circulating antigen, the ICT will also be useful in monitoring treatment efficiency and identifying VL patients with immunodeficiency.

4.2.2 Development of molecular diagnostics

4.2.2.1 Polymerase chain reaction (PCR)

Scientists from the NIPD-CTDR (Gao et al., 2006) selected six primer pairs for detecting Chinese strain of *L. infantum* by optimizing conditions. Their sensitivity and specificity were compared by using DNAs extracted from human blood seeded with cultured *L. infantum* promastigotes (MHOM/CN/86/GS) as a template. The results showed that the specificity of all six primer pairs reached 100%, and the sensitivity varied among the primer pairs. The primer pairs RV1-RV2 (0.1 parasite/mL blood) and K13A-K13B (1 parasite/mL blood) were most sensitive. This study suggested that RV1-RV2 and K13A-K13B primer pairs were suitable in detecting the asymptomatic infection of *L. infantum*. The PCR method was also suitable for detection of asymptomatic infection of *Leishmania* in humans, dogs and domestic mammals in the VL endemic area (Gao et al., 2015b; Han et al., 2018; Wang et al., 2006, 2007).

4.2.2.2 Loop-mediated isothermal amplification (LAMP)

Scientists from the NIPD-CTDR (Gao et al., 2015a) developed a loop-mediated isothermal amplification (LAMP) assay to detect *L. infantum* infections in dogs using conjunctival swab samples specifically. The primers used in the LAMP assay were designed to target kinetoplast DNA minicircle sequences of the *L. infantum* isolate MCAN/CN/90/SC. The *L. infantum*-positive rates obtained for field-collected samples were 61.3% by LAMP. The sensitivity and specificity of LAMP and PCR are similar, but conjunctival swab is a non-invasive method, which is easy to operate and more acceptable by dog owners. The findings indicate that the LAMP assay is a sensitive and specific method for the field surveillance of domestic dogs, particularly of asymptomatic canines, in ZVL-endemic areas in western China.

4.2.3 Control of exophilic sandflies

Individual protection by skin coating of repellent. The efficacy of five repellents were tested against *Ph. alexandri* on the southern slope of Bogda mountain, Turfan City, Xinjiang Uygur Autonomous Region during 1986–88. At the dose of 0.25 μL/cm^2, the protective durations of mosquito repellent perfume (MRP), N, N-diethyl-m-toluamide (DETA), mosquito repellent liquid (MRL), dimethyl phthalate (DMP) and di-butyl phthalate (DBP) were (6.94 ± 0.67)h, (5.19 ± 0.32)h, (4.98 ± 0.89)h, (3.77 ± 0.43)h and (1.94 ± 0.52)h, respectively (Jia et al., 1990). Another experiment showed that the protective durations of MRP, DETA and MRL against *Ph. wui* in Karamay were 6–9 h (Jia et al., 1988). All the repellents were proved to have practical value.

4.2.4 Animal infection sources in different types of endemicity

From 1964 to 1984, in collaboration with local professional institutes, the NIPD-CTDR conducted a series of examinations to detect *Leishmania* spp. infection in wild reservoir hosts in either the dry or the stony deserts in Xinjiang as well as in the Ejina Banner of Inner Mongolia. The method used was smear examination and Novy-MacNeal-Nicolle medium culture from samples of liver, spleen, bone marrow and lymph node. No infection of *Leishmania* spp. was observed in a total of 5,409 wild rodents, 114 hares, 157 carnivorous foxes, and 142 carnivorous hedgehogs. Wild rodents should therefore not be considered as VL reservoir hosts (Chai and Guan, 2006; Guan et al., 1984). In recent years, it was reported that Tarim rabbits were a suspicious reservoir host of VL in the dry desert area in Xinjiang, but further studies are required to confirm this (Liao et al., 2009; Lun et al., 2015).

In the Hexi Corridor Zone of Gansu Province, the Junggar Basin of Xinjiang and the Ejina Banner of Inner Mongolia, *L. gerbilli* and *L. turanica* were detected from subcutaneous tissues of gerbils. However, neither of those two leishmania species can cause human VL. Therefore, it was concluded that the gerbils were not a host reservoir for human VL (Guan et al., 1982; Liu et al., 1982; Wang et al., 1964b; Xiong et al., 1964b).

After the 1990s, in view of the reemergence of VL cases in the mountainous areas of western China, three methods, namely polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA) and rK39 immunochromatographic strip, were used to detect leishmania antibodies in healthy dog serum in Wenxian County in Gansu province, with positive rates for the three methods being 50.6% (40/79), 22.2% (16/72) and 33.3% (19/57), respectively (Wang et al., 2006). This demonstrated that highly infectious (Molina et al., 1994), but asymptomatic infected dogs played an important role in the epidemiology in MST-ZVL.

