Contributions to the lymphatic filariasis elimination programme and post-elimination surveillance in China by NIPD-CTDR

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Abstract

China was once one of the most heavily endemic for lymphatic filariasis (LF), with a heavy disease burden. Due to decades of sustained efforts, LF was eliminated from China in 2007. The historical tales in the control and elimination of LF in China and current post-elimination surveillance are reviewed and concluded. In the course of LF control and elimination, National Technical Steering Group for Filariasis Control and Research, and Collaborating Research Group on the Transmission Threshold of Filariasis, led by the National Institute of Parasitic Diseases, carried out researches, developed control measures, and applied in practical control and surveillance. The main of the results include: in theoretical study, (1) formulating the microfilaria rate below 1% as the transmission threshold of filariasis, (2) developing anti-filarial drugs and establishing animal model for drug screening, (3) studying the vectorial capacity of mosquitoes transmitted filariasis; in clinical diagnostic and therapy, (1) developing antigens for serological diagnostics, (2) studying different administration regimes for alleviating the side-response of diethylcarbamazine (DEC), (3) studying on the recurrence of acute adenolymphangitis and lymphadenitis of malayan filariasis, (4) observing lymphoedema of the lower extremity using lymphangiography; in practical control and surveillance, (1) establishing the control strategy taking elimination of infection source as the major focus, (2) formulating safe, feasible and effective DEC-

mass drug administration, (3) revealing the transmission pattern of filariasis at the post-control phase, (4) establishing comprehensive active surveillance system, (5) formulating the criteria of basic elimination and elimination of filariasis. In the post-elimination surveillance phase, special monitoring and investigation in key areas were conducted for clearing way potential residual infection sources. Two schemes on LF surveillance in the post-elimination phase and caring for chronic filariasis patients were issued to maintain the diagnosis and treatment skills of filariasis all levels of disease control and prevention workers in future. Also, the Notifiable Diseases Reporting System, which included LF in 2004, plays an important role in LF post-elimination surveillance to prevent LF resurgence in China. The strategies and measures of LF control, elimination and post-elimination surveillance in China provide valuable practical experience and promote the progress of Global Programme of Elimination of Lymphatic Filariasis in worldwide.

Abbreviations

CDC Center for Disease Control and Prevention
DEC diethylcarbamazine
ELISA enzyme-linked immunoassay
IFAT indirect fluorescent antibody test
LF lymphatic filariasis
MDA mass drug administration
MOPH Ministry of Public Health
P/A/M provinces/autonomous regions/municipalities
WHO World Health Organization

1. INTRODUCTION

Lymphatic filariasis (LF) is a parasitic disease that seriously endangers human health, listed as the second cause of disability in the world by World Health Organization (WHO) (WHO, 1995). The Chinese government paid great effort on LF control and elimination, and included it in the long-term work plan for control of key infectious diseases in the country. Therefore, the investigation, control and elimination, and scientific research on LF were organized systematically and comprehensively in the country. After more than 50 years of intensive and sustained efforts, there were three major stages for the national LF control and elimination programme, including preparation, control, and post-control stages (Fang and Zhang, 2019). Finally, the goal of elimination of LF in nationwide was achieved by 2006, which effectively guaranteed the health of the people and promoted the development of the social economy. In 2006, Chinese Ministry of Public Health (MOPH) submitted

the National Report on the Elimination of Lymphatic Filariasis in China to the fourth global alliance for the elimination of LF, which was approved by WHO on May 9th, 2007.

After the goal of elimination of LF in nationwide achieved in 2007, several documents including *Working Program for the Morbidity Management and Disability Prevention of Chronic Filariasis Patients* and *National Monitoring Program for the Post-elimination of LF* was issued in 2010, to prevent the resurgent of LF, and provide basic personal care for morbidity in local clinical systems in the post-elimination phase (Fig. 1). These sustainable works are very important to keep our capacity in the LF surveillance and response in future. This paper aims to review the historical tales in the control and elimination stages of the LF control and elimination programmes, and synthesize the lessons learnt from the previous efforts and current post-elimination surveillance.

2. THE PREVALENCE PATTERNS OF LF IN CHINA

Before 1949, according to the limited survey, LF due to *Wuchereria bancrofti*, and *Brugia malayi* has been detected in Guangdong, Fujian, Taiwan, Zhejiang, Jiangsu, Shandong, Hunan and Hubei Provinces at that time, with severe disease burden in some places (Feng, 1936). Two large-scale of LF investigation and control programmes in nationwide began in the late 1950s and early 1970s, respectively. Scientists in our Institute, and many medical workers from health institutions, medical colleges and military medical units participated in field studies in endemic areas with great enthusiasm (Fig. 2).

In the early 1980s, entrusted by former Department of Disease Control, Ministry of Health (MOPH), the Institute drew up a detailed outline of the survey on LF, in order to collect results obtained in the two large-scale programmes from the provinces/autonomous regions/municipalities (P/A/M). In further, retrieved data was carefully checked by the collaboration between our Institute and provincial sanitary and anti-epidemic stations, and institutes of parasitic disease. Since then, the distribution and prevalence of LF in China were relative comprehensive understanding. The disease was spreading in the temperate, subtropical, and tropical zone of China from Lelin County of Shandong Province in the

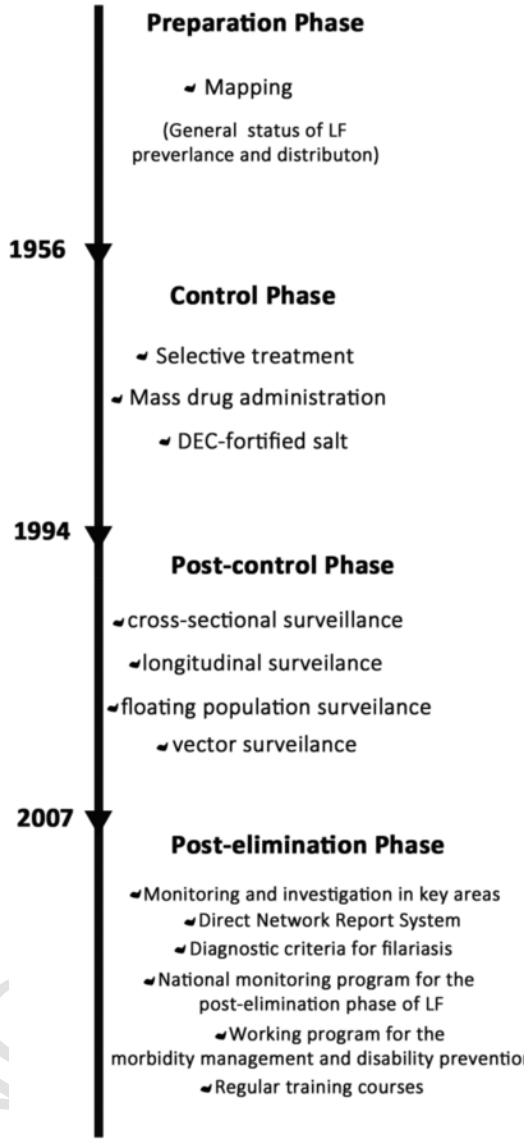

Fig. 1. The strategies implemented in each phase in the course of LF control and elimination in China. Abbreviations: DEC, diethylcarbamazine; LF, lymphatic filariasis.

north (37°48′ N), to Sanya City of Hainan Province in the south (24°10′ N), and from Zhoushan Archipelago of Zhejiang Province in the east (122°30′ E), to Ya'an City of Sichuan Province (103°E) in the west (Wang et al., 2003). It was endemic in 864 counties/cities in 16 P/

Fig. 2. Epidemiological investigations, vector control and establishment of cotton rat-filariasis animal conducted by NIPD members. (A) Prof. Lanchou Feng was catching larvae of *An. sinensis* in breeding sites (1960). (B) Catching mosquitoes inside the bed net (1965). (C) Mosquito dissection for filaria larvae detection (1965). (D) Infecting cotton rats with filaria larvae (ca. 1972). (E) Epidemiological survey on filariasis patients (ca. 1970).

