REVIEW

EPIDEMIOLOGY AND CONTROL OF PARAGONIMIASIS IN SOUTHEAST ASIA AND WESTERN PACIFIC REGIONS: LESSONS LEARNT AND THE WAY FORWARD

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Abstract. Food-borne trematode infections are among the neglected tropical diseases ignored in terms of attention, research, and funding, among which paragonimiasis remains a public health concern in the World Health Organization (WHO) Southeast Asia and Western Pacific regions. Adequate information on infection status is essential to provide a basis for policy formulation. A review of the epidemiology and control of paragonimiasis in selected countries in the two WHO regions based on published literature from January 1998 to December 2018 was undertaken to obtain lessons for improving control measures and delivery of service. Although various efforts to control paragonimiasis in the two regions showed progress, several challenges remain, such as need of a well-established surveillance system in endemic countries as the distribution of paragonimiasis is highly focal, development of more sensitive and field-applicable diagnostic tools, integrated surveillance of paragonimiasis due to misdiagnosis as tuberculosis, and investigation into the use of praziquantel in regions where co-endemicity with other parasitic infections exist. In addition, health promotion and capacity building of health care workers remain essential elements in future successful control of paragonimiasis in the Southeast Asia and Western Pacific regions.

Keywords: food-borne trematode, integrated control strategy, neglected tropical diseases, paragonimiasis, Southeast Asia Region, surveillance, Western Pacific Region

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INTRODUCTION

Food-borne trematode (FBT) infections are considered as one of the neglected tropical diseases (NTDs) targeted by the United Nations' Sustainable Development Goals (United Nations, 2016) and constitute an emerging public health concern in the Southeast Asian (SEA) (comprising Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste) and Western Pacific (WP) regions (comprising American Samoa, Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, French Polynesia (France), Guam (USA), Hong Kong SAR (China), Japan, Kiribati, Lao People's Democratic Republic, Macao SAR (China), Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, New Caledonia (France), New Zealand, Niue, Commonwealth of the Northern Mariana Islands (USA), Palau, Papua New Guinea, Philippines, Pitcairn Island (UK), Republic of Korea, Samoa, Singapore, Solomon Islands, Tokelau (New Zealand), Tonga, Tuvalu, Vanuatu, Vietnam, and Wallis and Futuna (France)) (WHO, 2021; WHO WPRO, 2021). Public health and economic impact of FBT infections are consequential in terms of absenteeism, morbidity, health care costs, and agricultural and productivity loss (WHO, 1995).

Paragonimiasis or lung fluke infection is an FBT infection caused by genus *Paragonimus*, with transmission occurring through ingestion of raw or inadequately processed crustaceans harboring the trematode (WHO, 1995). Light infection may be asymptomatic, but chronic infection exhibits clinical manifestations, such as chronic cough and hemoptysis, with similarity to tuberculosis (TB) (WHO WPRO, 2002). Ectopic paragonimiasis may also occur due to migration of the fluke into the abdominal cavity, subcutaneous tissues and brain (WHO, 1995).

Human paragonimiasis occurs in three endemic focal regions, namely, Asia, South and Central America, and Africa (Procop, 2009). *P. westermani* or oriental lung fluke is the most common species in Asia, especially in China, South Korea, Thailand, the Philippines, and Vietnam (CDC, 2013), while *P. heterotremus* is common in China, Lao People's Democratic Republic (PDR) and Thailand (Miyazaki and Harinasuta, 1966).

In 2010, an estimated two million disability adjusted life years (DALYs) were attributed to FBT infections, 50% of which were due to paragonimiasis. In the WP subregion B, which includes Cambodia, China, Lao PDR, Malaysia, South Korea, the Philippines, and Vietnam, 60% of DALYs per 100,000 owing to FBT infections were attributed to paragonimiasis (Havelaar *et al*, 2015). The survey conducted in 2013 showed an estimated 80 million people affected by FBT infections, about a 50%

increase from the 1990s (Global Burden of Disease Study 2013 Collaborators, 2015).

In order to minimize the impact of the infection, adequate information on the status of paragonimiasis is essential for planning, implementing, monitoring, and sustaining prevention and control activities (WHO WPRO, 2002). Here, a review on the epidemiology and control of paragonimiasis in the SEA and WP regions was carried out based on references published in the past 20 years to glean lessons learnt for future improvement in policy and service delivery towards successful control of paragonimiasis in the two regions.

MATERIALS AND METHODS

Data source

English language databases, namely, BIOSIS Preview, CAB Direct, Embase, Google Scholar, PLoS NTD, PubMed, Science Direct, Web of Science, and WHOLIS, were searched for articles on paragonimiasis published from January 1998 to December 2018. Published articles regarding countries of interest in SEA and WP regions were included in the study based on endemicity. Search terms used were "Asia", "Brunei Darussalam", "Cambodia", "China", "India", "Indonesia", "Japan", "Lao PDR", "Malaysia", "Mongolia", "Myanmar", "Nepal", "North Korea", "paragonimiasis", "*Paragonimus*", "*Paragonimus westermani*", "Southeast Asia", "South Korea", "Sri Lanka", "Timor-Leste", "Thailand", "the Philippines", and "Vietnam", singly or combined using the term "in".

Data analysis

Initial search results were screened based on title, abstract, and full text. Relevant quantitative data on human prevalence of morbidity and mortality due to paragonimiasis were extracted.

