Neglected Tropical Diseases

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Neglected Tropical Diseases - East Asia

Springer

Neglected Tropical Diseases

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Introduction

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Keywords Asia · Control · Elimination · Transition · Neglected tropical diseases

1 Introduction

East Asia, defined herein rather loosely as the region between the People's Republic of China and Japan in the North and the Indonesian and Philippine archipelagos in the South, has undergone changes over recent decades that are unprecedented in human history in terms of speed, scale and extent. Following rapid industrialization and modernization, Japan established itself as the second largest economy of the world in the decades following the Second World War. The People's Republic of China's rise in the post-Mao era from a derelict country with many socio-economic characteristics typical of low-income countries to a vibrant economy resulted in its relegating Japan to the world's third biggest economy and prospects that it will soon surpass the United States of America as the single largest economy (Banister and Zhang 2005; Sun and Ryder 2016). The rise of these two economies has facilitated

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the economic development of other countries in the region, most notably Singapore, Hong Kong, South Korea, Taiwan, and Brunei that were ranked very high (≥ 0.8) on the Human Development Index (HDI) in 2016. Note that the HDI is a composite statistic ranging from 0 to 1 with high values characteristic of societies with high life expectancy, education, and per capita income. Most other countries in the region are on a similar trajectory with its speed determined by local events and the integration into regional and global economies. As a consequence, Eastern Asia is today home to an extraordinary diversity of countries, from still largely isolated North Korea (though there are recent signs of increased engagement with other nations) over countries that recently opened up and entered a phase of rapid and sustained development such as Myanmar, Lao People's Democratic Republic, and Cambodia; to countries in the middle of a rapid economic expansion and social progress phase, including Vietnam and Indonesia; to upper-middle-income countries, including the People's Republic of China, Malaysia, and Thailand; and finally to the highly developed nations listed above (Table 1).

In the wake of these developments, hundreds of millions of people have progressed from a life in poverty to join a rapidly expanding middle class. Similarly, government services, including health care, have expanded in reach, breadth, and quality (Hu et al. 2008; Meng et al. 2015). These determinants have resulted in profound changes in nearly all aspects relevant for human health. The epidemiological transition, observed here as the rapid increase in population growth rates resulting from improved nutrition and the deployment of effective medical services that is typically followed by declining fertility rates resulting in decreased population growth, is well advanced in most East Asian nations. The demographic transition from high birth and death rates typically observed in low- and middle-income countries to a situation characterized by low birth and death rates has resulted in plummeting numbers of children per woman in the region—6 of the 20 nations with the lowest total fertility rate are located in East Asia, and Japan is one of the few major countries with a shrinking population. One consequence of the epidemiological transition, particularly relevant to this publication, is also evident: a rapid rise in noncommunicable diseases (NCDs), which today represent the main causes for morbidity and mortality in East Asia, replacing infectious diseases (GBD 2016 DALYs and HALE Collaborators 2017). Indeed, the diseases of affluent societies are mainly cardiovascular conditions, cancers, diabetes, chronic respiratory conditions, and neurodegenerative conditions, which are typically caused by lifestyle choices, including a more sedentary life, smoking and diet, and senescence. Such risk factors are further compounded by the effects of widespread environmental and indoor air pollution, underdeveloped and poor enforcement of work and traffic safety regulations, and other characteristics of transition countries (Hunter and Reddy 2013; Bollyky et al. 2015; Nugent et al. 2018).

2 Neglected Tropical Diseases in East Asia

This dynamic development is reflected in the regional epidemiology of neglected tropical diseases (NTDs), a group of conditions frequently found in impoverished communities in tropical and sub-tropical countries (Hotez et al. 2007; Utzinger et al.

Table 1 Key social and economic indicators of selected East Asian countries

Country	Human Development Index (HDI), 1990 (UNDP)	Human Development Index (HDI), 2015 (UNDP)	GDP per capita growth (annual), median 1990–2015 (World Bank)	Urban population (% of total), 2015 (World Bank)	Poverty (% population living on <US$1.9 a day, 2011) (World Bank)	% of population with access to improved sanitation, 2015 (World Bank)	Gini coefficient (World Bank)
Cambodia	0.357	0.563	5.4	20.7	n.a.	42.4	n.a.
People's Republic of China	0.499	0.738	8.8	55.6	1.9	76.5	42.2
Indonesia	0.528	0.689	4.2	53.7	6.8	60.8	39.5
Japan	0.814	0.903	1.3	93.5	0.3	100	32.1
Republic of Korea	0.731	0.901	4.8	82.5	0.3	100	31.6
Lao People's Democratic Republic	0.397	0.586	5.1	38.6	22.7	70.9	36.4
Malaysia	0.643	0.789	3.9	74.7	0.3	96.0	46.3
Myanmar	0.353	0.556	7.9	34.1	6.5	79.6	38.1
The Philippines	0.586	0.682	2.4	44.4	8.3	73.9	40.1
Taiwan	n.a.	0.885[a]	n.a.	78.0[b]	n.a.	n.a.	33.6[b]
Thailand	0.574	0.740	4.4	50.4	0.0	93.0	37.8
Vietnam	0.477	0.683	5.4	33.6	2.8	78.0	34.8

n.a. not available
GDP gross domestic product
[a]Calculated by Taiwan government; [b]CIA World Factbook

2012; WHO 2012). Fifteen of the currently 20 conditions recognized by the World Health Organization (WHO) as NTDs remain endemic in East Asia. However, unlike in the past when these diseases were widespread, they are now mainly localized in marginalized communities in deprived urban and remote rural areas. This extraordinary improvement is the result of both targeted and sustained efforts to control and eliminate NTDs as well as general socio-economic development manifesting itself in improved living conditions, including housing and sanitation, better nutrition, and effective regulations to protect public health in the food safety and veterinary public health areas (Nakagawa et al. 2015). Noted examples for the successful control and elimination of particular NTDs in East Asia include the interruption of *Wuchereria bancrofti* transmission in the People's Republic of China (Sun et al. 2013), which resulted in the certification of lymphatic filariasis elimination in the country. *Schistosoma japonicum* has been eliminated from Japan (Tanaka and Tsuji 1997) and a number of provinces in the People's Republic of China (Rollinson et al. 2013); and the epidemiological profile of leprosy in Japan, South Korea, and Taiwan shows the hallmarks of transmission interruption of *Mycobacterium leprae*, its causative agent (Koba et al. 2009; Lee et al. 2015). Meanwhile, the prevalence and infection intensity of soil-transmitted helminthiasis and lymphatic filariasis in a number of countries have also decreased substantially (Tun et al. 2013). However, none of the endemic NTDs has been eliminated from the entire region as transmission continues in marginalized populations (Hotez et al. 2015). Indonesia consistently reports the third highest number of new leprosy cases in any country in the world (Anonymous 2017), while *S. japonicum* continues to be endemic along the Yangtze River in the People's Republic of China as well as in the Philippines and in isolated area in Indonesia (Song et al. 2016). Lymphatic filariasis is also still endemic in many tropical countries in the region (Sudomo et al. 2010) (Table 2; Fig. 1).