A/M, including Shandong, Henan, Hubei, Anhui, Jiangsu, Zhejiang, Jiangxi, Fujian, Guangdong, Hunan, Guizhou, Hainan and Sichuan provinces, Shanghai Municipality, Chongqing Municipality, and Guangxi Zhuang Autonomous Region (Fig. 3). The total population at risk of LF in endemic areas across the country was about 342 million (National report

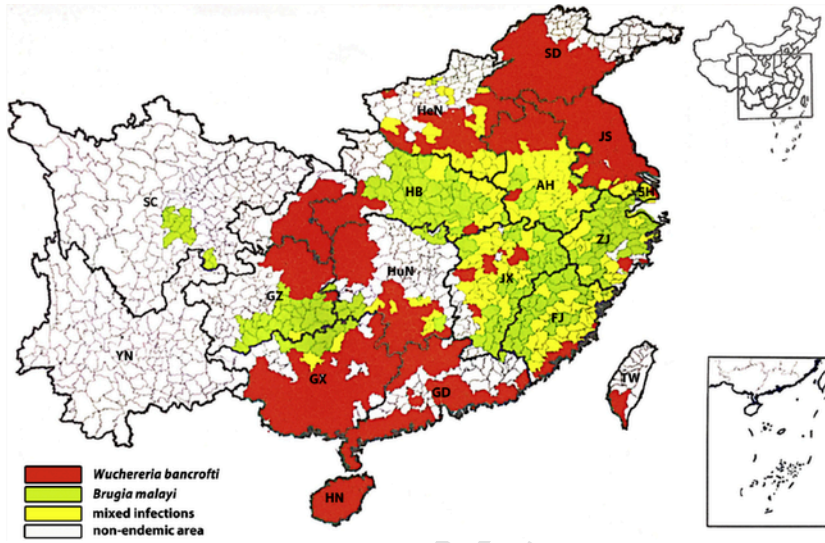

Fig. 3. The distribution of endemic areas of lymphatic filariasis in China before control was cited from a previous study (Wang et al., 2003). Abbreviations: AH, Anhui Province; FJ, Fujian Province; GD, Guangdong Province; GX, Guangxi Zhuang Autonomous Region; GZ, Guizhou Province; HB, Hubei Province; HN, Hainan Province; HeN, Henan Province; HuN, Hunan Province; JS, Jiangsu Province; JX, Jiangxi Province; SC, Sichuan Province; SD, Shandong Province; SH, Shanghai Municipality; TW, Taiwan Province; YN, Yunnan Province; ZJ, Zhejiang Province.

on elimination of lymphatic filariasis in China, 2007). Among the 864 counties/cities endemic for filariasis in China, 501 were hypo-endemic areas (microfilaria rate < 5%) and 317 were meso-endemic areas (microfilaria rate ranging from 5.1% to 20.0%), while 44 were hyper-endemic areas (microfilaria rate ranging from 20.1% to 30.0%) and two were super-endemic areas (the microfilaria rate > 30.1%).

According to epidemiological data, it was estimated that before the implementation of the national filariasis control programme in mainland China, the total number of filariasis patients (including bancroftian and malayan filariasis) was 30.994 million, while 25.594 million microfilaremia patients can be as infectious source attributed to the disease transmission, 5.4 million people have recurrent acute adenolymphangitis, lymphangitis, lymphedema, elephantiasis, chyluria, hydrocele, and other clinical manifestations, caused by LF (National Technical Steering Group for Filariasis Control and Research, 1983). In mainland China, there were 21.962 million patients with bancroftian filariasis (17.398 million with microfilaremia and 4.564 million patients with clinical manifesta-

tions) and 9.032 million patients with malayan filariasis (8.196 million patients with microfilaremia and 836,000 patients with clinical manifestations) (National Technical Steering Group for Filariasis Control and Research, 1991a).

The above survey results and data provided evidence-based information for the formulation of the national LF control programme, and evaluation and certification of LF elimination in China.

3. EPIDEMIOLOGICAL AND EXPERIMENTAL INVESTIGATIONS IN CHINA

Professor Lanchou Feng, a famous parasitologist and member of the Chinese Academy of Sciences, was the director of the Institute and chief of the Department of Filariasis Research. Based on the biological and entomological features of filariasis and prevalent characteristics, a control strategy based on elimination of infection source as the major focus was proposed by the research group led by Prof. Feng (Feng, 1933, 1936). Using the administration of diethylcarbamazine (DEC) to eliminate the source of infection as the control measure, could interrupt the LF transmission, and thereby achieve the goal of LF elimination (Feng, 1962).

Meanwhile, other members from Institute of Parasitic Diseases, Chinese Academy of Preventive (the predecessor of our Institute), Shandong, Guangxi and other Provincial Institute of Parasitic Diseases, went down to the field sites in hyper- and super-endemic areas. With the effort of several years, the experience of the strategy and measures for filariasis control obtained in a number of pilots indicated that repeated diagnosis and treatment of microfilaremia patients (selective treatment), and mass drug administration (MDA) in entire populations at-risk could reduce the microfilaria rate significantly in the human population in an economic way. It has a similar control effect to that of integrated measures, which is combined elimination of the source of infection and vector control. The integrative strategy required a major investment in human and material resources, and the effect of controlling mosquito vector was not ideal (Shi and Sun, 1983).

The suburb of Wuhan, was an originally hypro- and meso-malayan filariasis endemic area. In 1950s, after successive years (3–5 years) of extensive field investigations, and retreatment in target populations, the mi-

crofilaria rate reduced below 1%. The programme was interrupted since 1959. In 1970, surveying group entrusted by the office of National Technical Steering Leading Group for Schistosomiasis Control and Research, and MOPH, carried out blood survey in 1420 persons in local area. The results showed that after a lapse of 11 years, six microfilaremia patients were found, with the microfilaria rate of 0.4%, indicating that the control efficiency is sustained. Thus, the strategy of eliminating infection sources as the principle measure for LF control in China, supported by the practical evidence, was established.

From 1979 to 1981, as a technical personnel organized by the MOPH, members of our Institute divided into three groups to provide technology and professional training for three consecutive years, in order to verify the effect of LF control in 14 P/A/M (Hainan Province, and Chongqing Municipality have not been set up at that time) with a uniform approach. Under the direction of MOPH, national training courses on filariasis prevention and control techniques have been held by our Institute for 10 periods. In further, the Institute edited and published the *Manual of Filariasis Control*; coordinated the manufacture and supply of DEC and microscopes for filariasis control; and mobilize resources. Since 1982, under the organization of the MOPH, the Collaborating Research Group on the Transmission Threshold of Filariasis was founded. It was led by the Institute of Parasitic Diseases, Chinese Academy of Preventive, with the collaboration of relative provincial LF control organizations. According to species of filariasis, mosquito species, microfilaria rate, and microfilarial density, 21 sentinel sites in 11 P/A/M were set for longitudinal surveillance after intervention. The results showed that in endemic areas, where the microfilarial density was low in residual microfilaremia cases, when the microfilariae rate was $\leq 1.71\%$ in areas with bancroftian filariasis prevalence and $\leq 1.5\%$ in areas with malayan filariasis prevalence, which meant that transmission could no longer be sustained. The microfilaria rate had been declined to below 1% in the human population in most administrative villages after LF control. Obviously, filariasis transmission has already dropped down below the transmission threshold of filariasis, adopted in the LF control strategy. This study provided important theoretical basis for formulating technical strategies for LF surveillance in areas where filariasis had been basically eliminated, and developing strategies and criteria for LF elimination (Collaborating Research Group on the Transmission Threshold of Filariasis, 1994).

In further, the transmission threshold of filariasis has been evidenced by the results of surveillance obtained from the sentinel sites. Though several years of study it was found that in areas where filariasis had been basically eliminated, the microfilaria density in most residual microfilaremia patients and natural filarial infection in mosquitoes would decrease year by year. Majority of the residual microfilaremia patients, even do not receive drug treatment, could gradually turn to negative in 10 years. By 1994, all of the 864 endemic counties/cities had reached the criterion for the basic elimination of filariasis (Table 1). Since then, the strategy and criteria for the final elimination of filariasis were formulated. A comprehensive and active surveillance system, combining with longitudinal and cross-sectional surveillance was conducted in areas achieved basic filariasis elimination (National Technical Steering Group for Filariasis Control and Research, MOPH, 2002). Assessment of the elimination of filariasis in originally endemic areas, was strictly performed according to the *Criteria for Filariasis Elimination*, in order to achieve the goal of LF elimination in national wide.