STATUS OF SELECTED COUNTRIES

Paragonimiasis in WHO's Southeast Asia Region

India: Paragonimiasis is a public health concern in the Indian sub-continent, especially in Northeast India, where the first case of human paragonimiasis was documented in 1982 in Manipur state (Toscano *et al*, 1994) and 39 cases were detected in 1986 (Singh *et al*, 1986). Subsequently, several other endemic foci have been detected in Northeast India (Singh *et al*, 1993; Singh *et al*, 2009). A prevalence of 6.7% was observed by an intradermal test (IDT) in the same area 1993 (Singh *et al*, 1993), and up to 50% of patients attending TB clinics were positive for paragonimiasis based on an enzyme-linked immunosorbent assay (ELISA) test in Nagaland, another state in Northeast India (Singh *et al*, 2009).

In 2005, when paragonimiasis was detected in 20.9% of children and 4.1% of adults by sputum microscopy in a remote tribal village in Changlang

District, Arunachal Pradesh, infected patients were treated with praziquantel (PZQ), and villagers were educated on paragonimiasis awareness (Devi *et al*, 2007). In 2011, a re-survey in an independent sample population from the same areas has shown declines in seroprevalence from 51.7% to 15.9% among children (≤15 years of age), 22.4% to 8.2% among individuals 16-30 years of age, and 15.3% to 3.7% among adults ≥31 years of age (Narain *et al*, 2015). Sputum examination on the same occasion showed reduction of prevalence from 20.9% to 3.6% among children and 7.1% to 1.6% among adults 16 to 30 years of age, but prevalence is unchanged (1.5-2.2%) for those ≥31 years of age.

There was no available information on the prevention and control programs for paragonimiasis. However, there were two studies conducted in 2008 and 2012/2013 on integrated surveillance of paragonimiasis and TB (Singh *et al*, 2009; Das *et al*, 2016). Selective chemotherapy and community education in areas of high prevalence, such as in the Changlang District of Arunachal Pradesh was provided (Narain *et al*, 2015).

Thailand: The first case of paragonimiasis in Thailand was reported by Prommas in 1928 in a male patient from Lom Sak District, Phetchabun Province, northern Thailand (Toscano *et al*, 1994). Paragonimiasis was not given much attention until its endemicity was detected in Saraburi Province, Central Thailand in the late 1950's (Vajrasthira *et al*, 1959). In 1964, Nakhon Nayok, a province adjacent to Saraburi, was recognized as another endemic area (Miyazaki and Harinasuta, 1966).

In 1984/1985, prevalence of paragonimiasis in Chet Bung Mai Village, Kaeng Khoi District, Saraburi Province is 1.0, 6.3 and 90.9% as detected by stool, sputum and serologic examination, respectively, in individuals 10-60 years of age (Yoonuan *et al*, 2008). By 2005, serologic examination revealed a drop to 43.5% prevalence in Pong Kon Sao Village, Kaeng Khoi District, Saraburi Province in individuals 34-67 years of age, which could be attributed to the changing eating habits of the younger generation (Yoonuan *et al*, 2008).

Despite the decreasing trend of paragonimiasis in Thailand, the infection remains a public health concern due to its high-risk of transmission as shown by the high prevalence of *Paragonimus* metacercaria in crustaceans (21.0% in 1984/1985 and 35.9% in 2005) (Kawashima *et al*, 1989; Yoonuan *et al*, 2008) and local habit of consuming raw or improperly cooked mountain or waterfall crabs (Watthanakulpanich *et al*, 2005).

Paragonimiasis in WHO's Western Pacific Region

China: Around 195 million people in China are at-risk of paragonimiasis (Keiser and Utzinger, 2005). Before

1999, 23,703 cases were identified, and prevalence of neuroparagonimiasis is 4.2% (Lv *et al*, 2010). From 2001 to 2004, nationwide seroprevalence is 1.7%, the most affected provinces being Chongqing and Shanghai, with 4.1 and 5.1% prevalence respectively; ethnic groups Miao and Tong the most affected, with 20 and 14% prevalence respectively; and young children the most affected age group, with those <4 and 5-9 years of age having 2.8 and 2.4% prevalence respectively (Coordinating Office of the National Survey on the Important Human Parasitic Diseases, 2005).

The Three Gorges Dam spanning Yangtze River in Southwest China serves as a habitat for crabs. In 2009, paragonimiasis was detected in 724 individuals 2-49 years of age residing near the Three Gorges Dam, with a prevalence of 14.4 and 7.5% as detected by IDT and ELISA respectively, and prevalence of *Paragonimus* metacercaria in freshwater crabs is 39.6% (Zhang *et al*, 2012).

Until 1992, paragonimiasis control activities, such as health education and chemotherapy, were carried out only in highly endemic areas by institutions for disease control sponsored by local governments (WHO, 1995). In 1992, a national paragonimiasis control program, employing health education and selective chemotherapy as the major components, was implemented (WHO, 1995). Currently, control of paragonimiasis and other FBT infections are integrated into other parasitic diseases control programs (WHO WPRO, 2008). In addition, capacity building of health workers and preparation of information, education, and communication (IEC) materials for health promotion were undertaken (WHO, 2011).

Japan: In the late 1950's, Japan had a high paragonimiasis endemicity, with an estimate of more than 300,000 cases (Nagayasu *et al*, 2015). The infection was prevalent in southwestern Japan, especially in Southern Kyushu District (Yokogawa, 1965). Incidence significantly decreased due to intensive mass screening and treatment campaigns performed in endemic areas from the 1950's to the 1960's (Hayashi, 1978). By the 1970's, paragonimiasis was a rare local infection in Japan. In the late 1980's, however, it re-emerged and has become a major parasitic infection in southern Kyushu due to the traditional custom of eating freshwater crabs which were contaminated with the *P. westermani* metacercariae, although infection rate was <1.0% (Nawa, 1991).