While considerable progress has been made in the control and elimination of certain NTDs, sustained reductions are still to be achieved for others. Food-borne trematodiases, including clonorchiasis and opisthorchiasis, have their global hotspot in the region, sustained by particular dietary preferences that are deeply rooted in local cultures (Sripa et al. 2010; Qian et al. 2016). In the populations with the highest food-borne trematodiases burden, extraordinarily high rates of cholangiocarcinoma are observed, and the infections have now been officially recognized as carcinogenic (Hughes et al. 2017). Still, promoting the behavioural changes required to sustainably reduce food-borne trematode infection incidence has proven to be hard. Similarly, the interruption of echinococcosis transmission is in its infancy and only recently has the People's Republic of China, the country with the highest burden from the disease in the region and the global epicentre of *Echinococcus multilocularis* infections, i.e. alveolar echinococcosis, declared a special emphasis on the disease (Qian et al. 2017). Meanwhile, systematic mapping has established that some NTDs are less common than suspected, as is the case with trachoma (Taylor 2016), or have decreased more markedly than anticipated, as is the case with yaws (Marks et al. 2015). Finally, the full distribution of certain NTDs across East Asia is still to be established, including that of cysticercosis, leishmaniasis, snake bite, and mycetoma,

Table 2 Occurrence of NTDs in selected East Asian countries, endemicity and latest number of reported cases

Neglected tropical disease (NTD)	Country											
	Cambodia	People's Republic of China	Indonesia	Japan	Republic of Korea	Lao People's Democratic Republic	Malaysia	Myanmar	The Philippines	Taiwan	Thailand	Vietnam
Dengue and chikungunya	Epidemics	Epidemics	Epidemics	Epidemics	No epidemics	Epidemics	Epidemics	Epidemics	Epidemics	–	Epidemics	Epidemics
Echinococcosis	Not reported	Endemic (*Echinococcus multilocularis*, *E. granulosus*)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	–	Not reported	Not reported
Food-borne trematodiases	Endemic (F, O, P)	Endemic (C, F, P)	Endemic (P)	Endemic (C, F, P)	Endemic (C, F, P)	Endemic (F, O, P)	Endemic (F, P)	Endemic (P)	Endemic (C, F, O, P)	–	Endemic (C, F, O, P)	Endemic (C, F, O, P)
Leishmaniasis, endemicity status (C = cutaneous, V = visceral)	Not endemic	Endemic (C, V)	Not endemic	Not endemic	Not endemic	Not endemic	Not endemic	Not endemic	Not endemic	–	Endemic (C, V)	Not endemic
Leprosy, reported cases (2016)	154	677	16,826	3	4	64	206	2609	1721	–	163	138
Lymphatic filariasis (population requiring preventive chemotherapy; 2016)	Eliminated as public health problem	Eliminated	61,617,614	Eliminated	Eliminated	152,023	120,318	3,623,429	8,455,892	–	Surveillance	Surveillance
Mycetoma, chromoblastomycosis, and other deep mycoses	No data	No data	No data	No data	No data	No data	No data	No data	No data	–	No data	No data
Rabies, reported deaths (2014)	No data	854	No data	0 (2013)	0 (2013)	4	No data	No data	236	–	5	67
Scabies and other ectoparasites	No data	No data	No data	No data	No data	No data	No data	No data	No data	–	No data	No data
Schistosomiasis (population requiring preventive chemotherapy; 2016)	76,241 (*S. mekongi*)	153,436 (*S. japonicum*)	22,675 (*S. japonicum*)	Eliminated	Not endemic	89,042 (*S. mekongi*)	Not endemic	Not endemic	2,939,693 (*S. japonicum*)	–	Not endemic	Not endemic
Snakebite envenoming	No data	No data	No data	No data	No data	No data	No data	No data	No data	–	No data	No data

(continued)

Table 2 (continued)

Neglected tropical disease (NTD)	Country											
	Cambodia	People's Republic of China	Indonesia	Japan	Republic of Korea	Lao People's Democratic Republic	Malaysia	Myanmar	The Philippines	Taiwan	Thailand	Vietnam
Soil-transmitted helminthiasis	1–10%	10–20%	20–50%	Not endemic	Not endemic	20–50%	>50%	20–50%	>50%	–	20–50%	>50%
Taeniasis/cysticercosis	Endemic	Endemic	Endemic	Not endemic	No data	Endemic	Endemic	Endemic	Endemic	–	Endemic	Endemic
Trachoma	Eliminated (validated)	Eliminated (claimed)	Not endemic	Not endemic	Not endemic	Eliminated (validated)	Not endemic	Eliminated (claimed)	Not endemic	–	Not endemic	Endemic
Yaws	Previously endemic	Not endemic	Endemic	Not endemic	Not endemic	Previously endemic	Previously endemic	Previously endemic	Previously endemic	–	Previously endemic	Previously endemic

Data from Global Health Observatory http://www.who.int/gho/neglected_diseases/en/ and Pullan et al. (2014)

C clonorchiasis, *F* fascioliasis, *O* opisthorchiasis, *P* paragonimiasis

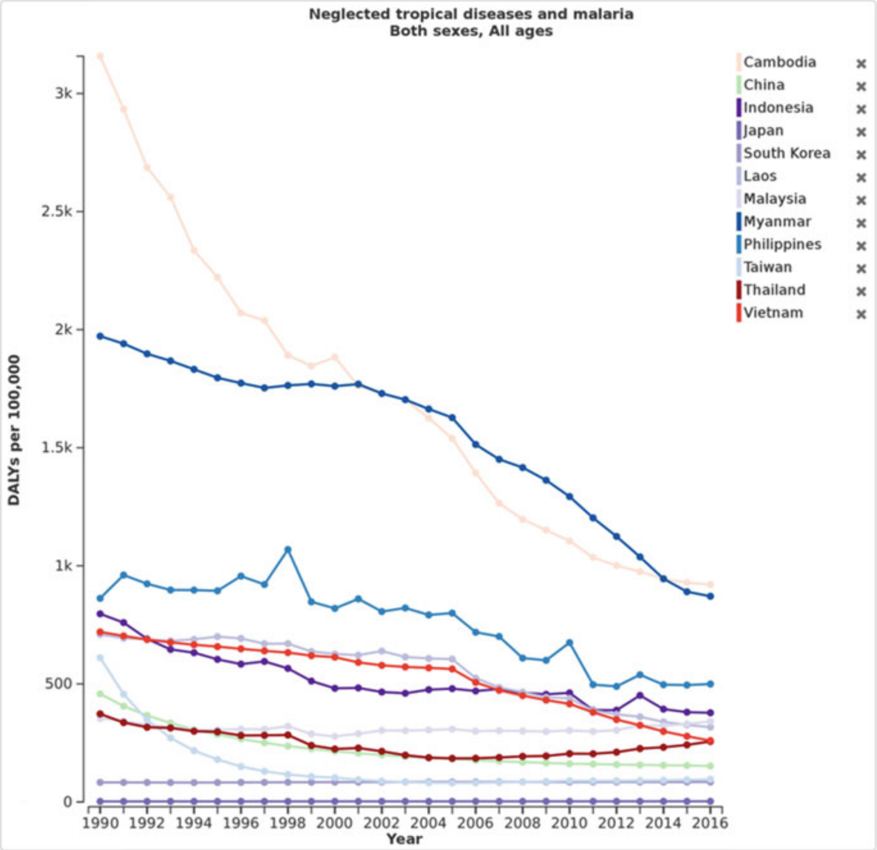

Fig. 1 Evaluation of estimated burden (expressed in disability-adjusted life years (DALYs) per 100,000 population) due to neglected tropical diseases and malaria in selected East Asian countries over the past 25 years. Source: Institute for Health Metrics and Evaluation (IHME), Seattle, United States of America

chromoblastomycosis and other deep mycoses. Of note, the last two groups of conditions have only recently been added to the list of NTDs maintained by WHO.

Still other NTDs are apparently expanding into new areas and populations, increasing in their incidence, or both. Facilitated by global warming, the most efficient dengue vectors are expanding their range, and dengue epidemics are now recorded more frequently, affecting more people and occurring in areas long spared from such calamities (Wartel et al. 2017). Meanwhile, intensive trade of foodstuff and increasing international tourism are fuelling a boom in ethnic cuisines, resulting in increased numbers of food-borne trematode and other food-related infections, as well as taeniasis/cysticercosis (Fürst et al. 2012). The illegal pet trade and other reasons for long-distance animal transports threaten to spread or reintroduce rabies into currently nonendemic areas (Tamashiro et al. 2007). Lastly, with the increase in intercontinental travel for tourism, trade, and labour, there is a latent threat that NTDs currently not endemic in East Asia, such as schistosomiasis mansoni and schistosomiasis haematobia, are introduced and local transmission cycles established, effectively expanding the endemic area of these currently alien diseases (Woodruff et al. 1985). In the absence of local transmission and given that large-scale long-distance travel is a relatively new phenomenon in most East Asian societies, the diagnosis of such infections is particularly challenging as local physicians and diagnostic laboratories are mostly unfamiliar with these diseases (Liu et al. 2018).