These investigations have laid the foundation for discovering the infection sources of zoonotic VL in China and then developing targeted prevention measures.

4.2.5 Development of VL diagnosis standard and management principles

The Ministry of Health issued standard document of "Diagnostic Criteria and Principles of Management of Kala-Azar (GB 15986-1995)" authored by the NIPD-CTDR in 1995, as the last national guidelines available for the management of leishmaniasis control programme (Qu and Guan, 1995), which served as the nationwide general guidelines and contributed a lot for the national VL control programme.

4.3 Monitoring and evaluation

After 1958, the prevalence of VL in former epidemic provinces, autonomous regions and municipalities has dropped significantly to less than 1/10,000. Thus, monitoring work has begun to take the priority for VL control in all areas of endemic areas which includes three aspects, namely, tracing the current VL patients to grasp the trend of the epidemic, using leishmanin intradermal test for delayed-type hypersensitivity (DTH) to evaluate the VL epidemic trend in local population from the perspective of immunology, and the investigation of the density of vector to assess whether the transmission has been blocked (Guan and Yang, 2012).

Large-scale monitoring and evaluation in control stage. Under the guidance of the NIPD-CTDR, from 1970s to 1990s, several rounds of large-scale monitoring and evaluation works were performed in previous major AVL endemic provinces, such as Shandong, Henan, Jiangsu, Anhui, Hubei province (Guan and Yang, 2012). However, no new VL case was found, except for a few imported cases and rare relapse cases infected before 1970. Leishmanin intradermal test was carried out among rural residents of different age groups. Nevertheless, no positive result was found in the population born after 1970. For the vector survey, no *Ph. chinesis* was found in the eastern China plain region, except for a few sergentomyia species, not a vector of VL. The above results indicated that VL in previous AVL endemic area in eastern and central plain in China has been eliminated (Guan and Yang, 2012). However, the persistence of AVL is evident in southern Xinjiang and that of MST-ZVL in the western mountain areas, mainly Sichuan and Gansu provinces.

Infection Disease Reporting Management System. In 2004, the web-based National Diseases Reporting Information System (NDRIS) which is a network covers all the medical and health institutions at or above the township level, was established in China and operated by the Chinese Center for Disease Control and Prevention (China CDC). According to the Law of the Infectious Disease Control and Prevention, each of the medical and health institutions in the country have to notify the cases of VL online within 24 h after the clinical cases confirmed with the diagnostic criteria of VL in China (WS258-2006), and county CDC where the patient resides will take responsibility for conducting epidemiological investigation of individual cases in 15 days after case notification in NDRIS to determine whether the patient is an autochthonic case or not, and taking counter-measures on-site according relevant guidance. The cases information reported through NDRIS includes age, gender, occupation, current residential address, symptom onset date, diagnosis date, and therapeutic outcome and so on, through which demographic distribution, geographic distribution, temporal distribution and the lag time between symptom onset and diagnosis can be analyzed. NIPD-CTDR takes the responsibility to analyze VL epidemic trend, evaluate local intervention measure and issue the epidemic analysis report to guide the prevention and control of VL.

Setting pilot monitoring site. Since 2015, pilot monitoring sites are gradually set up in accordance with epidemiological type and epidemic magnitude of the endemic area to carry out case monitoring based on NDRIS, vector surveillance and reservoir surveillance where applicable. NIPD-CTDR takes the responsibility to develop monitoring and evaluation programmes scheme and provide technical guidance, as well as evaluation. CDC at country level of monitoring sites are in charge of surveillance activities implementation. At present, the pilot monitoring of VL in China is still at the initial stage, however it could provide a favourable reference for formulating the strategies of VL control in China, especially through analysis of VL cases information reported in the NDRIS.

4.4 Training

Training of key technical personnel is critical for VL control. Since 1951, the NIPD-CTDR has been authorized by health ministry to embark on multidisciplinary training courses for health personnel. via which, thousands of trainees were trained to become proficient in dealing with patient diagnosis, clinical treatment and case management, as well as collection, identification, and control of vectors and reservoirs (Lun et al., 2015), which laid solid foundation for VL control programme in the endemic areas. In 1953, scientists from NIPD-CTDR have developed and extended IRS technology with DDT to control the vector to the whole country through national VL control technical training courses. Later a serial of diagnosis technology, technical standards for VL diagnosis and management principles, monitoring and evaluation scheme have been developed and promoted by NIPD-CTDR through regular training course every year. It plays an important role in promoting the VL control process in endemic areas in China.