From 1998 to 2004, a total of 152 referred cases of paragonimiasis were diagnosed using ELISA at the University of Miyazaki, Miyazaki Prefecture, among whom 34% were immigrants, 89 and 11% from China and Thailand respectively (Obara *et al*, 2004). From 2001 to 2012, 443 out of 5,200 (8.5%) cases of parasitic infections referred to the University of Miyazaki were diagnosed using ELISA, among whom 23, 30 and 44% were immigrants from South Korea, Thailand and China, respectively. The annual number of immigrant cases ranges from 4 in 2003 to 23 in 2007, remaining consistent (25-30) until 2009 and then gradually decreasing (Nagayasu *et al*, 2015). The same study reported the vast majority (63%) of the cases were from Prefectures on Kyushu Island, with a small percent cases from outside Kyushu Island, namely, Gifu (4%), Kanagawa (3%), Osaka (4%), and Tokyo (4%). Immigrant cases comprise 67% of those from Osaka and Tokyo, while all cases from Gifu were native Japanese.

Since 1949, national surveys of paragonimiasis have been carried out by the Japan Association of Parasite Control every five years (WHO, 1995). At present, a referral scheme, whereby samples from different areas were referred to a laboratory, such as one in the city of Miyazaki, provides data on cases and demographics to include possible places of origin (Obara *et al*, 2004; Nagayasu *et al*, 2015).

Lao PDR: Human paragonimiasis in Lao PDR was first documented in 1946 among the hill tribesmen in San Neua Province (Miyazaki and Fontan, 1970). In 1973, a nationwide epidemiologic investigation using IDT in 15 provinces reported a 9.8% prevalence among 1,531 individuals (Soh, 1973). In 2003, direct microscopic sputum examination from 33 patients with chronic cough lasting 3-36 months revealed 12 clustered cases of paragonimiasis, all of whom come from Naphong Village, Hinheub District and have reported consumption of raw or undercooked freshwater crabs (Tran *et al*, 2004). In 2004, field investigations carried out by examining three sputum samples collected on two consecutive days in three villages of Hinheub District revealed 12.7% of patients with chronic cough lasting for more than three weeks were positive for paragonimiasis (a prevalence of 0.6%), with 3.4% positive for TB (prevalence of 0.2%) and one case of co-infection (Odermatt *et al*, 2007). Among patients with chronic cough, 92% reported regular consumption of local crabs or prawns, while 60%, particularly children, reported consumption of raw crab meat as fever remedy. Moreover, *Paragonimus* metacercariae were found in freshwater crabs collected from Nam Sêt River, demonstrating possible widespread transmission in the area (Odermatt *et al*, 2007). In 2006, prevalence of paragonimiasis in Kasy District, Vientiane by immunoblot was 6.6% (Vonghachack, 2007).

At present, case detection and selective treatment of patients are integrated into the existing TB program (WHO WPRO, 2017), while preventive chemotherapy against paragonimiasis is integrated with that for schistosomiasis (Montressor *et al*, 2008). Capacity building of health workers and health promotion using

IEC materials were also undertaken (WHO, 2011).

South Korea: Paragonimiasis already existed in South Korea in 1924 (Cho *et al*, 1997). In the late 1960's, an estimated two million people were infected (Cho *et al*, 1997) and in 1970, stool examinations in elementary, middle and high school students by the Korean Association for Parasite Eradication (KAPE) revealed a prevalence of 0.01% (Cho, 2009). Subsequent national surveys conducted by the Ministry of Health and Social Affairs and KAPE on random samples of the whole South Korean population showed prevalence in 1971, 1976, 1981, 1986, and 1992 of 0.090, 0.007, 0.000, 0.002, and 0.000%, respectively of egg positivity rate (Cho *et al*, 1997; Cho, 2009).

Most cases of paragonimiasis were reported in tertiary hospitals in Seoul with a lack of information regarding origin of infection (Lee *et al*, 2010). From 1993 to 2006, 74,448 serum and cerebrospinal fluid specimens were referred to Chung-Ang University Hospital from 121 hospitals nationwide, revealing an annual seroprevalence of paragonimiasis ranging 0.5-3.0%, with referrals from Seoul having the highest annual overall seroprevalence of clonorchiasis, cysticercosis, paragonimiasis, and sparganosis, although transmission occurs in rural areas outside of Seoul (Lee *et al*, 2010). From 1996 to 2006, 6,017 serum samples were submitted for examination to the Institute of Endemic Diseases, Seoul National University, which reported an overall seroprevalence of lung fluke infection of 2.8% (Jin *et al*, 2017). Although seroprevalence of paragonimiasis has been consistently low over the years, the infection remains a public health concern due to new cases occurring sporadically (Sohn *et al*, 2009; Choi *et al*, 2014). In 2009, a case series of familial paragonimiasis was reported after ingestion of "Kejang" or freshwater crabs soaked in soybean sauce (Sohn *et al*, 2009). Among 320 clinical samples analyzed in Hanyang University from 2004 to 2011, five were positive for paragonimiasis using ELISA (Choi *et al*, 2014).