Developing epidemiologically effective, scalable and economically sustainable interventions to control NTDs is a challenge in all settings. In East Asia, notable progress has been made in this regard, and a number of innovative technical approaches embedded in comprehensive integrated interventions that are sustained by appropriate funding and political support, have demonstrated the potential of well-designed and multipronged intersectoral programmes with a surveillance-response component readily tailored to local conditions and regularly reviewed to adapt to changing epidemiological, societal, and economic realities, technological progress, and updated long-term goals (Nakagawa et al. 2015). Notable examples for comprehensive, long-term multifaceted control and elimination programmes include the *S. japonicum* control programme in the People's Republic of China, initiated shortly after the establishment of the country in 1949 and sustained ever since (Utzinger et al. 2005; Zhou et al. 2010). In terms of technological innovations, the systematic destruction of snail habitats through the lining of canals and afforestation of marshlands, reduction of buffalo numbers and their separation from water bodies as well as preventive treatment with artemisinins of exposed populations, are particularly noteworthy. Similarly, salt fortification with ivermectin was piloted in the People's Republic of China and contributed to the successful elimination of lymphatic filariasis from the country (Sudomo et al. 2010). Comprehensive video cartoon-based health education to reduce the risk of soil-transmitted helminthiasis has been shown to be effective in the southern part of the People's Republic of China (Bieri et al. 2013), and to combat dengue, innovative vector control measures such as the use of *Wolbachia-Aedes* mosquitoes, community sensitization and the first commercial vaccine against dengue are now widely used across East Asia (O'Neill 2018). Increasingly, the rich experience and apparent effectiveness of NTD control approaches pioneered in East Asia, particularly in the People's Republic of China, are attracting international attention and are studied by other countries. In particular, South-South collaboration and exchange is actively encouraged and financially supported by the Chinese government, which sees international assistance as yet another tool for expanding its international reach and recognition (Xu et al. 2016).

Besides the challenge of ensuring the timely diagnosis of increasingly rare locally endemic NTDs and nonendemic NTDs in travellers and migrants (Liu et al. 2018), East Asian health systems face a new reality where residual infectious diseases including NTDs co-exist with the ever more prominent chronic conditions as well as emerging infections such as HIV. There is only very limited evidence available regarding the interplay between NTDs and other conditions, and both protective (e.g. helminth infections and allergies), neutral (HIV and many parasitic infections), and detrimental (trichuriasis and inflammatory bowel disease; paragonimiasis and hemoptysis) associations and causal links have been described (Hotez 2013). The full effects of global warming; natural disasters; massive infrastructure investments, including reservoirs and canals (Steinmann et al. 2006); and environmental degradation, including the rapid deforestation observed over recent years across much of Southeast Asia and since decades in the People's Republic of China, Indonesia, and the Philippines, remain to be shown.

3 Focus and Content of this Volume

The current book has been developed against this rich and varied backdrop. The second chapter focuses on food-borne trematodiases, a diverse group of diseases that is of premier public health relevance across several East Asian countries and populations. The chapter reviews the remarkable diversity of food-borne trematodiases and their epidemiology, summarizes the options for diagnosis and the clinical manifestations and sequelae of infection, and discusses options for control, including the possible contributions from mathematical modelling.

The third chapter reviews the history of the epidemiology of leprosy across East Asia. Starting more than 100 years ago, it traces the evolution of the efforts to treat and interrupt transmission of *Mycobacterium leprae*, recounts the slow disappearance from societies as they become more affluent, and identifies key factors influencing the reported numbers in each time period. It concludes by drawing attention to the fact that the interruption of transmission does not mean the end of the public health burden from a much-feared disease associated with low mortality but strong stigma and irreversible disability and disfigurement.

The fourth chapter is dedicated to dengue, an NTD with apparently ever-increasing public health relevance. After a short introduction to the disease and review of its epidemiology in East Asia, this chapter focuses on the factors governing the recurrent epidemics, draws attention to the economic impact of these increasingly frequent and massive events, and discusses available and emerging options for control, both of mosquito populations and through vaccination.

The fifth chapter pertains to yaws. The biological basics of this bacterial NTD are reviewed, followed by a detailed discussion of the epidemiology and distribution of the disease in East Asia. Sections on the diagnosis and treatment follow, including a presentation of recent technological advancements in the field. The chapter concludes with an overview of recent attempts to eliminate yaws and the challenges these efforts face.

Rabies is the topic of the sixth chapter. The history of rabies is reviewed and its control in East Asia discussed, together with the prevailing paradigms of the different periods, starting with neglect resulting from insufficient surveillance and consequent lack of effective control. It then describes the advent of post-exposure prophylaxis to control human disease and the shift of attention towards dog rabies vaccination to try and eliminate rabies from cities and countries. Expanding the topic, it then describes "One Health" approaches and discusses the surveillance needs of post-elimination areas to detect any reintroduction of the disease. It concludes with sections on the rabies risk of travellers and recent efforts to achieve rabies elimination across East Asia by 2020.

The penultimate chapter seven pertains to possible interactions of helminth infections and HIV, and opens the focus from a disease-specific view to the significance of co-infections involving helminth NTDs and HIV, a virus that has considerable public health relevance in certain East Asian communities. Following a review of the epidemiology and distribution of various helminth NTDs, the distribution of HIV in East Asia is summarized before focusing on the evidence for co-infections. Possible interactions between helminth and HIV infections in the same patient are then discussed, both based on immunological considerations, survey data, and clinical evidence. The last paragraph focuses on the implications for public health of such co-infections.

The concluding chapter opens the view even further and reviews the evidence for interactions between NCDs and NTDs in East Asia. It analyses the disease and economic burdens of both NTDs and NCDs in East Asia and discusses the significance of NTDs as risk factors for developing NCDs. Next, shared determinants including poverty, urbanization, migration, and psychosocial status are discussed. The second part of the chapter focuses on various aspects related to the control of NTDs and NCDs, discussing policies, integrated service delivery through primary health care, and community involvement.

The book represents the result of the joint efforts of many individuals and groups. First and foremost, we thank the authors of the different chapters for contributing their time and sharing their expertise. Without their dedication and commitment, the development of this book would not have been possible. We also thank the staff at Springer for inviting us to freely develop the concept and content of the book and recruit authors to write the different chapters, for their gentle reminders to keep focused on the project, and for the generous understanding when delays occurred. Finally, we thank the production team for the careful editing of the manuscripts and beautiful layout of the final book.

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Food-borne Trematodiases in East Asia: Epidemiology and Burden

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Contents

Abstract Food-borne trematodiases are a cluster of parasitic helminth infections in humans and animals and belong to the cluster of neglected tropical diseases. The causative helminths dispose of a complex life cycle. As with many helminth infections, most infected people may only experience mild and non-specific clinical signs and symptoms. However, repeated, heavy and long-term infections may lead to severe clinical manifestations and also potentially fatal complications such as cholangiocarcinoma. Diagnosis remains a challenge as reliable, affordable, rapid, and simple-to-use diagnostic techniques are not available. If correctly and early diagnosed, safe, cheap, efficacious, orally administered drugs are available. Globally, the disease burden of food-borne trematodiases is estimated to be well within the range of other and better known neglected tropical diseases (e.g. dengue, leishmaniasis, lymphatic filariasis, onchocerciasis, and schistosomiasis) with a concentration in East and Southeast Asia. Food-borne trematodiases are zoonoses and may also have a negative impact on agri- and aquacultural production in affected regions. Mathematical modelling and analysis of food-borne trematodiases transmission dynamics to inform control and prevention is still in a very early stage, also due to the very limited availability of essential data. The current mainstay of human food-borne trematodiases control is drug-based morbidity control. For improved control, prevention or even elimination, more integrated efforts adopting also an ecosystem and "One Health" perspective are needed.