5. Conclusion and way forward

The number of VL patients in China has decreased from 530,000 in 1951 to 180 in 2019, showing a remarkable achievement has been made, which is undoubtedly attributable to the control programmes that were launched over half a century ago as a national priority at an unprecedented scale of historical proportion (Wang and Wu, 1956). In the process of the control, NIPD-CTDR has made a great contribution in various aspects of VL control. AVL rampant in eastern and central plain in China in history has been eliminated. However, the remaining problems are zoonotic VL transmission mostly in mountainous and desert areas in western China, and a few remnant AVL cases in the Kashgar ancient oasis in southern Xinjiang. Thus, more efforts are required to fill the knowledge gaps. Advances are also surprisingly limited in the areas of diagnosis, for example, on asymptomatic infection in AVL endemic areas in southern Xinjiang, and what the role it plays in local VL transmission remains to be studied (Wang et al., 2006, 2007). On infected dogs culling, it is still difficult in practice for lacking sufficiently sensitive and specific diagnosis agents to identify infected dogs (Courtenay et al., 2002). On clinical diagnosis, a point-of-care biomarker is still unavailable for diagnosis of patients with relapse VL (Burza et al., 2018). In recent years, DST-VL outbreaks have occurred in southern Xinjiang. However, the wild animal host remains to be elucidated and a suitable control strategy is still unavailable for control exophilic sandfly at present (Wang et al., 2010). In MST-ZVL endemic areas, a suitable control strategy is still unavailable for control exophilic *Ph. chinesis* and more efforts are needed to develop a canine vaccine for protection of dogs. Until now, none of the four major vector species in China has been successfully colonized for laboratory breeding, as is needed for xenodiagnoses examination and other studies (Molina et al., 1994). Surveillance in the endemic areas is as necessary as new laboratory and field investigation toward better control of VL in the western regions. Epidemiological dynamics should be introduced to model and predict epidemic trend.

Strictly, MSZ-VL is a zoonotic disease with both dogs and wild animals serving as reservoir hosts, so it is impossible to completely eliminate the disease. In order to restrict the prevalence of human VL and canine leishmaniasis to very low level, the health department in endemic areas must establish a long-term combat ideology against VL, maintain a relatively stable prevention and research team, strengthen investigations and field experiments, and propose prevention methods that can be promoted and applied as much as possible to control the spread of VL to reduce the number of cases. As the increasing national and international travel related to economic development, more and more imported VL cases were reported. It is especially necessary considering the need for managing VL cases in no-endemic areas, especially, regular training of health personnel for diagnosis skills and knowledge relevant to VL under the framework of One Health concept, for doctor there usually are unfamiliar with it and leads to misdiagnosis and mistreatment. Adequate support from government is still very necessary, not only to make advances but also to maintain the past success of keeping VL under control.

What can other countries learn from China

There are numerous sites of endemicity for VL in the world widespread in temperate, subtropical, and tropical areas. So knowledge and experiences gained from the Chinese VL control programmes will be of special value to those low and middle income endemic countries. In the process of VL control programme in China, there has been gradually formulating a working environment or mechanism, which is the government-led initiative, multisector cooperation, society participation and technical support from professional institutions. Professional institutions top-down from national to village level were established in the country forming an integrated anti-VL network, and thousands of professionals were trained who became the mainstay for VL control in endemic areas. Control pilot sites were set up to explore control technology and successful experience which was extended to the whole country later. Sufficient supply of homemade highly-effective, low toxic therapeutic drugs for VL; development of a suitable therapeutic regime; and implementation of effective sandflies control aiming to ensure achieving the goal of VL elimination. The massive and effective mobilization of the general public and health workers also great contributed to the success of the control programmes. The control programmes mainly consisted of (i) massive screening to identification patients for timely treatment, (ii) identification and disposal of infected dogs, and (iii) residual insecticide indoor spraying for vector control.

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Competing interest

The authors declare that they do not have competing interests.

Authors' contributions

Z.-B. Zhou, J.-Y. Wang and X.-N. Zhou conceived the study; Z.-B. Zhou, J.-Y. Wang, C.-H. Gao, S. Han, Y.-Y. Li, Y. Zhang, X.-N. Zhou wrote and revised the manuscript; Z.-B. Zhou, J.-Y. Wang, Y. Zhang, X.-N. Zhou revised the manuscript and gave approval of the version to be published. All the authors read and approved the final version of the manuscript.

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