At present, information on paragonimiasis prevalence primarily comes from studies through a well-established referral system (Lee *et al*, 2010; Choi *et al*, 2014; Jin *et al*, 2017). KAPE continues to provide extensive health education in South Korea through mass media, such as radio and television broadcasts, leaflets, and posters in schools and health agencies (Crompton *et al*, 2003)

The Philippines: Paragonimiasis in the Philippines was first reported in 1907 (Musgrave, n.d.) and in 1958, Leyte and Sorsogon Provinces were recognized as the first endemic foci (Yogore *et al*, 1958). Sputum examinations performed from 1973 to 1975 revealed a prevalence of 0.57% in three municipalities in Leyte, and a survey conducted from 1977 to 1978 reported a prevalence of 0.15% in nine municipalities in Sorsogon (Cabrera, 1984). In 1997, sputum examination among 160 individuals in Sorsogon Province demonstrated a prevalence of 16.3%, and among paragonimiasis positives, 46% were previously diagnosed with TB while the remaining individuals manifested signs and symptoms characteristic of TB (Belizario *et al*, 1997). In 1998, duplicate sputum examination of 252 subjects ≥15 years of age in Casiguran, Sorsogon Province showed a prevalence of 25% (Belizario *et al*, 1998). In addition to Leyte and Sorsogon Provinces, other known endemic provinces were Basilan, Camarines, Cotabato, Davao, Davao Oriental, Mindoro, Samar, and Zamboanga del Norte (Cabrera, 1984). A longitudinal study of paragonimiasis in Roxas Municipality in Zamboanga del Norte Province commencing in 2002 showed a prevalence of 27.2% (de Leon and Piad, 2005). In 2005 to 2006, 15% of 378 individuals suffering from chronic productive cough lasting for at least four weeks or with a history of anti-TB treatment without clinical improvement, who were positive for paragonimiasis by sputum examination underwent treatment regimens using PZQ and triclabendazole (Belizario *et al*, 2007). In 2011, an integrated surveillance of paragonimiasis and TB revealed only 6.8% of 605 individuals were positive for lung fluke infection, while 1.7% were positive for pulmonary TB; and among 231 individuals in Katipunan Municipality in the same province, prevalence of paragonimiasis and pulmonary TB are similar at 6.5% and 2.6%, respectively (Belizario *et al*, 2014).

No nationwide survey has been conducted in the Philippines, but the Department of Health (DOH) has recognized the results of investigations conducted by independent researchers (WHO WPRO, 2008). Active integrated active surveillance of paragonimiasis and TB has been carried out since 1997 (Belizario *et al*, 1997; Belizario *et al*, 1998; Belizario *et al*, 2007; Belizario *et al*, 2014). In 2016, a model was developed to integrate surveillance and control of TB and paragonimiasis and was tested and optimized in Zamboanga del Norte Province, which was later extended to include two other regions, namely, Bicol and Davao Regions (Belizario *et al*, 2016). Furthermore, DOH issued an administrative order on guidelines for diagnosis and treatment of paragonimiasis, which requires individuals with unresolved symptoms, such as chronic cough, with or without hemoptysis, despite receiving adequate anti-TB treatment, to undergo sputum examinations for diagnosis of paragonimiasis on three separate days (DOH, 2010).

Vietnam: The first case of paragonimiasis in Vietnam was reported in 1906 (Monzel, 1906). From 1907 to 1992, over 30 cases of paragonimiasis were reported (Nguyen, 2004). In 1994, 44 individuals from Sin Ho District, Lai Chau Province, Vietnam were paragonimiasis positive by sputum examination (Vien *et al*, 1997). To date, there are at least eight known endemic provinces in Northwest Vietnam, namely, Dien Bien, Hoa Binh, Lai Chau, Lang Son, Lao Cai, Nghe An, Son La, and Yen Bai (Nguyen, 2004). From nine sites of the eight endemic provinces surveyed, prevalence of paragonimiasis determined from 5,340 stool and 2,216 sputum samples is 1.9% and 6.4% respectively, with children comprising the majority of cases (68.5%) (Nguyen, 2004). A similar majority (68.1%) of the population have a habit of eating undercooked freshwater crabs, which have *Paragonimus* metacercaria infection prevalence ranging 78.7-98.1% (Nguyen, 2004).

In 2007, an intensive health education and mass drug administration (MDA) of a single dose of 40 mg/kg body weight of PZQ for two consecutive days were carried out in Lai Chau, Lao Cai and Yen Bai Provinces, resulting in paragonimiasis prevalence detected by ELISA in Lai Chau Province declining from 12.7 to 7.9% in 2014 (Doanh *et al*, 2011). Prevalence in other provinces also declined and MDA has been discontinued (WHO WPRO, 2017).

The majority of epidemiological information on paragonimiasis in Vietnam are obtained from independent research work (WHO, 2011). Control of paragonimiasis and FBT infections are covered by programs targeting NTDs, and an integrated surveillance of paragonimiasis and TB, capacity building of health workers and health promotion using IEC materials were also undertaken (WHO, 2011).

PERSPECTIVE ON CURRENT SITUATION OF PARAGONIMIASIS IN SOUTHEAST ASIA AND WESTERN PACIFIC REGIONS OF WHO

Epidemiology

Paragonimiasis is an emerging public health concern in the WHO's SEA and WP Regions, with distribution of the infection being highly focal. Periodic surveys, research, and passive and active community-based surveillance have been undertaken to identify cases and describe endemic foci. Recently, Japan and South Korea have deposited research on paragonimiasis prevalence in a central referral system. However, data on paragonimiasis are scarce in some countries, such as in Cambodia (WHO WPRO, 2008). Thus, there is a need to establish a central referral system to collect information on the epidemiology of paragonimiasis and determine focal areas in endemic countries for strategic implementation of service delivery and appropriate policy on control and prevention and improvement of service.