Keywords Food-borne trematodiases · Neglected tropical diseases · East and Southeast Asia · Epidemiology · Burden of disease · Life cycle · Transmission · Clinical signs and symptoms · Diagnosis · Treatment · Veterinary issues · Economic issues · Mathematical disease modelling · Control and prevention

1 Introduction

Food-borne trematodiases are a group of zoonotic infections caused by parasitic worms of the class Trematoda. Food-borne trematodes (FBT) are transmitted to humans via the ingestion of contaminated food. Depending on their target organ in the definitive host, FBT are also called liver, lung, or intestinal flukes (Fürst et al. 2012a, c). Over 80 different FBT species have been described from human infections (Sithithaworn et al. 2007; Chai 2007; Blair et al. 2007; Mas-Coma et al. 2007; Fürst et al. 2012b), with the first documented cases dating back several thousand years (Mas-Coma et al. 2005; Keiser and Utzinger 2009). Nevertheless, new species are continuously identified, and considerable taxonomic uncertainty remains (Chai 2007; Blair et al. 2007). Currently, only some FBT species are considered to be of public health relevance, namely, *Clonorchis sinensis*, *Fasciola gigantica*, *Fasciola hepatica*, and *Opisthorchis viverrini* among the liver flukes, *Paragonimus* spp. among the lung flukes, and *Echinostoma* spp., *Fasciolopsis buski*, *Gymnophalloides seoi*, *Haplorchis* spp., *Heterophyes* spp., and *Metagonimus* spp. among the intestinal flukes (Blair et al. 2007; Chai 2007; Sithithaworn et al. 2007; Mas-Coma et al. 2007; Fürst et al. 2012a, b, c).

In this chapter, we will focus mostly on the above-mentioned FBT species but will also refer to other species where appropriate. The chapter explains the life cycles and modes of transmission of FBT and highlights epidemiological information about risk factors and population at risk of infection. It continues by describing clinical signs and symptoms, diagnostic methods, treatment options, the current distribution, and burden estimates of food-borne trematodiases. Finally, we conclude by discussing veterinary and economic issues of FBT, opportunities and challenges for mathematical disease modelling, and strategies for disease control and prevention.

2 Life Cycle and Transmission

FBT have species-specific life cycles, but all share certain characteristics, which are illustrated in Fig. 1. A wide range of animals serve as definitive hosts for FBT besides humans. Infections with the liver flukes *C. sinensis* and *O. viverrini* occur in humans and are also frequently found in cats, dogs, pigs, and rats (Sithithaworn et al. 2007). In the case of *Fasciola* spp., although humans are often infected, a variety of domesticated (e.g. buffalos, cattle, donkeys, goats, horses, pigs, and sheep) and more rarely wild animals (e.g. beavers, deer, elks, kangaroos, llamas, rabbits, and rats) act as main definitive hosts (Robinson and Dalton 2009; Mas-Coma et al. 2005; Haridy et al. 2002; Keiser and Utzinger 2009). Canids, felids, and small mammals represent non-human definitive hosts for the lung flukes *Paragonimus* spp. (Blair et al. 2007). Finally, a broad range of mammals and birds feeding on aquatic second intermediate hosts serve as definitive hosts for the diverse group of intestinal fluke infections besides humans (Chai 2007).

After mating in the definitive hosts, FBT produce fertilised eggs. The fecundity varies between species (from <100 eggs per fluke per day, e.g. *Haplorchis taichui*, to often >1000 eggs per fluke per day, e.g. *C. sinensis*) (Lun et al. 2005; Mas-Coma et al. 2005; Andrews 1999; Sato et al. 2009). However, density-dependent effects within the host such as parasite overcrowding can lead to a reduction in parasite egg production (Sithithaworn et al. 1991; Elkins et al. 1991; Valero et al. 2006). The

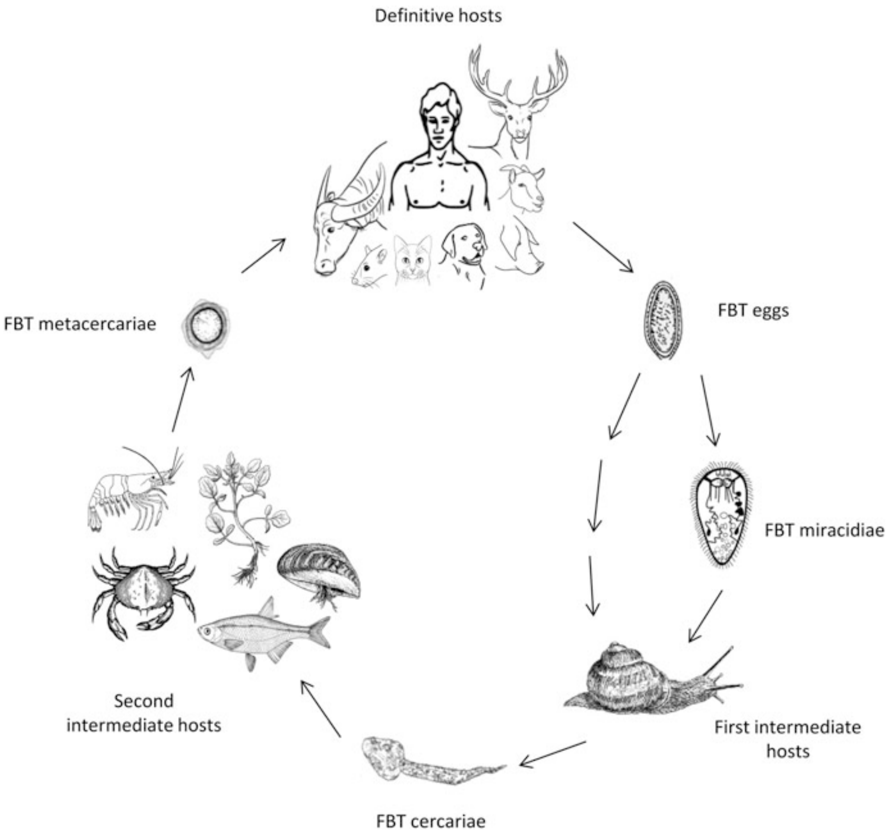

Fig. 1 Schematic life cycle of food-borne trematodes (FBT) (adapted from references Fürst et al. 2012a, c; Keiser and Utzinger 2009)

parasite eggs are released via the hosts' faeces and in case of the lung flukes also via the hosts' sputum. The eggs need to encounter suitable environmental conditions, including appropriate levels of humidity, temperature, and oxygen, and must reach water bodies, which are populated by aquatic snails, the first intermediate hosts for all FBT. There are species-specific idiosyncrasies regarding the exact snail species and the way they are invaded. Eggs of *C. sinensis*, *O. viverrini*, and some intestinal flukes (e.g. *Heterophyes* spp.) are usually directly ingested by the intermediate host snails, and miracidia hatch only within the snails (Lun et al. 2005; Keiser and Utzinger 2009; Fürst et al. 2012a). In contrast, miracidia of *Fasciola* spp., *Paragonimus* spp., and some other intestinal flukes (e.g. *Echinostoma* spp.) already hatch in suitable water bodies and, using chemotaxis and chemokinesis, are either ingested by or actively penetrate the intermediate host snails (Fürst et al. 2012a; Mas-Coma et al. 2005; Andrews 1999). Within the snails, miracidia reproduce and multiply asexually, developing into sporocyst, rediae, and cercariae over several weeks (Fürst et al. 2012a; Keiser and Utzinger 2009).

FBT cercariae are released from the intermediate host snails either by passive extrusion or active escape (Keiser and Utzinger 2009). A single host snail infected with a single *F. hepatica* miracidium may release up to 4000 free-swimming cercariae, for instance (Krull 1941). Cercariae then invade FBT species-specific second intermediate hosts, which include a variety of amphibian, crustacean, fish, insect, and mollusc species, by penetrating the hosts' skin (Fürst et al. 2012a; Keiser and Utzinger 2009). Exceptionally, *Fasciola* spp. and *F. buski* do not need second intermediate hosts as their cercariae directly encyst on aquatic plants such as water caltrop, water chestnut, water cress, water lily, or water lotus (Keiser and Utzinger 2009; Fürst et al. 2012a; Andrews 1999; Mas-Coma et al. 2007). In the second intermediate hosts or attached to aquatic plants, the encysted cercariae develop into metacercariae, which are the infective stage for the definitive hosts (Fürst et al. 2012a; Keiser and Utzinger 2009; Mas-Coma et al. 2007; Andrews 1999). In an annex of a comprehensive technical report on food-borne trematodiases, the World Health Organization (WHO) has published a list of all known first and second intermediate hosts (WHO 1995).