The *Criteria for Verification of Elimination of Filariasis* (trial) and *Verification of Elimination of Filariasis* (trial) was issued by MOPH in 1994 and implemented in 1996. The *Criteria for Verification of elimination of filariasis* (trial) included the following major points. By county or equivalent administrative region as a unit, through provincial level assessment, filariasis transmission has been interrupted (basic elimination) for more than 10 years: (1) parasitological surveillance covers 3% of the total population in 30% of the endemic towns or townships, no microfilaremia case was found; and (2) no human filarial larva infection was detected in mosquitoes. The content about the survey, treatment, and caring of chronic patients of filariasis has been added in the *Criteria for Elimination of Filariasis* issued by State Administration for Market Regulation and State Standardization Administration.

As the major drafters, scientists in our Institute participated in research and formulation of three national standards, *Criteria for Elimination of Filariasis* (GB20048–2006), *Diagnostic Criteria and Principles of Management of Filariasis* (GB15985–1995), and *Diagnostic Criteria for Filariasis* (WS260–2006).

TABLE 1 Time of each previous endemic province (autonomous regions/municipalities) achieved basic elimination and elimination of filariasis through national assessment.

Province	Year achieved basic elimination	Year achieved elimination	References
Guangxi	1985	1995	Pan et al. (1992), Pan et al. (1995)
Guizhou	1984	1996	Liu et al. (2002), Tao et al. (1987)
Shanghai	1984	1996	Ji et al. (1991)
Sichuan	1986	1997	Wei et al. (1994), Zhang (2004), Zhang et al. (1993), Zhang et al. (2001), Zhang et al. (2002b), Zhu (1990)
Chongqing	1986	1997	Li et al. (2002)
Hunan	1986	1997	Deng et al. (2008), Duan (2001, 2004), Duan et al. (2001)
Jiangsu	1989	1998	Liu (1990), Sun et al. (2001), Xu et al. (2008)
Guangdong	1987	2000	Huang et al. (1995), Huang et al. (2003), Huang et al. (2004b), Ou (1990)
Hubei	1988	2001	Pei and Zhang (1996), Peng et al. (2000), Zhan et al. (2012), Zhang (1990)
Zhejiang	1989	2001	Wang et al. (1989), Yao et al. (2002)
Fujian	1988	2002	Lin et al. (1996), Liu et al. (1989), Liu et al. (1990), Liu and Liu (1984)
Shandong	1983	2004	Cui et al. (1984), Deng and Chen (2002), Sheng et al. (1995), Wang (2005)
Henan	1987	2004	Chang et al. (1992), Lin et al. (2005), Ru et al. (1991), Xu et al. (2002), Zhao et al. (1992)

TABLE 1 (Continued)

Province	Year achieved basic elimination	Year achieved elimination	References
Jiangxi	1990	2005	Liu et al. (1991), Zhang et al. (2002a), Zhang et al. (2006a,b)
Hainan	1987	2005	Hu et al. (2008), Wu et al. (1990), Wu et al. (1997), Wu et al. (2003a)
Anhui	1994	2006	Chen et al. (2007), Hu et al. (2009), Zou et al. (1996), Zou et al. (2002)

4. RESEARCH AND DEVELOPMENT OF CONTROL TOOLS, INCLUDING DIAGNOSTICS AND MDA DRUGS

4.1. Study on the transmission threshold of filariasis

In 1982, the MOPH approved the study of the transmission threshold of filariasis as a key project. A unified research method was designed and formulated by Collaborating Research Group on the Transmission Threshold of Filariasis. Twenty-one representative sentinel sites were selected in 10 provinces, and one autonomous region. All the sentinel sites were in previously hyper-endemic areas where the microfilaria rate in the population had decreased to a low level through LF control with DEC administration. Four levels were set according to the microfilaria rate in population: 0.5%, 1.0%, 1.5%, and 2.5%. Three levels were set by the mean microfilaria density per 60 μL peripheral blood: < 5, 5–10, and > 10. The dynamics of the microfilaria rate and residual microfilaremia cases in populations from different levels were systematically observed after interruption.

The research results from the 21 sentinel sites were collected, analysed and concluded by the Collaborating Research Group on the Transmission Threshold of Filariasis in 1994. It was demonstrated that after intervention, where the man-biting rate of mosquito vectors

was within 20–50 mosquito/person/night, and about 40% of the population used bed-nets seasonally, the microfilaria rate in the 20 sentinel sites was found to be below 1.71% in bancroftian filariasis endemic areas, and it was below 1.55% in endemic areas of malayan filariasis. The mean microfilaria density in residual microfilaremia cases in most sites was below 10/60 μL blood. The microfilaria rate in population and the positive rate of filarial larvae in mosquito vectors would decrease year by year, and the filariasis transmission tended to be interrupted. The above results confirmed that the microfilaria rate below 1% in the population of an administrative village, which is the criterion for the basic elimination of filariasis, is less than the transmission threshold of filariasis in field.

The achievement obtained in the study on the transmission threshold of filariasis has been proved in the large scale filariasis control campaign (Table 2). Through strict evaluation, the results of the systematic surveillance showed that all the 16 LF endemic P/A/M had reached the criteria of filariasis elimination until January 2006.

4.2. Pathogen biological research

4.2.1. Comparative studies on the morphology of larva stage of four species of Setaria and Dirofilaria repens

The filaria larvae in mosquito vectors in China are mainly from cattle, horse and dog. During 1986–1987, to distinguish the species of filarial larvae in vectors in filariasis epidemiological investigation and surveillance, our Institute cooperated with Hunan provincial sanitary and anti-epidemic station, and Xiangxi Tujia and Miao autonomous prefectural sanitary and anti-epidemic station, used the infective larvae of *Setaria* (*S. labiatopapillosa*, *S. erschovi*, *S. equina*, and *S. leichungwingi*), and *D. repens* to infect laboratory strains of *Anopheles sinensis* and *Culex pipiens pallens* (Li et al., 1989). The morphology of different larval stages of the above filaria was described. In further, with the addition of *W. bancrofti*, *B. malayi*, *D. immitis*, and *S. digitate,* the identification key of nine common filariae in the infective stage in mosquitoes was compiled.

4.2.2. Establishment of the animal model of cotton rat-filariasis

For screening anti-filariasis drugs, cotton rat-filaria model consisting of cotton rats (*Sigmodon hispidus*) infected with *Lito-*

TABLE 2 Studies on the role of low density microfilaremia cases in the transmission of filariasis in late stage of filariasis control in China.

Time	Endemic area	County/ village	Province	Microfilaria rate	Microfilaria density	No. people	Trans-negative rates	References
1988–1992	Bancroftian filariasis	Jiaoshang Village	Jiangxi	5.33% (70/1257, 1986)–0% (0/1144, 1989)–0% (0/1244, 1992)	≥ 50/60 μL	3	33.33% (4th year)	Fang and Zheng (2002)
					6–50/60 μL	3	100% (4th year)	
					≤ 5/60 μL	3	100% (4th year)	
1981–1986	Malayan filariasis	Deqing County	Zhejiang	0.53% (5/945, 1981)	4.2/60 μL (1–8)	5	100% (4th year)	Shi et al. (1988)

TABLE 2 (Continued)

Time	Endemic area	County/ village	Province	Microfilaria rate	Microfilaria density	No. people	Trans-negative rates	References
	Bancroftian filariasis	Queshan County	Henan	14.96% (1982)–1.04% (87/8329, 1984)–0.20% (15/7320)	0.5–29.5/ 60 μL	87	82.9% (3rd year)	
1982–1985	Malayan filariasis	Linhai City	Zhejiang	< 0.5%	1–10/60 μL	11	90.9% (5th year)	Li et al. (1987)
1984–1988	Bancroftian filariasis	Pingle Village, Yining County	Guangxi	0.5% (1983)–0.34% (1986)–0% (1988)	34.4/60 μL (1–62)	5	100% (5th year)	Pan et al. (1990)

TABLE 2 (Continued)

Time	Endemic area	County/ village	Province	Microfilaria rate	Microfilaria density	No. people	Trans-negative rates	References
1982–1996	Bancroftian filariasis	Xiangxi Autonomous Prefecture	Hunan	0.396% (1982)–0.086% (1986)–0.005% (1991)–0% (1996)	27.5/60 μL	1	0% (5th year)	Zhang et al. (1999)
					43/60 μL	1	0% (5th year)	
					≤ 7/60 μL	7	100% (5th year)	

TABLE 2 (Continued)

Time	Endemic area	County/ village	Province	Microfilaria rate	Microfilaria density	No. people	Trans-negative rates	References
1984–1993	bancroftian filariasis	Tan County	Shandong	0.56% (9/1611, 1984)–0.64% (11/1707, 1986)–0.33% (5/1538, 1989)–0.12% (2/1680, 1993)	6–50/60 μL	4	75% (5th year)	Wang et al. (1997)
					≤ 5/60 μL	5	60% (5th year)	