Rapid mapping techniques, such as geographic information systems and remote sensing techniques, can be used to identify high-risk areas for paragonimiasis and predict presence of *Paragonimus* intermediate hosts, as has previously been achieved for other trematodes such as *Schistosoma* spp (Guo *et al*, 2005). Questionnaires for field surveys or active surveillance should also be considered. For example, in Lao PDR a questionnaire approach was used for detection of paragonimiasis wherein suspected individuals with certain characteristics (ie chronic cough, blood in sputum and absence of fever) were subjected to sputum examination (Odermatt *et al*, 2009). In contrast with active case detection using cross-sectional parasitologic and serologic surveys, the questionnaire approach can be performed at a lower cost (Odermatt *et al*, 2009).

Detection

Although identification of *Paragonimus* eggs in stool and sputum specimens is simpler and at a lower cost compared with more sophisticated laboratory techniques, sensitivity is low (WHO, 2011). ELISA techniques to detect antigen or antibody have higher sensitivity, but are expensive and hence less accessible to member countries in the lower less-developed group. Detection of antibody cannot distinguish between active and past infections, hence, its limitation for clinical use (WHO WPRO, 2017). X-ray, which is relatively accessible, lacks reliability because findings are indistinguishable from those of pulmonary TB (WHO, 2011). Thus, diagnostics development for more sensitive and field-ready tools needs to be prioritized.

A loop-mediated isothermal DNA amplification (LAMP) assay developed in 2011 is able to detect *P. westermani* adults, metacercariae and eggs in human and animal samples (Chen *et al*, 2011). LAMP assay is highly sensitive, specific, and more rapid than the conventional PCR assay as it requires just a water bath or heat block, in lieu of the more complicated and expensive PCR instrument, providing a convenient option for point-of-care tests (Chen *et al*, 2011). The need to extract DNA from specimens and to train personnel, however, would have to be considered. A newly developed point-of-care testing tool using immunochromatography has proven to be rapid and effective in diagnosing paragonimiasis and has a diagnostic sensitivity, specificity, positive and negative predictive values, and accuracy of 97.9, 87.6, 78.0, 98.9, and 90.8%, respectively (Sadaow *et al*, 2020). The turnover time of the assay is 15 minutes and does not require experienced technician, sophisticated equipment or complicated analytical tools. Furthermore, results can be determined by the naked eye. However, improvements are needed to prevent cross-reaction with other parasites, provide a stable adequate and reliably supply of antigens, simplify quality control, and improve diagnostic sensitivity and specificity (Sadaow *et al*, 2020).

Diagnosis

Misdiagnosis of paragonimiasis is common due to similarities between clinical manifestations and radiological findings with TB, thereby concealing the existence of this parasitic infection, especially in co-endemic areas. Misdiagnosis may lead to unnecessary costs due to ineffective treatment and continued morbidity of infected individuals, leading to ineffective control of the infection. WHO (2002) recommends an integrated surveillance of paragonimiasis and TB. In addition, a Ziehl-Nelseen staining technique for sputum examination is useful for differential diagnosis for paragonimiasis and TB (Slesak *et al*, 2011), but its optimization needs to be explored.

Intervention and control

The core intervention measure for control of paragonimiasis and other FBT infections is treatment with PZQ (WHO, 1995). Selective chemotherapy or "test and treat" with a standard PZQ dose [25 mg/kg body weight, three times a day for three days (WHO, 2011)] results in a cure rate of 96-100% with 90 days post-treatment (Rim *et al*, 1981; Calvopina *et al*, 1998; Belizario *et al*, 2007), but at present, there are no data on efficacy of PZQ for MDA. Control for paragonimiasis can be integrated with preventive chemotherapy for schistosomiasis and opistorchiasis in co-endemic areas, such as Cambodia (WHO WPRO, 2008), Lao PDR (Rim *et al*, 2003; Montressor *et al*, 2008), the Philippines (DOH, 2012), and Vietnam (Carrique-Mas and Bryant, 2013).

Paragonimiasis is transmitted through consumption of undercooked or raw crabs, consumed in endemic areas, either as a delicacy (Obara *et al*, 2004; Keiser and Utzinger, 2005; Sohn *et al*, 2009; Balderia and Belizario, 2012) or a remedy for fever (Tran *et al*, 2004; Odermatt *et al*, 2007). The prevalence of paragonimiasis is reduced significantly after provision of health education promoting safe food preparation and practices, as well as good health-seeking behavior, together with selective treatment (Yoonuan *et al*, 2008; WHO, 2011).

Capacity building of health workers in known endemic and possible future endemic areas is important in case detection, provision of proper treatment, and as well as generation of data to provide evidence-based policy development (WHO WPRO, 2002). Academic health science centers and research institutes can play an important role not only in capacity building, but also in provision of centers for reference whereby further diagnosis and management may be provided to patients in need of expert attention. Such reference centers could be sources of data to provide evidence for policy formulation and improvement of service delivery.