Definitive hosts, including humans, become infected when ingesting viable metacercariae by consuming contaminated food (Fürst et al. 2012a; Keiser and Utzinger 2009; Lun et al. 2005; WHO 1995). Sufficiently high or low temperature kills the metacercariae and, hence, properly cooked or deep-frozen food is considered safe. The inhibition of metacercariae infectivity by means of other food processing methods (e.g. acidification, disinfection, drying, irradiation, pressure treatment, salting, smoking, or washing) remains debated (Fürst et al. 2012c; WHO 1995; Graczyk and Fried 2007; Sithithaworn et al. 2009). A theoretical risk of water-borne infection exists for *Fasciola* spp. and *F. buski*, but such risk is considered small (WHO 1995; Fürst et al. 2012c; Graczyk and Fried 2007). In the definitive host, metacercariae excyst in the intestine, and the hermaphroditic juvenile flukes migrate to their target organs (i.e. liver, lung, or intestine), where they mature, mate, and start producing eggs, thereby completing their life cycles (Fürst et al. 2012a, c; Keiser and Utzinger 2009). In the human host, adult FBT may live from several months (many intestinal flukes) (Fried et al. 2004; Andriamanantena et al. 2005; Huffman and Fried 1990) to several years (e.g. *Fasciola* spp., *Paragonimus* spp., and some intestinal flukes) (Mas-Coma et al. 2005; Blair et al. 2007; Sithithaworn et al. 2009; Sithithaworn and Haswell-Elkins 2003) and even up to more than two decades (e.g. *C. sinensis* and *O. viverrini*) (Kaewpitoon et al. 2008b; Lun et al. 2005; Attwood and Chou 1978).

3 Epidemiology

The epidemiology of food-borne trematodiases is governed by complex interactions between ecological, socio-economic, and behavioural factors. Together, these factors need to permit the different parasite stages to survive and reach susceptible intermediate and definitive hosts. Environmental factors such as air temperature, vegetation, rainfall, water current, water quality, and water temperature influence the population dynamics of host species and therefore the possibility for FBT to establish their life cycles. For instance, the influence of climatic factors on fascioliasis transmission has been demonstrated (Fuentes 2006, 2007). Also, examples of man-made water pollution leading to local extinction of the *Paragonimus* spp. intermediate hosts and consequently reduced paragonimiasis prevalences in humans have been documented (Keiser and Utzinger 2009; Blair et al. 2007). Other socio-economic developments such as the exponential growth of aquaculture production and the implementation of irrigation systems, coupled with often still inadequate sanitary facilities at less wealthy production sites, have favoured the spread of the disease (Keiser and Utzinger 2004, 2005, 2009; Mas-Coma et al. 2007; WHO 1995; Sithithaworn et al. 2009). Demographic changes such as human population growth, increasing urbanisation and mobility, together with expanding food distribution networks, have led to the occurrence of human food-borne trematodiases in locations distant from naturally endemic areas. This effect has been amplified by the increasing wealth and associated lifestyle changes, which has led to the increased consumption of exotic foods (Li et al. 2010; Fürst et al. 2012a; Keiser and Utzinger 2009; Blair et al. 2007). However, the main behavioural driver behind human FBT infections is probably still the ingestion of undercooked or pickled aquatic products because of their high ethnic, cultural, and nutritional value (Keiser and Utzinger 2009; Fürst et al. 2012a). Hence, most human FBT infections still occur in distinct areas, where the parasites successfully sustain their life cycles and people consume certain traditional food dishes (Schratz et al. 2010; WHO 1995). Such traditional foods include raw grass carp and pickled or wine-soaked ("drunken") crabs in the People's Republic of China, raw oysters and raw crab meat with soy sauce (*gejang*) in Korea, dishes containing raw crab or fish (*kinilaw*) in the Philippines, and uncooked and fermented small- or medium-sized fish (*koi pla*, *lab pla*, *pla ra*, and *pla som*) and raw crabs (*poo*) in Thailand and Lao People's Democratic Republic (WHO 1995; Sripa et al. 2011; Sithithaworn et al. 2007; Kaewpitoon et al. 2008a).

Probably because of differing traditions and eating habits, men are more often suffering from clonorchiasis and opisthorchiasis, while women are more frequently affected by fascioliasis. For instance, men may consume more risky food during certain traditional festivities or—as a patient's perspective from Lao People's Democratic Republic (Fürst et al. 2012c)—may be more frequently engaging in recreational fishing with friends and subsequent consumption of the raw or undercooked catch. Gender-specific differences appear to be less marked for paragonimiasis and intestinal fluke infections (Fürst et al. 2012b; Keiser and Utzinger 2009; Mas-Coma et al. 1999, 2005; Sithithaworn et al. 2007, 2009). Age-prevalence curves demonstrate that already young children are at risk of liver and lung fluke infections and the age-specific prevalence rates usually steadily increase until plateauing in the middle age groups. Often, the liver and lung fluke infections are sustained by the longevity of the parasites and by continuous re- and superinfection due to unchanged eating habits. Age-prevalence profiles for intestinal fluke infections are less certain because of the lack of data but may resemble those of liver and lung flukes (Fürst et al. 2012b; Keiser and Utzinger 2009; Mas-Coma et al. 2005; Sithithaworn et al. 2007, 2009;

Sithithaworn and Haswell-Elkins 2003; Upatham and Viyanant 2003; Choi et al. 2010). However, gender- and age-specific prevalence profiles may vary locally as changes in the interplay between ecological, socio-economic, and behavioural factors, and effects of disease control efforts over the past years, may alter local epidemiological situations (WHO 1995; Fürst et al. 2012a, b; Keiser and Utzinger 2009; Blair et al. 2007; Li et al. 2010).

4 Clinical Signs and Symptoms

In common with other helminthiases, most people infected with FBT are asymptomatic, and when symptoms occur they are often non-specific. Among the clinical symptomatic group, severity is associated with worm burden, typically measured by faecal egg counts, and the duration of infection. Because of the diverse habitats occupied by the trematodes in humans, clinical presentations depend on the affected organs (Fürst et al. 2012c).

As the human liver flukes *C. sinensis* and *O. viverrini* inhabit the biliary system, the pathogenesis of clonorchiasis and opisthorchiasis is confined to the hepatobiliary region. The primary pathogenesis occurs in the bile duct epithelial tissue and is caused by irritation and damage due to mechanical, chemical, and/or immune-mediated effects (Saijuntha et al. 2014; Sripa et al. 2012; Hong and Fang 2012; Rim 2005). Mechanical injury is caused by the suckers of feeding and migrating flukes and contributes to biliary ulceration. Chemical irritation arises from metabolic products from the liver flukes' tegument and excretory openings. Some of these products, such as *O. viverrini* granulin-like substances, are highly mitogenic to fibroblast or biliary cells and have been implicated in the induction of epithelial cell proliferation leading to hyperplasia of biliary epithelial cells (Smout et al. 2009, 2011; Sripa et al. 2007). Increased endogenous formation of N-nitroso compounds (i.e. nitric oxide and other reactive oxygen intermediates resulting from inflammatory cells during infection) and enhanced hepatic activation of carcinogens play central roles in pathogenesis and create highly mutagenic conditions for subsequent cancer development (Yongvanit et al. 2012). As a result, an increased susceptibility to cholangiocarcinoma (CCA) is the most severe clinical aspect of liver fluke infection (Fig. 2a–d). CCA is a primary malignancy of the biliary tract, and patients usually have very poor prognosis (Patel 2014). In Asia, liver fluke infections (*C. sinensis* and *O. viverrini*) are main risk factors for CCA, while further to the West, CCA is mainly associated with primary sclerosing cholangitis and other gall bladder diseases (Sithithaworn et al. 2014; Khan et al. 2012; Haswell-Elkins et al. 1994).