TABLE 2 (Continued)

Time	Endemic area	County/ village	Province	Microfilaria rate	Microfilaria density	No. people	Trans-negative rates	References
1986–1989	Malayan filariasis	Xiantao City	Hunan	1.55% (1986)–0.84% (1987)–0.42% (1988)–0.31% (1989)	≥ 50/60 μL	1	100% (3rd year)	Guo et al. (1989)
					6–50/60 μL	1	0% (3rd year)	
					≤ 5/60 μL	19	89.47% (3rd year)	

TABLE 2 (Continued)

Time	Endemic area	County/ village	Province	Microfilaria rate	Microfilaria density	No. people	Trans-negative rates	References
1984–1993	Bancroftian filariasis	Erketuo Village	Hunan	19% (19/100, 1984)–1.3% (1/79, 1986)–1.8% (2/112, 1990)–0% (1991)–0% (1993)	6–50/60 μL	2	50% (7th year)	Luo et al. (1996)
1982–1985	Bancroftian filariasis	Zou County	Shandong	0.08% (4/4597, 1982)–0% (1984)	≤ 5/60 μL	4	100% (3rd year)	Song and Ma (1988)

TABLE 2 (Continued)

Time	Endemic area	County/ village	Province	Microfilaria rate	Microfilaria density	No. people	Trans-negative rates	References
1984–1996	Bancroftian filariasis	Leshan City	Sichuan	1.29% (46/3554, 1984)–1.01% (36/3569, 1985)–0.33% (12/3599, 1987)–0.14% (5/3621, 1988)	≥ 25/60 μL	3	66.7% (3rd year)	Zhang et al. (1996)
					6–25/60 μL	12	100% (7th year)	
					≤ 5/60 μL	55	98.2% (7th year)	

mosoides carinii, and rat mites (*Ornithonyssus bacoti*) were introduced in 1972 through the courtesy of the Swiss scholar, Dr. Friedheim (Xi et al., 1979). Since then, the model has been well maintained in NIPD to screen known or newly synthesized compounds and herbs. The effective drug DEC for filariasis treatment was found subsequently.

4.2.3. Studies on the transmission of malayan filariasis via An. sinensis and An. lesteri

In the late 1950s and early 1960s, two types of the primary malayan filariasis vector, *An. sinensis* were found in thorough studies of the classification of the *An. hyrcanus* group and the relationship between some species of this group and filariasis (Zhang et al., 1964). Two types of *An. sinensis* are significantly different in their role in the transmission of malayan filariasis (Feng and Ma, 1956). The survey (Zhang et al., 1964) in the two malayan filariasis endemic areas, Wujiang County in Jiangsu Province and Yihuang County in Jiangxi Province showed that the natural infection rates of filarial larvae in *An. sinensis* were 28.0%, and 22.1% respectively in the above two areas. And the positive rates of natural infection with L3 *B. malayi* were 1.5%, and 1.9%, respectively. While the natural infection rates to filarial larvae of *An. lesteri* was 47.6%, with natural infection of L3 larvae was 12.9% in Wujiang; and the natural infection rates to filarial larvae of *An. lesteri* was 40.7%, with natural infection of infective larvae L3 was 5.8% in Yihuang. In addition, the positive rates of experimental infection with L3 in *An. sinensis* and *An. lesteri* were close, which were 83.7%–95.7%, and 94.3%–95.5%, respectively. *An. lesteri* is an indoor-resting species, prefers human blood, while *An. sinensis* is a semi-indoor resting species, fed on humans, poultry and other animals, but prefers animal blood (Wang and Zheng, 1989). Since *An. lesteri* is much more closely related to the human being, it is more important than *An. sinensis* in the transmission of malayan filariasis.

4.2.4. Study on the susceptibility of An. lesteri to experimental infection with W. bancrofti

In the literatures on the relationship between *An. sinensis* (*s.l.*) and filariasis published before 1950s, *An. lesteri* was mixed in the mosquito samples in some sympatric places of both species. To illuminate the

role of *An. lesteri* in the transmission of bancroftian filariasis, study on the susceptibility of *An. lesteri* to experimental infection with *W. bancrofti*, comparing with that of *An. sinensis*, *Cx. p. quinquefasciatus*, and *Aedes togoi* was conducted (Xu et al., 1993). Of 188 *An. lesteri*, 202 *An. sinensis*, 280 *Cx. p. quiquefasciatus* and 129 *Ae. togoi* infected by the blood of a bancroftian microfilaremia patient with microfilarial density of 190/20 μL, the infective rates were 35.64%, 9.41%, 30.00%, and 65.98%, respectively; while of 188 *An. lesteri*, 134 *An. sinensis*, 289 *Cx. p. quinquefasciatus* and 176 *Ae. togoi* infected by the blood of another bancroftian microfilaremia with microfilarial density of 83/20 μL, the infective rates were 18.09%, 3.73%, 13.84% and 39.77%, respectively. It is concluded that the susceptibility of *An. lesteri* to experimental infection with *W. bancrofti* is significantly higher than that of *An. sinensis*, significantly lower than that of *Ae. togoi*, and at the same level with that of *Cx. p. quinquefasciatus*.

4.3. Research of the pathogenesis of filariasis

4.3.1. Study of the recurrence of acute adenolymphangitis and lymphadenitis of malayan filariasis

To clarify the impact of filarial and bacterial infection on the acute adenolymphangitis and repeated lymphadenitis, our Institute carried out relative studies in malayan filariasis endemic areas, Zhenze commune of Wujiang County in Jiangsu Province, and Miaoxi commune of Wuxing County in Zhejiang Province, during 1961 to 1973. The results showed that (1) the acute attacks had a clear seasonal fluctuation. The transmission season of filariasis coincided with the vector activity season. In Zhenze, a patient with historical lymphadenitis, stopped attacking of lymphadenitis for up to 35 years after leaving the endemic area, but re-attacked every year when back to the original living place. It indicates that the seasons of onset of lymphadenitis probably associate with the repeated infection of infective filarial larvae, transmitted by mosquitoes. (2) In the majority of patients with acute adenolymphangitis, except in the abscess, bacteria were absent in inflammatory site (Xie and Yuan, 1987). In the serum antistreptolysin 'O' titer assay on target patients, the antistreptolysin 'O' titer only increased 27.2% in cases of elephantiasis complicated with acute adenolymphangitis. Whereas cases with primary adenolymphangitis and lymphadenitis, and simple ade-

nolymphangitis and lymphadenitis without the complication of elephantiasis, the antistreptolysin 'O' titer hardly increased. This suggests that bacterial infections, especially hemolytic streptococcal infections, were not the cause of acute adenolymphangitis. In a small number of patients with elephantiasis, it is one of the factors in complex aetiology. (3) After the filariasis transmission has been effectively controlled, not only in cases with primary adenolymphangitis and lymphadenitis, and simple adenolymphangitis, but also in cases with elephantiasis complicated with acute adenolymphangitis, the inflammatory attack was decreased significantly, indicating that repeated inflammatory attack is related to the filariasis transmission. (4) The positive effect of treatment against adult filaria to reducing inflammatory attack has not been found. It is included that in the endemic areas of bancroftian filariasis, the recurrent acute adenolymphangitis and lymphadenitis is mainly caused by the existence of filariasis transmission, induced by repeated infection of infective larvae injected in the human body.

4.3.2. Observation of lymphoedema of the lower extremity using lymphangiography

To understand the mechanism of leg lymphoedema caused by malayan filariasis, in endemic areas of malayan filariasis, located at the border of Wuxing County in Zhejiang Province and Wujiang County in Jiangsu Province, our Institute, collaborating with the Chinese People's Liberation Army 99 Hospital, started to observe lymphoedema of the lower extremity using lymphangiography, in selected elephantiasis cases caused by malayan filariasis (Sun et al., 1964). Twelve lower extremities of nine patients were observed, including three main types (1) one with no experience of acute adenolymphangitis or lymphadenitis (the other one with experience of acute adenolymphangitis or lymphadenitis, and lymphedema), (2) three with experience of acute adenolymphangitis or lymphadenitis, and no lymphedema, (3) eight with both lymphedema, and experience of acute adenolymphangitis or lymphadenitis (disease of duration ranging from 2 to 16 years). The technology of direct lymphangiography on superficial lymphatic vessels was performed. First, 3–5 mL 0.4% indigo carmine was injected subcutaneously in toe-webs. Then, find subcutaneously dyed blue peripheral lymphatic vessels after small transverse incision on the middle of dorsum pedis, and inject 5–18

mL sodium acetrizoate as contrast media. X-ray anterior, lateral views were performed on each patient from foot to groin.