CONCLUDING REMARKS

While various efforts in control of paragonimiasis in the SEA and WP regions show promise, several challenges remain. As the distribution of paragonimiasis is highly focal, a well-established surveillance system in endemic countries is a necessity. Development of appropriate diagnostics tools that are sensitive, applicable on-site and inexpensive requires to be prioritized. As misdiagnosis with TB remains a major concern in some endemic areas, integrated surveillance of TB and paragonimiasis is a necessity. Integration of PZQ treatment with other parasitic infections should also be explored in areas with co-endemicity. Continuing health promotion and capacity building of health workers still remain essential in the control and prevention of paragonimiasis in Southeast Asia and Western Pacific Regions of WHO and should not be neglected.

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CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

Balderia PG, Belizario VY. Review of food-borne trematodiases in the Philippines. *Acta Med Philipp* 2012; 46: 45-53.

Belizario V, Guan M, Borja L, Ortega A, Leonardia W. Pulmonary paragonimiasis and tuberculosis in Sorsogon, Philippines. *Southeast Asian J Trop Med Public Health* 1997; 28 (Suppl 1): 37-45.

Belizario VY, de Leon WU, Solon JAA, Marquez AI, Galang JMT, Valderama MTG. The clinical epidemiology of paragonimiasis and tuberculosis in Sorsogon, Philippines: Part I. Misdiagnosis of pulmonary paragonimiasis and tuberculosis in Sorsogon, Philippines. *J Natl Res Council Philippines* 1998; 5: 45-63.

Belizario VY, Jorge MC, Ng JV, *et al*. A model for integrating paragonimiasis surveillance and control with tuberculosis control program. *Southeast Asian J Trop Med Public Health* 2016; 47: 625-37.

Belizario VY, Mallari AO, de Leon WU, Lucero AC. Assessment of the efficacy, safety, and tolerability of praziquantel and triclabendazole in the treatment of paragonimiasis. *Southeast Asian J Trop Med Public Health* 2007; 38 (Suppl 1): 97-105.

Belizario VY, Totanes FI, Asuncion CA, *et al*. Integrated surveillance of pulmonary tuberculosis and paragonimiasis in Zamboanga del Norte, the Philippines. *Pathog Glob Health* 2014; 108: 95-102.

Cabrera BD. Paragonimiasis in the Philippines: current status. *Arzneimittelforschung* 1984; 34(9B): 1188-92.

Calvopina M, Guderian RH, Paredes W, Chico M, Cooper PJ. Treatment of human pulmonary paragonimiasis with triclabendazole: clinical tolerance and drug efficacy. *Trans R Soc Trop Med Hyg* 1998; 92: 566-9.

Carrique-Mas JJ, Bryant JE. A review of foodborne bacterial and parasitic zoonoses in Vietnam. *Ecohealth* 2013; 10: 465-489.

Centers for Disease Control and Prevention (CDC). Paragonimiasis epidemiology and risk factors, 2013 [cited 2020 May 25]. Available from: URL: https://www.cdc.gov/parasites/paragonimus/epi.html

Chen MX, Ai L, Zhang RL, *et al*. Sensitive and rapid detection of *Paragonimus westermani* infection in humans and animals by loop-mediated isothermal amplification (LAMP). *Parasitol Res* 2011; 108: 1193-8.

Cho SY, Kong Y, Kang SY. Epidemiology of paragonimiasis in Korea. *Southeast Asian J Trop Med Public Health* 1997; 28 (Suppl 1): 32-6.

Cho SY. Fifty years of the Korean Society for Parasitology. *Korean J Parasitol* 2009; 47 (Suppl): S7-19.

Choi SC, Lee SY, Song HO, Ryu JS, Ahn MH. Parasitic infections based on 320 clinical samples submitted to Hanyang University, Korea (2004 - 2011). *Korean J Parasitol* 2014; 52: 215-20.

Coordinating Office of the National Survey on the Important Human Parasitic Diseases. A national survey on current status of the important parasitic diseases in human population. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zh* 2005; 23 (Suppl 5): 332-40. [in Chinese]

Crompton DWT, Montressor A, Nesheim MC, Savioli L. Controlling disease due to helminth infections, 2003 [cited 2020 May 05] Available from: URL: https://apps.who.int/iris/rest/bitstreams/50656/retrieve

Das M, Doleckova K, Shenoy R, *et al*. Paragonimiasis in tuberculosis patients in Nagaland, India. *Glob Health Action* 2016; 9: 32387.

de Leon WU, Piad JNC. Paragonimiasis in the Philippines. In: Arizono N, Chai JY, Nawa Y, Takahashi Y, editors. Food-borne helminthiasis in Asia. Chiba, Japan: Federation of Asian Parasitologists; 2005. p. 133-7.

Department of Health (DOH). Administrative Order No. 2010-0037. Diagnosis and treatment guidelines for paragonimiasis. Manila, Philippines; 2010 [cited 2020 Apr 12] Available from: URL: https://efoi-ph.appspot.com/requests/aglzfmVmb2ktcGhy-HQsSB0NvbnRlbnQiEERPSC02Mz-cyMTU1NjIwNjcM

Department of Health (DOH). National objectives for health Philippines, 2011-2016, 2012 [cited 2020 Apr 12]. Available from: URL: https://doh.gov.ph/sites/default/files/publications/noh2016.pdf

Devi KR, Narain K, Bhattacharya S, *et al*. Pleuropulmonary paragonimiasis due to *Paragonimus heterotremus*: molecular diagnosis, prevalence of infection and clinicoradiological features in an endemic area of Northeast India. *Trans R Soc Trop Med Hyg* 2007; 101: 786-92.

Doanh PN, Dung DT, Thach DTC, Horii Y, Shinohara A, Nawa Y. Human paragonimiasis in Viet Nam: epidemiological survey and identification of the responsible species by DNA sequencing of eggs in patients' sputum. *Parasitol Int* 2011; 60: 534-7.

Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386: 743-800.

Guo JG, Vounatsou P, Cao CL, *et al*. A geographic information and remote sensing based model for prediction of Oncomelania hupensis habitats in Poyang Lake area, China. *Acta Trop* 2005; 96: 213-22.

Havelaar AH, Kirk MD, Torgerson PR, *et al*. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. *PLoS Med* 2015; 12: e1001923.

Hayashi E. A study on paragonimiasis. In: Tashiro I, editor. Medical History of Miyazaki Prefecture. Miyazaki: Miyazaki Prefectural Doctors Association; 1978. p. 1627-80. [In Japanese]

Jin Y, Kim EM, Choi MH, Oh MD, Hong ST. Significance of serology by multi-antigen ELISA for tissue helminthiases in Korea. *J Korean Med Sci* 2017; 32: 1118-23.

Kawashima K, Sukiyama H, Ketudat P. Paragonimus infection in crabs in Thailand. In: Kawashima K, editor. Paragonimus in Asia: biology genetic variation and speciation (Paragonimus Research Report). Fukuoka: Kyushu University School of Health Sciences; 1989. p. 84-92.

Keiser J, Utzinger J. Emerging foodborne trematodiasis. *Emerg Infect Dis* 2005; 11: 1507-14.

Lee MK, Hong SJ, Kim HR. Seroprevalence of tissue invading parasitic infections diagnosed by ELISA in Korea. *J Korean Med Sci* 2010; 25: 1272-6.

Lv S, Zhang Y, Steinmann P, Zhou XN, Utzinger, J. Helminth infections of the central nervous system occurring in Southeast Asia and the Far East. *Adv Parasitol* 2010; 72: 351-408.

Miyazaki I, Fontan R. Mature *Paragonimus heterotremus* found from a man in Laos. *Jpn J Parasitol* 1970; 19: 109-13.

Miyazaki I, Harinasuta T. The first case of paragonimiasis caused by *Paragonimus heterotremus* Chen et Hsia, 1964. *Ann Trop Med Parasitol* 1966; 60: 509-14.

Montresor A, Cong DT, Sinuon M, *et al*. Large-scale preventive chemotherapy for the control of helminth infection in western pacific countries: six years later. *PLoS Negl Trop Dis* 2008; 2: e278.

Monzel R. An observation of pulmonary distomiasis in Co-chinchina. Some notes on toxic accidents due to animal parasites in the intestine. *Ann Hyg et Med Colon* 1906; 9: 258-262. [in French]

Musgrave WE. Paragonimiasis in the Philippine Islands, n.d. [cited 2020 May 25]. Available from: URL: https://www.elib.gov.ph/downloadfile.php?uid=53e64b095875d7d5cbad-45513bc6ef08

Nagayasu E, Yoshida A, Hombu A, Horii Y, Maruyama H. Paragonimiasis in Japan: a twelve-year retrospective case review (2001-2012). *Intern Med* 2015; 54: 179-86.

Narain K, Devi KR, Bhattacharya S, Negmu K, Rajguru SK, Mahanta J. Declining prevalence of pulmonary paragonimiasis following treatment and community education in a remote tribal population of Arunachal Pradesh, India. *Indian J Med Res* 2015; 141: 648-52.

Nawa Y. Recent trends of paragonimasis westermani in Miyazaki Prefecture, Japan. *Southeast Asian J Trop Med Publ Health* 1991; 22 (Suppl): 342-4.

Nguyen VD. Epidemiology, pathology and treatment of paragonimiasis in Vietnam. *Southeast Asian J Trop Med Public Health* 2004; 35 (Suppl 1): 331-6.

Obara A, Nakamura-Uchiyama F, Hiromatsu K, Nawa Y. Paragonimiasis cases recently found among immigrants in Japan. *Intern Med* 2004; 43: 388-92.

Odermatt P, Habe S, Manichanh S, *et al*. Paragonimiasis and its intermediate hosts in a transmission focus in Lao People's Democratic Republic. *Acta Trop* 2007; 103: 108-15.

Odermatt P, Veasna D, Zhang W, *et al*. Rapid identification of paragonimiasis foci by lay informants in Lao People's Democratic Republic. *PLoS Negl Trop Dis* 2009; 3: e521.

Procop GW. North American paragonimiasis (caused by *Paragonimus* kellicotti) in the context of global paragonimiasis. *Clin Microbiol Rev* 2009; 22: 415-46.

Rim HJ, Chai JY, Min DY, *et al*. Prevalence of intestinal parasite infections on a national scale among primary schoolchildren in Laos. *Parasitol Res* 2003; 91: 267-72.

Rim HJ, Chang, YS, Lee JS, Joo KH, Suh WH, Tsuji M. Clinical evaluation of Praziquantel (Embay 8440; Biltricide®) in the treatment of *Paragonimus westermani*. *Kisaengchunghak Chapchi* 1981; 19: 27-37.

Sadaow L, Sanpool O, Yamasaki H, Maleewong W, Intapan P. Development of point-of-care testing tool using immunochromatography for rapid diagnosis of human paragonimiasis. *Acta Trop* 2020; 203: 105325.

Singh TS, Mutum SS, Razaque MA. Pulmonary paragonimiasis: clinical features, diagnosis, and treatment of 39 cases in Manipur. *Trans R Soc Trop Med Hyg* 1986; 80: 967-71.