People with chronic *C. sinensis* and *O. viverrini* infections usually present with few specific signs and symptoms. An increased frequency of palpable liver may be diagnosed, but biochemical and haematological tests remain unremarkable (Elkins et al. 1996; Rim 2005). Furthermore, patients presenting with clonorchiasis and opisthorchiasis may suffer from loss of appetite, fullness, indigestion, diarrhoea, pain in the right upper quadrant, lassitude, weight loss, ascites, and oedema (Rim

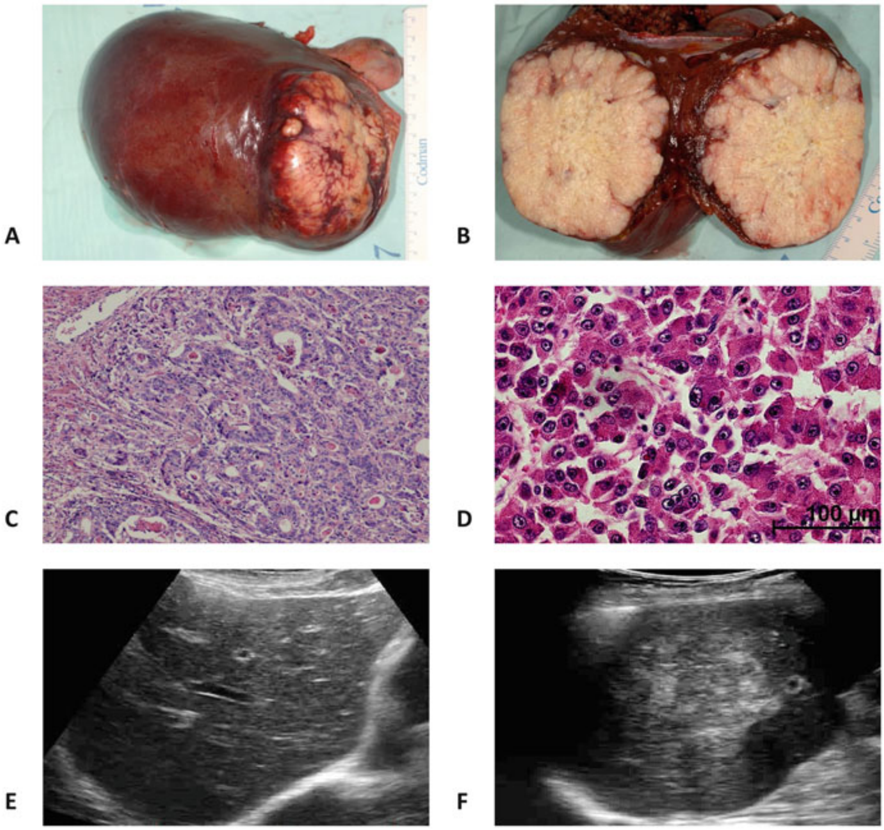

Fig. 2 Clinical manifestations of liver fluke-induced cholangiocarcinoma. Gross specimen from a liver resection from a cholangiocarcinoma patient (**a**, **b**); histology section of cholangiocarcinoma at low (10×; **c**) and high (40×; **d**) magnification; and ultrasonogram of periportal fibrosis (**e**) and cholangiocarcinoma (**f**) (Source: Profs. Puangrat Yongvanit, Narong Khuntikeo, Paiboon Sithithaworn)

2005; Pungpak et al. 1985). Cholangitis, obstructive jaundice, intra-abdominal mass, cholecystitis, and gallbladder or intrahepatic stones may occur as complications (Pungpak et al. 1985; Rim 1986). Ultrasonography is used for screening high-risk groups with biliary fibrosis and other hepatobiliary diseases such as gallbladder enlargement, sludge, gallstones, and poor renal function (Fig. 2e, f) (Chamadol et al. 2014; Choi et al. 2005; Elkins et al. 1996; Mairiang et al. 2012). Even CCA patients usually present with non-specific signs and symptoms such as fever, anorexia, and dyspepsia, and only a few may experience hepatomegaly and obstructive jaundice (Uttaravichien et al. 1999; Khuntikeo et al. 2014).

Liver flukes of the genus *Fasciola* can cause serious medical conditions, not least because of their size. Symptomatic human fascioliasis can be classified as acute or chronic based on the clinical manifestations and laboratory findings. Clinical manifestations are similar to those of clonorchiasis and opisthorchiasis, may start around 2 months after the ingestion of metacercariae, and include constitutional symptoms, upper abdominal pain, and headache (Mas-Coma et al. 2014; Chen et al. 2013). Signs of acute fascioliasis are weakness, hepatomegaly, splenomegaly, anaemia, eosinophilia, and leukocytosis. Often after a latent phase, chronic fascioliasis may present with ascending cholangitis, cholelithiasis, cholecystitis, pancreatitis, biliary cirrhosis, and hepatic fibrosis.

Pathological changes and clinical features associated with infections of the lung fluke *Paragonimus* spp. depend upon the parasites' migratory routes and maturational stages (Nakamura-Uchiyama et al. 2002; Blair 2014). During migration, extrapulmonary paragonimiasis is characterised by pathological changes around the juvenile flukes. Once in the lungs, the flukes mature, mate, and produce eggs, thereby causing the typical pathological changes and clinical manifestations of pulmonary paragonimiasis. Regardless of location or maturational stage, the parasites provoke an accumulation of inflammatory cells, which is often called eosinophilic abscess. Over time, fibrosis progresses to granulomatous lesions. In the lungs, these lesions and physic-chemical actions of the flukes result in fibrotic, greyish-white capsules harbouring pairs or triplets of worms, eggs, and thick, blood-streaked fluid (Blair 2014; Yi et al. 2014).

Characteristic manifestations of pulmonary paragonimiasis are chronic productive cough with brownish purulent sputum containing blood streaks and parasite eggs ("rusty sputum"). Maybe one fifth of all paragonimiasis patients remain asymptomatic. Others may experience fever, night sweats, and chest pain (Nakamura-Uchiyama et al. 2002; Blair 2014). Eosinophilia occurs during acute to subacute infection but may disappear in chronic infection (Nakamura-Uchiyama et al. 2001). In acute and subacute stages, when the worms migrate in the pleural cavity, pleural effusion and pneumothorax are common.

Unlike liver and lung flukes, most intestinal fluke infections cause no or only very mild symptoms. A recent study in Lao People's Democratic Republic found a person harbouring more than 120,000 *H. taichui* without significant symptoms (Chai et al. 2013b). Symptoms of intestinal fluke infections may include poor appetite, flatulence, mild abdominal pains, fever, diarrhoea, and vomiting (Rim et al. 1982; Gutierrez 2000). Severe cases may also suffer from indigestion, anaemia, ascites, or oedema of the face, abdomen, and legs, as well as intestinal obstruction. Extensive intestinal ulceration may result in malabsorption, leading to severe malnutrition and wasting (Chai 2007; Fürst et al. 2012c; Sithithaworn et al. 2009).

Sometimes FBT substantially deviate from their usual migratory paths in the human host and end up in atypical sites. Reports indicate that such a phenomenon is most frequently observed in *Paragonimus* spp., but *Fasciola* spp. and some intestinal flukes have also been identified in such ectopic infections. Reported ectopic locations include the skin, abdominal organs, genitalia, eyes, heart, or central nervous system including the brain. Depending on the ectopic location, clinical manifestations may vary and fatal infections occur (Sithithaworn et al. 2009; Fürst et al. 2012b, c).