In the case of type 1, contrast agent leaked to surrounding subcutaneous tissue in a lumpy way. In cases of type 2, lymphatic contortion and mild collateral hyperplasia were visualized in the lower limb of one lower extremity. Whereas, contrast agent only raised to 1/3 of the low limb in the other two lower extremities. In cases of type 3, seven legs showed lymphatic varicose in different degree, with following characteristics: the obvious phenomenon of lymphatic contortion collateral hyperplasia, enlarged and unevenly thicken lymphatic spaces, indistinguishable trunk and the lateral branch of lymphatic vessels, unorganized distribution of lymphatic vessels. In severe cases, the lymphatic vessels representing as spider network with the disappearance of valve shadow. Contrast media back flowed to the distal lymphatic vessels and leaked in subcutaneous tissue. The degree of lymphatic varices was consistent with the patient's clinical manifestation. The distal portion of the extremity was the most severe part. Femoral lymphatic vessels were observed in four lower extremities. Inguinal lymph nodes, linking with the afferent lymphatic vessel, were visualized in two of them, with clear contour. Thickening fibrosis in the subcutaneous tissue of foot was observed in one lower extremity with severe elephantiasis.

The above results suggest that there are two main reasons, which may cause lymphoedema of the lower extremity in patients with malayan filariasis. One is that repeated attacks of adenolymphangitis and lymphadenitis would induce different degrees of obstruction of the lymphatic vessel and a change in the circulation dynamics of lymph, resulting in backflow obstruction of lymph, followed by the appearance of lymphedema in the related extremity. The other is that granulation tissue proliferation, and fibrosis inside the lymphatic vessels would cause lymphatic obstruction, and result in lymphoedema of the lower extremity.

4.4. Research of diagnostic methods

4.4.1. Four antigens were used to diagnose filariasis by intradermal test

Since 1973, the study on the serological diagnostic techniques was started to carry out. Four prepared polypeptide antigens, including adult *D. immitis* polypeptide antigen (DFPT), adult *Setaria* sp. polypeptide antigen (SFPT), and other two adult *Setaria* spp. polypeptide anti-

gens ($SFSC_1$ and $SFSC_4$) isolated and purified to evaluate the effect of purified antigen from animals to filariasis diagnostic by intradermal tests. The study was performed in the malayan filariasis endemic area (Wuxing County of Zhejiang Province), non-endemic area (Chongming County of Shanghai Municipality, and Fushan County of Shandong Province), and bancroftian endemic area (Teng County of Shandong Province). The intradermal test results were compared with that performed in local microfilaremia patients.

Serum samples for malayan microfilaremia detection were diagnostic by the four antigens, DFPT, SFPT, $SFSC_1$, and $SFSC_4$, with 94.1% (176/187), 87.5% (35/40), 74.0% (37/50), and 78.3% agreement to results of the blood test, respectively. While in samples for bancroftian microfilaremia detection, the results of the serological method using DFPT, SFPT, and $SFSC_1$ antigens were 88.3% (136/154), 73.6% (39/53), and 44.9% (22/49) agreed to that of the blood test. In microfilaremia negative populations from non-endemic areas, the false positive rate of DFPT antigen was 4.8%, and 9.6% in Chongming County, Shanghai, and Teng County, Shandong Province, respectively. In Chongming, the false-positive rates of SFPT, $SFSC_1$, and $SFSC_4$ in microfilaremia negative populations were 33.5%, 20.8%, and 76.9%, respectively. In Teng County, the false-positive rates of SFPT, and $SFSC_1$ in microfilaremia negative populations were 26.1%, and 5.0%, respectively. In crossover test, the DFPT antigen showed 6% (3/50) false-positive cross-reactions with sera from patients infected by schistosomiasis, and 8.6% (2/23) false-positive rate with sera from patients infected by hookworm and whipworm.

4.4.2. Application of intradermal test in the evaluation of filariasis longitudinal surveillance

Intradermal test with the filariasis polypeptide antigen (FPT) purified from *D. immitis*, as a donation from Guizhou Provincial Institute of Parasitic Disease, was applied in two villages of Queshan County in Henan Province for longitude surveillance from 1982 to 1987, in order to trace the dynamic of filarial specific anaphylaxis level in populations before and after the implementation of DEC mass chemotherapy for the whole population. The two administrative villages Zhaozhuang and Zhongdian were located in meso- bancroftian endemic area treated as two sentinel sites in the survey.

The microfilaria density in populations of Zhaozhuang and Zhongdian were 9.98% and 18.66%, respectively, in the whole population blood survey conducted in 1982. The control strategy of treatment of microfilaremia cases followed by DEC-fortified salt for the whole population was implemented since May 1983. After intervention in May 1984, the microfilaria density decreased to 0.42% and 1.75% in populations of Zhaozhuang and Zhongdian, respectively. With the residual microfilaremia cases gradually turned to negative, the microfilaria density in populations continued to decline, and down to 0.05%, and 0.42% in populations of Zhaozhuang and Zhongdian, respectively, in May 1986.

The diameter of skin papule exceeds 9 mm after injection of antigens, as a positive criterion in intradermal test. Surveys by the intradermal test in spot-check sites were conducted in October 1982 (before control), September 1983 (5 months after control), and May 1987 (4 years after interruption). In the three surveys, the positive rates in populations from Zhaozhuang were 48.9%, 35.4%, and 20.6%, respectively, and 63.2%, 43.7%, and 19.4%, respectively in Zhongdian. The results showed that the positive rates of filarial specific anaphylaxis in populations from both spot-check sites started to decline sustainably after the implementation of selective treatment and MDA.

The false-positive rate of the serological diagnostic in non-endemic areas was approximately 5%, indicating that the method may not be sensitive in the lower age group, which is reflecting in the results in the field survey. No significant change in positive rate has been observed in the group with 1–4 years old children, comparing with the results of surveys, conducted in 1982 and 1987. Whereas the mean diameter of skin papule obviously appeared declining in this group before and after the control. If setting the diameter of skin papule exceeds 13 mm as a significant positive criterion, the positive rate in populations from Zhaozhuang was declined significantly from 19.1% to 3.0%, since 1982 to 1987, and it declined from 29.5% to 2.5% in Zhongdian. The serologic test result showed negative in a few persons in the primary survey, while turned to positive in the tracing surveys from 1983 to 1987. The annual positive conversion rate can reflect the level of filariasis transmission in a period. Thus, the dynamic of annual positive conversion rate is one indicator to evaluate the control effect. In conclusion, the positive rate, significant positive rate, and annual positive conversion rate obtained from the intradermal test of FPT antigen in the population can be a valuable refer-

ence to evaluate the filariasis transmission level and tendency in duration, in a systematic and comprehensive way.

4.4.3. Studies on detection anti-filarial antibodies by dot-enzyme-linked immunoassay (Dot-ELISA)

In order to improve the accuracy and sensitivity serological diagnosis of filariasis, Dot-ELISA was carried out in the late 1980s to detect anti-filarial antibodies. In further, the comparative study among Dot-ELISA, and other two methods indirect fluorescent antibody test (IFAT) and ELISA, which had been widely used in China at that time, was conducted for detecting antibody levels in bancroftian microfilaremia patients. The conjugate, carrier, and substrate of dot-ELISA were Horseradish peroxidase Rabbit Anti-Human IgG, nitro cellulose membrane, and 4-chloro-1-neophenol, respectively. Negative, positive and TBS controls were set in each experiment. The appearance of the blue spot on the membrane was determined as a positive reaction. Serum samples were collected from patients with *B. malayi* microfilaremia in Anhui Province and patients with *W. bancrofti* microfilaremia in Jiangxi Province. In addition, sera of healthy persons from non-endemic areas in Shanghai were selected as the negative control. Serum samples of patients with schistosomiasis from non-endemic areas in Jiangxi Province and samples of co-infection with hookworm and ascaris from non-endemic areas in Henan Province were chosen for cross-reaction test. The results showed the positive rates of the sera from 62 *B. malayi* microfilaremia patients, and 49 *W. bancrofti* microfilaremia patients were 96.8%, and 85.7%, respectively; while in 50, and 39 healthy individuals the false-positive rates were 4.0%, and 5.1%, respectively. In 18 patients with schistosomiasis, and 39 patients with hookworm and ascaris, the false-positive rates were 5.6%, and 17.9%, respectively (Yuan et al., 1992). It indicates that this method was highly sensitive, simple and convenient, and might be suitable for serological surveillance of filariasis. Dot-ELISA is simple, sensitive, and saving the use amount of antigen. Additionally, the reaction results can be identified by the naked eye and don't have to use a special instrument. It could be used for monitoring the control of filariasis transmission. However, there were some cross-reactions with the sera of persons infected with hookworm and ascaris.