Singh TS, Mutum S, Razaque MA, Singh YI, Singh EY. Paragonimiasis in Manipur.

Indian J Med Res 1993; 97: 247-52.

Singh TS, Sugiyama H, Umehara A, Hiese S, Khalo K. *Paragonimus heterotremus* infection in Nagaland: a new focus of paragonimiasis in India. *Indian J Med Microbiol* 2009; 27: 123-7.

Slesak G, Inthalad S, Basy P, *et al*. Ziehl-Neelsen staining technique can diagnose paragonimiasis. *PLos Negl Trop Dis* 2011; 5: e1048.

Soh CT. Epidemiological investigation of paragonimus infection in Laos. *Yonsei Rep Trop Med* 1973; 4: 65-77.

Sohn BS, Bae YJ, Cho YS, Moon HB, Kim TB. Three cases of paragonimiasis in a family. *Korean J Parasitol* 2009; 47: 281-5.

Toscano C, Yu SH, Nunn P, Mott KE. Paragonimiasis and Tuberculosis – Diagnostic Confusion: A Review of Literature, 1994 [cited 2021 Feb 08]. Available from: URL: https://apps.who.int/iris/bitstream/handle/10665/59147/WHO_HPE_94.3.pdf

Tran DS, Nanthapone S, Odermatt P, Strobel M. A village cluster of paragonimiasis in Vientiane Province, Lao PDR. *Southeast Asian J Trop Med Public Health* 2004; 35 (Suppl 1): 323-6.

United Nations. Sustainable Development Goal 3: Ensure healthy lives and promote well-being for all at all ages, 2016 [cited 2020 Apr 12]. Available from: URL: https://sustainabledevelopment.un.org/sdg3

Vajrasthira S, Harinasuta C, Maiphoom C. Study on helminthic infections in Thailand: the incidence of paragonimiasis in the first recognized endemic area. *Jpn J Exp Med* 1959; 29: 159-66.

Vien CV, Phue NC, Ha LD, *et al*. Paragonimiasis in Sin Ho, Lai Chau Province, Viet Nam. *Southeast Asian J Trop Med Public Health* 1997; 28 (Suppl 1): 46.

Vonghachack Y. Paragonimiasis in Kasy District Vientiane Province, Lao PDR, 2007 [cited 2020 Apr 12]. Available from: URL: https://www.tm.mahidol.ac.th/jitmm2007/pdf/301107_Youthanavanh.pdf

Watthanakulpanich D. Waikagul J, Dekumyoy P, Muangkhum P, Praevanit R, Mongkhonmu S. Paragonimiasis in Nan Province, Northern Thailand. *Southeast Asian J Trop Med Public Health* 2005; 36: 853-7.

World Health Organization (WHO). About WHO in the South-East Asia Region, 2021 [cited 2021 Oct 12] Available from: URL: https://www.who.int/southeastasia/about

World Health Organization (WHO). Control of foodborne trematode infections: a report of a WHO study group, 1995 [cited 2020 May 25]. Available from: URL: https://apps.who.int/iris/handle/10665/41544

World Health Organization (WHO). Report of the WHO expert consultation on foodborne trematode infections and taeniasis/cysticercosis, 2011 [cited 2020 May 25]. Available from: URL: https://www.who.int/neglected_diseases/preventive_chemotherapy/WHO_HTM_NTD_PCT_2011.3.pdf

World Health Organization Regional Office of the Western Pacific (WHO WPRO). Expert consultation to accelerate control of foodborne trematode infections, taeniasis, and cystercosis, Seoul, Republic of Korea, 17-19 May 2017: meeting report, 2017 [cited 2020 Apr 12]. Available from: URL: https://apps.who.int/iris/bitstream/handle/10665/260007/RS-2017-GE-35-KOR-eng.pdf?sequence=1&isAllowed=y

World Health Organization Regional Office of the Western Pacific (WHO WPRO). Joint WHO/FAO workshop on foodborne trematode infections in Asia, Ha Noi, Viet Nam, 26-28 November 2002: report, 2002 [cited 2020 Apr 12]. Available from: URL: https://apps.who.int/iris/handle/10665/208026

World Health Organization Regional Office of the Western Pacific (WHO WPRO). Review of epidemiological profile of helminthiases and their control in Western Pacific Region 1997-2008, 2008 [cited 2020 May 05] Available from: URL: https://apps.who.int/iris/bitstream/handle/10665/260007/RS-2017-GE-35-KOR-eng.pdf?sequence=1&isAllowed=y

World Health Organization Regional Office of the Western Pacific (WHO WPRO). Where we work, 2021 [cited 2021 Oct 12] Available from: URL: https://www.who.int/westernpacific/about/where-we-work

Yogore MG, Cabrera BD, Noble GA. Studies in paragonimiasis. IV. A survey in Casiguran, Sorsogon, Philippines. *Phil Jour Sci* 1958; 87: 197-215.

Yokogawa M. *Paragonimus* and paragonimiasis. *Adv Parasitol* 1965; 3: 99-158.

Yoonuan T, Vanvanitchai Y, Dekumyoy P, Komalamisra C, Kojima S, Waikagul J. Paragonimiasis prevalences in Saraburi Province, Thailand, measured 20 years apart. *Southeast Asian J Trop Med Public Health* 2008; 39: 593-600.

Zhang X, Wang Y, Wang G, *et al*. Distribution and clinical features of Paragonimiasis skrjabini in Three Gorges Reservoir Region. *Parasitology Int* 2012; 61: 645-9.