5 Diagnosis

Currently available diagnostic methods for FBT are unsatisfactory, and diagnostic problems commonly occur for patients with light and mixed species infections. An affordable, rapid, and simple to use diagnostic approach with high sensitivity and specificity is urgently needed to improve individual patient care, monitoring and evaluation of disease control programmes, disease surveillance, and burden estimation (Johansen et al. 2015). The current diagnostic techniques used for FBT are similar to those for other helminths (Hong and Fang 2012; Sithithaworn et al. 2007). The most widely used diagnostic method is based on the microscopic detection of parasite eggs in patients' faeces, sputum, and/or duodenal content. Techniques used for faecal examination include the formalin-ether concentration, Kato-Katz thick smear, and Stoll's dilution egg count. Depending on the available facilities, direct smear or sedimentation techniques may also be used. Repeated stool examinations are necessary to provide sufficient sensitivity, particularly with regard to the confirmation of low-intensity infections (Johansen et al. 2010). However, multiple sample collection can be difficult in practice and costly. Morphological similarity of eggs from different trematodes, frequently occurring co-infections, low egg production by some FBT, crowding effects, obstruction in hosts' organs, and uneven distribution of eggs in samples further complicate the diagnosis (Kaewkes et al. 1991; Tesana et al. 1991; Nguyen et al. 2007; Pitaksakulrat et al. 2013; Bless et al. 2015; Fürst et al. 2012c). Occasionally, adult flukes in faeces or sputum (*Paragonimus* spp.) or their identification during surgery facilitate the direct parasitological diagnosis. Complementary tools in well-equipped institutions include ultrasound, X-ray, computed tomography, and magnetic resonance imaging (Keiser and Utzinger 2009; Fürst et al. 2012c; Blair et al. 2007; Sithithaworn et al. 2007, 2009; Mas-Coma et al. 2007; WHO 1995).

FBT antigen detection in serum and faecal samples has been tested with variable success and efficiency (Mas-Coma et al. 2014; Johansen et al. 2010; Hong and Fang 2012). Detected antigens may indicate active infections, and such methods could become useful as a supplement or replacement for more direct parasitological methods in field surveys in the near future, particularly as the use of recombinant antigen technology has reduced the respective labour intensity and cost (Gonzales Santana et al. 2013). Also of note, the diagnosis of fascioliasis by antibody detection is highly sensitive, and an Enzyme-Linked ImmunoSorbent Assay (ELISA) kit is commercially available (Cabada and White 2012; Caban-Hernandez et al. 2014).

Even more accurate, but still infrequently used in clinical diagnostics, are modern molecular diagnostic methods such as real-time polymerase chain reaction (PCR), multiplex PCR, restriction fragment length polymorphism (RFLP), random amplification of polymorphic DNA (RAPD), single-stranded conformation polymorphism (SSCP), loop-mediated isothermal amplification (LAMP), and pyrosequencing. These methods are particularly suited to diagnose environmental and clinical samples as multiple genotypes can be detected. Molecular markers have been proven to be reliable and accurate as long as appropriate development and testing are performed within the limitations of each method (Johansen et al. 2010; Monis and

Andrews 1998). Importantly, such methods also have the potential to detect all life cycle stages of the parasites and offer new perspectives for monitoring parasite transmission and food safety. The disadvantages, however, are high costs and the need for specialist expertise and facilities, which limit the routine use of these methods at the point of care in endemic regions in the foreseeable future (Fürst et al. 2012c).

6 Treatment

A single dose praziquantel of 40 mg/kg body weight is effective against clonorchiasis and opisthorchiasis and is the treatment of choice in large-scale treatment programmes (Keiser and Utzinger 2004; Sithithaworn et al. 2009). However, experience from East Asia indicates that higher dosages such as three times 25 mg/kg per day for 2 days have to be administered to cure heavy *Clonorchis* and *Opisthorchis* infections. Adverse events occur frequently but are transient and rarely severe and may include dizziness, vomiting, and abdominal pain (Sithithaworn et al. 2009). If treated in time, most pathological changes in the gallbladder are also reversed by elimination of the parasites (Sithithaworn et al. 2009; Pungpak et al. 1997). A recent randomised trial conducted in Lao People's Democratic Republic found that a single dose of 200 mg (age below 14 years) or 400 mg (age above 14 years) tribendimidine results in a 99% egg reduction rate in individuals with opisthorchiasis, which is equivalent to praziquantel (Soukhathammavong et al. 2011). Another randomised trial from the People's Republic of China suggested that tribendimidine also has a comparable efficacy to praziquantel in the treatment of clonorchiasis but with fewer adverse events (Qian et al. 2013). Furthermore, artesunate and artemether showed relatively high efficacy against *C. sinensis* and *O. viverrini* in rodent models (Keiser et al. 2006).

The treatment of choice against fascioliasis is triclabendazole in a single dose of 10 mg/kg. This treatment offers acceptable cure rates and is active against both juvenile and adult parasites, and adverse events are usually temporary and mild (Keiser and Utzinger 2004). Of note, praziquantel is ineffective against *Fasciola* spp. even at high doses (Sithithaworn et al. 2009).

The recommended treatment for paragonimiasis is 25 mg/kg praziquantel three times a day for 2–3 days (Nakamura-Uchiyama et al. 2002). Usually, adverse events are mild, and pulmonary pathology resolves within 4 months, but urticaria may occur after praziquantel treatment for pulmonary disease (Sithithaworn et al. 2009). Triclabendazole was evaluated as an alternative with some promising results but has proven less effective in Japan (Nakamura-Uchiyama and Nawa 2003) and the Philippines (Belizario et al. 2007) where *Paragonimus westermani* is endemic.

Praziquantel is also effective against all intestinal flukes and is usually administered as 10–20 mg/kg single dose or as 25 mg/kg three times a day (Keiser and Utzinger 2004, 2009; Chai 2007; Sithithaworn et al. 2009). A recent clinical review provides a concise list of all first-choice treatments against the different FBT infections in humans, alternative drugs or dosages, adverse events, limitations to use, and main contraindications (Fürst et al. 2012c). The same clinical review also contains a first suggestion of an integrated diagnostic and treatment algorithm (Fürst et al. 2012c).

7 Current Distribution and Burden Estimates

Despite prevalence reductions in some limited places over the past decades (e.g. Japan) (Nawa et al. 2005; Yoshida 2005), human food-borne trematodiases are currently considered a cluster of emerging infectious diseases (Keiser and Utzinger 2005, 2009). In 1995, WHO estimated the total global number of people infected by FBT at 41.7 million (WHO 1995). A systematic review indicated that the same indicator may have reached 56.2 million a decade later, with 7.9 million suffering from severe sequelae and more than 7000 people dying because of their infection (Fürst et al. 2012b). Another systematic review from 2005 estimated that more than 1 billion people are at risk of FBT infections (Keiser and Utzinger 2005). The most recent Global Burden of Disease Study 2016 (GBD 2016) extrapolated the total global number of people infected by FBT at 74.7 million and the global burden at 1.8 million disability-adjusted life years (DALYs) lost due to human food-borne trematodiases in 2016 (Global Burden of Disease 2016 DALYs and HALE Collaborators 2017; Institute for Health Metrics and Evaluation 2017).

Currently, most human FBT infections and the majority of the respective disease burden are reported from East and Southeast Asia (Table 1) (Institute for Health Metrics and Evaluation 2017; Fürst et al. 2012b; WHO 1995). The distribution and disease burden of *C. sinensis* are concentrated in East and Southeast Asia, including the far eastern part of the Russian Federation. Likewise, *O. viverrini* is mainly endemic in East and particularly Southeast Asia, with another Opisthorchiidae species, *O. felineus*, occurring only further to the North and West in Central, Northern, and Western Eurasia. Of note, the highest incidence of CCA occurs in Northeast Thailand, where the carcinogenic *O. viverrini* is endemic, with an estimated 20,000+ deaths due to CCA annually (Bundhamcharoen et al. 2011). Last, the liver fluke *Fasciola* spp. is present in East and Southeast Asia but is also found beyond in significant numbers. For the lung fluke *Paragonimus* spp. and the group of intestinal flukes, East and Southeast Asia represent a major hotspot. Other *Paragonimus* spp. endemic areas are in Latin America, and human case reports of intestinal fluke infections come from all continents (WHO 1995; Fürst et al. 2012a, b, c; Keiser and Utzinger 2005; Sithithaworn et al. 2009). Because of the increasing food trade, human migration, the popularity of certain dishes beyond their traditional origin, and international travel, cases of human food-borne trematodiases increasingly occur also in non-endemic areas (Fürst et al. 2012a, c; Keiser and Utzinger 2005; Nawa et al. 2005; Sithithaworn et al. 2009).