A comparative study was conducted for detecting antibody levels of *W. bancrofti* microfilaremia cases by using three serologic tests,

IFAT, ELISA and dot-ELISA (Sun et al., 1994). IFAT was performed with the frozen sectional antigen of adult *B. malayi*. While adult *B. malayi* soluble antigen was used for ELISA. A total of 102 serum samples were collected from *W. bancrofti* microfilaremia cases in bancroftian filariasis endemic area in Guzhen County, Anhui Province. The positive rate was 89.2% with IFAT, 84.3% with ELISA, and 89.2% with dot-ELISA, respectively. While in healthy individuals from non-endemic areas, the false-positive rate was 0%, 1.8%, and 0%, respectively. The results suggested that there were no statistically significant differences among three serologic tests, and no correlation was found in this study between microfilaria density and the antibody level. Therefore, all the three methods can be used to monitor the trend of the antibody level in the population for post-control surveillance. Each sentinel site can choose the method for the serologic test, according to its own conditions and the advantages and disadvantages of each method. The results can be compared with each other.

In further, other sero-epidemiological diagnostic methods have been used in post-control (after basic elimination) and post-elimination phase in China for filariasis surveillance (Table 3). Additionally, DNA probe was applied for *W. bancrofti* identification in vectors for filariasis surveillance in the late stage of post-control phase (Huang et al., 2000; Zheng et al., 1992).

4.5. Study on anti-filarial drugs and treatment methods

4.5.1. Development of anti-filarial drugs

The National of Bureau of Medical Pharmaceutical Administration and the Shanghai Academy of Pharmaceutical Industry cooperated with the Shanghai Institute of Parasitic Diseases to study new anti-filariasis drugs. Several thousand chemical compounds were screened. Through experimental tests on animals, it was found that furapyrimidone (M170) could not only kill *L. carinii* microfilaria and adult worms, but also *B. malayi* microfilaria and adult worms in the blood and abdominal cavity in jirds, especially in killing the adult *L. carinii*. By the end of 1979, our Institute cooperated with the Shandong Institute of Parasitic Diseases in clinical trials, and then Guangdong, Hubei, Jiangsu, Henan, Zhejiang, Fujian, Jiangxi, Shandong and Shanghai provinces/cities continued further clinical observations. Till 1983, 981 cases had been treated. Among

TABLE 3 Sero-epidemiological diagnosis for filariasis detection in post-control (after basic elimination) and post-elimination phase in China.

Method	Test principle	Subjects			Purpose of use in LF control and elimination in China	Technical difficulty	Cost	Referen
		Sensitivity	Specificity					
		Microfilaremia	Control	Patients infected by other parasites				
ICT card	Antigen (finger prick)	95.7% (111/116)	0% (71)	0% (12 malayan filariasis, 33 ascaris, 20 schistosomiasis, 6 trichinosis)	case diagnosis, monitoring and investigation in key areas after the elimination	+	+++	Zheng e (1998)

TABLE 3 (Continued)

Method	Test principle	Subjects			Purpose of use in LF control and elimination in China	Technical difficulty	Cost	Referen
		Sensitivity	**Specificity**					
		Microfilaremia	Control	Patients infected by other parasites				
		88.24%–93.33% (15/17, 14/15, 11/12)	0% (69)					He et al (1999)
		94.92% (56/59)	0% (40)	0% (30 cysticercosis, 25 clonorchiosis)				Deng et (2000)

TABLE 3 (Continued)

Method	Test principle	Subjects			Purpose of use in LF control and elimination in China	Technical difficulty	Cost	Referen
		Sensitivity	Specificity					
		Microfilaremia	Control	Patients infected by other parasites				
(McAb)-ELISA	Antibody (venous blood)	96.61% (57/59)	0% (40)	0% (30 cysticercosis, 25 clonorchiosis)	Systematic surveillance in previous endemic areas in post-control and post-elimination phase	++	+	Deng et (2000)

TABLE 3 (Continued)

Method	Test principle	Subjects			Purpose of use in LF control and elimination in China	Technical difficulty	Cost	Referen
		Sensitivity	**Specificity**					
		Microfilaremia	Control	Patients infected by other parasites				
		94.1% (64/68)	0% (38)	0% (60, each 10 of schistosomiasis, ascaris, cysticercosis, clonorchiosis, hydatidosis, paragonimiasis)				Huang (2004a)

TABLE 3 (Continued)

Method	Test principle	Subjects			Purpose of use in LF control and elimination in China	Technical difficulty	Cost	Referen
		Sensitivity	**Specificity**					
		Microfilaremia	Control	Patients infected by other parasites				
		97.10% (67/69)	3.66% (3/82)	17.65% (6/34, children borne after control) 12.50% (6/48, control from original endemic areas) 18.03% (11/61, previous microfilaremia cases)				Wang a Gao (19

TABLE 3 (Continued)

Method	Test principle	Subjects			Purpose of use in LF control and elimination in China	Technical difficulty	Cost	Referen
		Sensitivity	**Specificity**					
		Microfilaremia	Control	Patients infected by other parasites				
		95.91% (47/49)	0% (50)	0% (77 chronic filariasis) 0% (30 intestinal helminthes, 20 clonorchiosis, 20 cysticercosis)				Xu et al (1996)

TABLE 3 (Continued)

Method	Test principle	Subjects			Purpose of use in LF control and elimination in China	Technical difficulty	Cost	Referen
		Sensitivity	**Specificity**					
		Microfilaremia	Control	Patients infected by other parasites				
		96.3% (104/108)	0% (90)	0% (302, children born after control) 0.30% (10/3291, population in previous endemic area) 0% (132, chronic filariasis) 0.78% (1/129, previous microfilaremia but turn negative) 0% (30 intestinal helminthes, 45 clonorchiosis, 50 cysticercosis)				Chen et (2002)
ELISA	Antibody (venous blood)	92.64% (63/68, malayan filariasis) 83.33% (70/84, bancroftian filariasis)	1.24% (2/161)		Sentinel site surveillance in previous endemic areas in post-control phase	+++	++	Deng et (1986)

		87.8% (79/90)	1.63% (2/123)					Li et al. (1993)
IFAT	Antibody (venous blood)	97.50% (39/40)	2.44% (2/82)	13.33% (10/75, chronic filariasis) 4.44% (2/45, children born after control) 16.31% (46/282, floating population)	Sentinel site surveillance in previous endemic areas in post-control phase	++	+	Zou et a (1995)
		87.2% (20, malayan filariasis) 97.1% (105, bancroftian filariasis)	6.55% (62)	0% (7 hookworm, 30 ascaris, 20 suspected schistosomiasis)				Li et al. (1988)
		93.88% (92/98, malayan filariasis) 90.48% (38/42, bancroftian filariasis)	3.6% (4/111)	3.23% (1/31, children born after control)				Jiang an Zhong (1990)

	86.8% (99/114)	1.57% (3/191)	0% (54, more than one parasite of hookworm, ascaris, or trichuriasis) 0% (96, pneumonia)		Ji et al. (1988)
	89.2% (91/102)	0% (0/30)			Sun et a (1994)
	99.1% (226/228, malayan filariasis) 92.8% (412/444, bancroftian filariasis) 96.9% (31/32, chronic filariasis)	99.3% (149/150)			Wang e (1987)

Dot-ELISA	Antibody (venous blood)	96.8% (60/62, malayan filariasis) 81.6% (40/49, bancroftian filariasis)	4.0% (2/50) 5.1% (2/39)	0% (20, schistosomiasis) 5.1% (2/39, schistosomiasis) 17.8% (8/45, hookworm and ascaris) 17.9% (7/39, hookworm and ascaris)	Sentinel site surveillance in previous endemic areas in post-control phase	++	++	Yuan et (1992)
		89.2% (91/102)	0% (54)					Sun et a (1994)

The rating of technical difficulty is based on the steps of the test and the time required, with '+' lowest and '+++' highest. Cost ratings are based on the cost of materials, laboratory equipment is not included. The control group is healthy person from non-endemic area. Abbreviations: ELISA, enzyme-linked immunoassay; ICT, immunochromatorgraphic test; IFAT, indirect fluorescent antibody test; LF, Lymphatic filariasis.

them, 755 cases were bancroftian filariasis and 266 cases were malayan filariasis. The results showed that using M170 in a total dose of 140 mg/kg body weight for 7 days had a good effect on bancroftian microfilaria and adult worms. The effect was better than using the DEC standard dose in long-term or short-term treatment. Therapy consisting of M170 total dosage of 120 mg/kg body weight for 6 days in malayan filariasis did not have a good effect. The general side reaction was similar to DEC, and vomiting usually occurred. When the total dosage was increased to 200 mg/kg body weight, many patients showed significantly increased serum glutamic pyruvic transaminase, which indicated that a large dosage could damage the liver (Ren and Wang, 1984; Wu, 1984). Pharmacological studies found that a large dosage was toxic on rat embryos. TA_{100} and TA_{98} could be mutations. Finally, M170 was not submitted for production.

4.5.2. Study on alleviating the therapeutic response of DEC

DEC is known to be an effective therapeutic drug for filariasis, with low toxicity. The side reactions are mainly due to the heterologous protein released by the microfilaria killed. Generally, the reaction is mainly the febrile symptom, which is a therapeutic response. It greatly hindered the promotion of DEC-MDA in filariasis control. Therefore, in 1974–1975, investigations on reducing the DEC side reaction, combing with surveillance on DEC-MDA spot-check sites were carried out in malayan filariasis endemic areas, Deqing County and Tongxiang County in Zhejiang Province, and bancroftian filariasis endemic area, Yongning County in Guangxi Province.

Practices have proved that antipyretic and analgesic drugs can reduce the febrile reaction. But antipyretic drugs maintain in the blood for a short time. Therefore, the interval time of administration should not be too long. Through observation, taking paracetamol regularly can effectively reduce and restrain the reaction caused by DEC in the treatment of microfilaremia, thus ensuring the smooth implementation of MDA.

Two regimes of the administration and dosage of taking paracetamol have been designed successively for alleviating the therapeutic response of DEC (Sun et al., 1990). The first was to take the first dose of diethylcarbamazine together with paracetamol rapid-release tablet (ordinary dosage) 0.5 g, every 4 h for 2 days. A total of 31 microfilaremia cases

of *B. malayi*, with microfilaria density more than 30/60 μL, undergoing DEC chemotherapy for the first time were investigated. The dose of DEC was 0.75 g each time, once a day for 2 days, 1.5 g in total. Fifty patients in the control group were selected as the same requirement of the experimental group, but paracetamol was not given. The results showed that in the experimental group, the fever rate was 71.0% after taking DEC, with 9.7% high fever (≥ 39 °C) reaction. The mean cumulative duration of fever was 16 h. Whereas in the control group, the fever rate was 100% after taking DEC, with 74.0% high fever reaction. The mean cumulative duration of fever was 36 h. Compared with the control group, the fever rate was reduced by 29.0% in the experimental group, and the hyperthermia response rate was reduced 64.3% in the experimental group. The cumulative fever duration of the febrile patients was shortened 29 h. The concomitant symptom was also lessened and relieved.

In order to reduce the times of administration of paracetamol, the second regime was developed. The difference from the first regimen was that paracetamol rapid-release tablets and sustained-release tablets (enteric-coated tablets) were given at the same time, 0.5 g each, every 8 h for six times for malayan filariasis therapy, and every 8 h for eight times for bancroftian filariasis therapy. The dose of DEC for therapy of malayan filariasis patients was the same as regime 1. Whereas for patients of bancroftian filariasis, the DEC treatment regimen was 3 g for 3 days, given 0.5 g each time, twice a day. The results showed that in the experimental group of malayan filariasis patients, the fever rate was 80.9% in 110 cases, with 17.3% high fever reaction. The mean cumulative duration of fever was 14.2 h; while in the control group, the fever rate was 100% in 15 cases, with 63.8% high fever reaction. The mean cumulative duration of fever was 19.2 h. In the experimental group of bancroftian filariasis patients, the fever rate was 63.8% in 47 cases, with 6.4% high fever reaction. The mean cumulative duration of fever was 14.3 h; while in the control group, the fever rate was 94.7% in 19 cases, with 15.8% high fever reaction. The mean cumulative duration of fever was 29.3 h. The investigation results were consistent with regime 1. Since compared with regime 1, the administration interval time of paracetamol was extended to 8 h in regime 2, and the times of taking the drug were reduced by half, regime 2 is easy to be accepted by the public.

4.6. The project 'Research achievements on the strategy and technical measures for interrupting the transmission of LF in China' provide technical support for LF elimination

Based on the of pathogenic biological characteristics of filariasis, through studies on the dynamics and threshold of filariasis transmission, it was for the first time that the control strategy taking elimination of source of infection as the major focus was established, the residual low-density microfilaremia cases being of no practical importance in filariasis transmission at the post-control stage was elucidated (Shi et al., 1988), the indicator for filariasis transmission interruption was proposed, and the technical measures were worked out accordingly. The main of the results include: (1) establishing the control strategy taking elimination of infection source as the major focus, (2) formulating safe, feasible and effective MDA and DEC-fortified regimens, (3) revealing the transmission pattern of filariasis at the post-control phase, and proposing indicators for filariasis transmission interruption, (4) establishing longitudinal, cross-sectional, and floating population active surveillance system, (5) formulating the criteria of basic elimination and elimination of filariasis and corresponding technical indicators to guide the realization of the goal of basic elimination (transmission interrupting) and the elimination of filariasis in the whole country by stages (Shi and Sun, 1999).

The above research results are implemented nationwide, which plays an important and crucial role in realizing the elimination of filariasis in China (Shi et al., 2001). The project 'Research achievements on the strategy and technical measures for interrupting the transmission of LF in China' led by our Institute, with the cooperation of other provincial institutes of parasitic control, was won the first prize of National Science and Technology Advance Award in 2000.

5. MONITORING AND EVALUATION SUPPORTED BY INFORMATION MANAGEMENT BOTH IN ELIMINATION AND POST-ELIMINATION STAGES

5.1. The surveillance system in elimination stages

Summing up the parasitological data in cross-sectional surveillance conducted in 16 endemic P/A/M from 1972 to 2005, a total of 3.315 million persons received blood examination, and 21,710 residual microfilaremia cases were found. The residual microfilaremia cases distributed in 456 counties/cities, occupying 53.3% sentinel counties/cities. After basic elimination of filariasis in China, microfilaremia cases have been found in Longyan city and Shaowu city, Fujian Province in the last 14 years (the longest). While the last microfilaremia case was found in Sixian County, Anhui Province in 2005. During 1976–2005, cross-sectional mosquito vector surveys were performed. A total of 4.71 million mosquitoes were dissected and 809 filarial larvae positive mosquito were found. Since almost all the original filariasis endemic counties/cities reached the level of basic elimination, mosquito vector and their natural infection rate with filaria larvae has decreased gradually. In 1976, the natural infection rate of filarial larvae in *Cx. pipiens* complex (*Cx. p. pallens*, and *Cx. p. quiquefasciatus*) was 0.19% in bancroftian filariasis endemic area. In the malayan filariasis endemic area, the infection rate of *Anopheles* spp. (*An. sinensis* and *An. lesteri*) was 0.84%. Subsequently, both the infection rates of vectors of bancroftian filariasis and malayan filariasis has been dropped to 0%. Filaria-infected mosquitoes have been detected in Dejiang County, Guizhou Province and Cangshan City, Shandong Province in the 12th year (the longest) after basic elimination. While Xiamen is the place where the last positive mosquito of filaria was found in 1992. Eighty-two longitudinal surveillance sentinel sites were established between 1980 and 2004. Among them, 45 sites of which conducted long-term and effective surveillance. After the intervention, the majority of residual microfilaremia cases turned to negative successively in 10 years. In the fifth and ninth year, no microfilaremia case was found for bancroftian and malayan filariasis sentinel sites, respectively, in the surveillance. The microfilaria rate has decreased subsequently. The positive rate of mosquitoes decreased gradually, and af-

ter the eight-year of the surveillance, no positive mosquito was found. Neither new infection, nor new chronic patient has been found in sentinel sites during filariasis surveillance. In order to consolidate the achievements of filariasis control after basic elimination, the search for residual epidemic foci has been intensified in various regions. Only in a few administrative villages in Huilai, Haikang of Guangdong Province, and Gao'an and Zhangshu of Jiangxi Province, the microfilaria rates were found higher than 1% (National Technical Steering Group for Filariasis Control and Research, MOPH, 1991b). All residual endemic foci have been treated timely and effectively. From 1984 to 2005, LF surveillance of the floating population was carried out. The total number of 363.5 thousand persons received blood test and 419 microfilaremia cases were found, all of them being detected before 1992. The results indicated that the probability of detecting microfilaremia cases in the floating population reduced greatly since all the original filariasis endemic counties/cities reached the level of basic elimination (National Technical Steering Group for Filariasis Control and Research, MOPH, 2002; Sun, 2005).

From 1995 to 2006, the MOPH organized evaluation in Guangxi (1995), Guizhou (1996), Shanghai (1996), Sichuan (1997), Chongqing (1997), Hunan (1997), Jiangsu (1998), Guangdong (2000), Hubei (2001), Zhejiang (2001), Fujian (2002), Shandong (2004), Henan (2004), Jiangxi (2005), Hainan (2005), and Anhui (2006), altogether 16 P/A/M, to assess the elimination of filariasis (Wu et al., 2003b) (Table 1). In May 2007, China was officially confirmed as having achieved the elimination of LF as a public health problem by the WHO (Sun et al., 2013). The success of LF elimination in China provides practical evidence for the call of elimination of LF as a public health problem, which was adopted at the 50th World Health Assembly in 1997 (Fang and Zhang, 2019; Sun, 2001; WHO, 1997, 2011).

5.2. Special monitoring and investigation in key areas after the elimination of filariasis

In order to consolidate the achievements of filariasis elimination in China, further clear away the infective sources, and provide scientific evidences for filariasis surveillance at the post-elimination phase, entrusted by Disease Control Bureau, MOPH and Chinese Center for Disease Control and Prevention (CDC), our Institute, cooperating with Guangxi, Hunan, Hubei, Guizhou, Chongqing, Jiangxi and An-

hui Provincial CDC carried out special monitoring and investigation in key areas, with a unified guideline, from January to June in 2008. The investigation was divided into three steps: baseline survey in previous endemic areas, spot check in key areas, and review of the results of spot checks.

The investigation was conducted previous bancroftian filariasis endemic area (including the endemic area with mixed infection areas with bancroftian filariasis as the primary). The principles of sentinel sites were as follows: (1) lack historical material on mass blood survey for filariasis; (2) remote areas with inconvenient transportation and poor sanitary conditions; (3) sites at the boundary of provinces or counties; (4) low frequency of mass blood survey and selective treatment; (5) low coverage or less than the prescribed amount of DEC-fortified salt; (6) relatively high microfilaremia rate at the end of the mass blood survey or spot check (The evaluation unit is based on the administrative village). Where, the administrative villages accord with one item of (1), (2) or in any two items of (3), (4), (5), and (6) were identified as key areas. According to the results of the baseline survey, 80 administrative villages in 38 counties/cities of 7 P/A/M were selected as the sentinel sites.

The filariasis-specific IgG4 testing kit was applied for serologic diagnostic in permanent residents over 10 years old (no less than 600 people) in sentinel sites. In the large administrative village, random cluster sampling was adopted for selecting natural villages as spot-check sites. In villages with resident population less than 600, the scope of the investigation was expanded to neighbouring villages, in order to meet the requirement of sample size. Filter paper blood specimens were collected and examined by Shandong Provincial Institute of Parasitic Diseases. The results showed that 165 were found positive among 50,424 samples, with a rate of 0.327% (0.051–0.630). The results of the pathological examination in serologic positive persons showed that all were negative, no microfilaremia case was found.

The project of ‘Special monitoring and investigation in key areas after the elimination of filariasis’ indicates that the achievements of filariasis elimination in China is very consolidated. Considering the following factors: long period and difficult in filariasis control, imbalance in different endemic areas, and the impact of the floating population, the residual foci of filariasis cannot be completely excluded. It suggests that the surveillance work after elimination of filariasis should be carried out in

a certain period after the declaration of LF elimination in China. Firstly, the LF should be included in the direct-network reporting of the Notifiable Disease Monitoring System continuously. Secondly, all levels of disease prevention and control agencies at the endemic areas should continue to take the initiative surveys for clearing away the potential infective source. Thirdly, imported cases from aboard should be paid serious attention.

6. TECHNICAL SUPPORTS TO THE ELIMINATION AND POST-ELIMINATION PROGRAMMES

Lymphatic filariasis, as a national statutory B infectious disease, has been included in the Notifiable Diseases Reporting System since 2004. Annually, approximately 450 direct-network reported cases of LF have been identified over the last 10 years. But, the majority of these cases were false alarms due to mis-clicking, and the remaining cases were chronic filariasis. Until now, almost no case was identified as microfilaremia through direct-network reporting of the Notifiable Disease Monitoring System, except that in August 2007, a clinically confirmed case of bancroftian filariasis from Fuchuan County of the Guangxi Zhuang Autonomous Region, has been found through the system. Since the case has been detected, our Institute, together with the Guangxi provincial CDC, carried out an emergency investigation in the residual focus promptly (Li et al., 2008). Nineteen microfilaremia cases (1052 persons involved) with the positive rate of 1.8%, were found by pathological examination in Changtang Village; no microfilaria-positive case (4119 residences involved) was found in three other villages in Fuchuan County. Immunochromatographic technology was conducted for those going out but retuned and those in neighbouring areas. Positive individuals were checked by thick blood smear for pathological diagnostic. Mosquitoes were collected in human dwellings. No filaria larva was found in 54 dissected *Cx. p. quinquefasciatus*. More identified patients were more than 60 years old, indicating that the residual focus was an original hypro-endemic area of bancroftian filariasis. Based on the discovery and timely disposal of the residual foci, two experiences can be concluded in the progress of filariasis elimination. In the preliminary stage of post-control, evaluation on the historical control process should be conducted with regular surveillance simultaneously, such as special monitoring

and investigation in weak points, which can make more effective in the endeavour. In the later of post-control and post-elimination phases, besides health personnel of the disease control system, the medical personnel of the medical system should maintain the diagnosis and treatment skills of filariasis and keep high vigilance against filariasis, which is important to discovery of residual foci.

Since the declaration of lymphatic filariasis elimination in China, in 2007, the *Working Program for the Morbidity Management and Disability Prevention of Chronic Filariasis Patients* was issued by the MOPH. The dynamic digital management of chronic filariasis patient documents and the providing of basic personal care for morbidity in local clinical systems were proposed. In 2010, the *National Monitoring Program for the Post-elimination of Lymphatic Filariasis* was issued. The program was created for the timely discovery of possible residual and imported sources of infection, thereby preventing retransmission of filariasis. For the filariasis cases, which are reported through the Notifiable Diseases Reporting System, our Institute is in charge to inform and cooperate provincial CDC to verify the cases based on evidence from epidemiology, pathogenic diagnosis, serologic tests, and molecular biologic tests.

7. CONCLUSION

The achievements and experience of the elimination of LF in China are highly appraised and valued in the word. The strategies and technical measures for preventing LF transmission implemented in China have been recognized and widely recommended by WHO (Fig. 1). They are included establishing the control strategy taking elimination of infection source as the major focus; formulating the microfilaria rate below 1% as the criteria for termination of control measures; including DEC-fortified salt in the MDA; establishing the surveillance strategy after the termination of control measures. In the post-control phase, special monitoring and investigation in key areas were conducted for clearing way potential residual foci. Two schemes and one criterion were issued to guild all levels of disease control and prevention workers on LF surveillance, epidemic disposal, and managing and caring for chronic filariasis patients in the post-elimination phase. In addition, the Notifiable Diseases Reporting System keeps an eye on the LF cases reported in national wide. These ef-

forts prevent the LF resurgence in China, and simultaneously, promote the progress of Global Programme of Elimination of Lymphatic Filariasis in worldwide.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

All the authors have read and approved the submitted version of the manuscript to this journal.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in the published article.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

D.-J.S, Y.F., Y.H., and Y.Z. designed the study; D.-J.S., and Y.F. wrote the original manuscript; D.J., Y.F., Y.H., and Y.Z. revised the manuscript and gave approval for its publication. All the authors read and approved the final version of the manuscript.

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