Table 1 lists the different FBT species that have been reported from autochthonous human infections in the different East and Southeast Asian countries. Furthermore, Table 1 presents the DALYs lost per 100,000 population and the total DALYs lost in

Table 1 Distribution and burden estimates for human food-borne trematodiases in East and Southeast Asia in 2016

Reference area (global, national)	Food-borne trematode species reported from autochthonous human cases in the literature[a]	DALYs per 100,000 population[b]	95% UI[b]	Total DALYs[b]	95% UI[b]
Total global	Cs, Ov, F, P, IF	23.7	12.2–42.0	1,771,200	923,900–3,158,400
Thailand	Cs, Ov, F, P, IF	148.8	32.4–346.8	100,458	21,846–234,061
People's Republic of China	Cs, F, P, IF	113.6	55.2–213.6	1,553,550	755,158–2,920,287
Lao People's Democratic Republic	Ov, F, P, IF	64.3	17.1–147.5	4640	1230–10,634
South Korea	Cs, F, P, IF	49.0	31.7–69.5	24,679	15,952–34,999
Vietnam	Cs, Ov, F, P, IF	24.3	15.4–34.4	22,860	14,544–32,386
Philippines	Cs, Ov, F, P, IF	5.4	2.7–9.8	5558	2759–10,060
Japan	Cs, F, P, IF	2.2	0.9–4.2	2768	1188–5258
Bangladesh	IF	ND[c]	ND[c]	ND[c]	ND[c]
Cambodia	Ov, F, P, IF	ND[c]	ND[c]	ND[c]	ND[c]
India	Cs, Ov, F, P, IF	ND[c]	ND[c]	ND[c]	ND[c]
Indonesia	P, IF	ND[c]	ND[c]	ND[c]	ND[c]
Malaysia	F, P, IF	ND[c]	ND[c]	ND[c]	ND[c]
Myanmar	P, IF	ND[c]	ND[c]	ND[c]	ND[c]
Nepal	F, P	ND[c]	ND[c]	ND[c]	ND[c]
Papua New Guinea	P	ND[c]	ND[c]	ND[c]	ND[c]
Singapore	Cs, F	ND[c]	ND[c]	ND[c]	ND[c]
Sri Lanka	P	ND[c]	ND[c]	ND[c]	ND[c]
Taiwan	Cs, F, P, IF	ND[c]	ND[c]	ND[c]	ND[c]

DALYs, disability-adjusted life years; UI, uncertainty interval; Cs, *Clonorchis sinensis*; Ov, *Opisthorchis viverrini*; F, *Fasciola* spp.; P, *Paragonimus* spp.; IF, intestinal flukes; ND, not determined

[a] Data from a comprehensive systematic review, considering literature published between January 1, 1980, and September 30, 2011, without any language restriction. For further information on the systematic review, see Fürst et al. (2012a, b, c)

[b] Data from Institute for Health Metrics and Evaluation (2017), Global Burden of Disease 2016 DALYs and HALE Collaborators (2017)

[c] East and Southeast Asian countries with reports of autochthonous human food-borne trematodiases cases identified in a comprehensive systematic review (see also footnote 'a' above), but no human burden estimates due to insufficient information for modelling predictions

the respective countries due to human FBT infections. The data originate from a comprehensive systematic review (Fürst et al. 2012a, b, c) and the GBD 2016 (Institute for Health Metrics and Evaluation 2017; Global Burden of Disease 2016 DALYs and HALE Collaborators 2017). At the top of Table 1 are some of the countries, which are currently well-known for their FBT endemicity, namely, Thailand, People's Republic of China, Lao People's Democratic Republic, Korea, and Vietnam. At the bottom are some countries with reports of autochthonous human FBT infections in the literature, but no disease burden estimates (i.e. Bangladesh, Cambodia, India, and Indonesia) due to insufficient information for modelling predictions. Also of note, the different GBD estimates [GBD 2010 (Murray et al. 2012), GBD 2013 (Global Burden of Disease 2013 DALYs and HALE Collaborators 2015), GBD 2015 (Global Burden of Disease 2015 DALYs and HALE Collaborators 2016), and GBD 2016 (Global Burden of Disease 2016 DALYs and HALE Collaborators 2017)] for prevalence-based DALYs lost due to FBT globally and during the respective reference years varied substantially from 1.7 to 3.6 million. The uncertainty surrounding the respective burden estimates was also explicitly mentioned in the GBD 2010 (Murray et al. 2012) and is still reflected in sometimes very wide 95% uncertainty intervals (Murray et al. 2012; Global Burden of Disease 2013 DALYs and HALE Collaborators 2015; Global Burden of Disease 2015 DALYs and HALE Collaborators 2016; Global Burden of Disease 2016 DALYs and HALE Collaborators 2017; Institute for Health Metrics and Evaluation 2017). Besides, there are also two incidence-based DALY estimates of 0.7 and 2.0 million, which both—and unlike the aforementioned GBD estimates—consider also human death due to severe complications of FBT infections (i.e. CCA and ectopic infections) (Torgerson et al. 2015; Fürst et al. 2012b). All these ambiguities require further clarification. Hence, the figures presented in Table 1 should be considered as intermediate results of continuous efforts to better capture the burden of human FBT infections and should be interpreted with caution.

Within endemic countries, human food-borne trematodiases often have a highly focal occurrence (WHO 1995; WHO and FAO 2004). This focal occurrence is the result of the previously mentioned complex interactions between ecological, socio-economic, and behavioural factors as the change in just one of these factors may lead to the spread or decline of human infections (Fürst et al. 2012c; Sithithaworn et al. 2009; Keiser and Utzinger 2009). Within the endemic foci, the distribution of the trematode worms is usually highly aggregated with a few people harbouring most of the flukes (Fürst et al. 2012b, c). Furthermore, infections with more than one FBT species are common in endemic areas as they are all acquired by the consumption of raw and undercooked food (Fürst et al. 2012c; Sayasone et al. 2009).

8 Food-borne Trematodiases as a Veterinary and Economic Issue

FBT are also of veterinary importance as they infect agricultural and aquacultured animals, domestic pets, and wildlife. Besides reductions in animal wellbeing, animal infections result in economic losses in livestock and are an important issue for human disease control and prevention (Sithithaworn et al. 2009; Fürst et al. 2012a, b; WHO 1995; Keiser and Utzinger 2009; Over et al. 1992). As in humans, animal morbidity and mortality depend on the susceptibility, the pathogenicity of the parasite species, and the intensity and duration of infection (Over et al. 1992). Animal infections may result in lowered growth rates, weight loss, reduced quantity and quality in meat, milk, and wool production, and decreased fecundity (Over et al. 1992; WHO 1995; Saleha 1991).

Because of the importance of herbivores in agricultural production and the transmission route and worldwide distribution of the plant-borne liver flukes *Fasciola* spp., fascioliasis is—from an economic point of view—among the most important parasitic diseases of livestock. Globally, high prevalences of fascioliasis have been reported in cattle, buffalos, sheep, and goats (Over et al. 1992; Torgerson and Claxton 1999). In 1997, it was estimated that 350 million cattle and 250 million sheep were at risk of fascioliasis (Hillyer and Apt 1997). As *Fasciola* spp. feed on the blood and parenchymal cells of their hosts, they can cause serious animal morbidity and mortality and as a consequence substantial productivity losses (WHO 1995). For instance, estimates from the 1980s indicated that 22% of water buffalo livers and 2–3% of cattle livers had to be condemned after slaughtering in Leyte, Philippines (Sabarez et al. 1981). Mortality and lowered weight may have resulted in losses of US$35 million and US$15 million in cattle and buffalos, respectively, in Indonesia (Ronoharjo et al. 1985). In 1992, the United Nations Food and Agriculture Organization (FAO) compiled a database on the distribution and impact of helminth diseases of livestock in developing countries and concluded that liver fluke infections are "an important regional threat to animal production" (Over et al. 1992). Two years later, FAO estimated the total economic loss attributable to livestock fascioliasis at over US$3 billion per year (FAO 1994). However, extrapolations published in 2008 by the Australian Centre for International Agricultural Research concluded that the costs due to fascioliasis in cattle and buffalos alone and only in some selected East and Southeast Asian countries may range between 4.2 and 11.6 billion Australian dollars (≈US$3.5–9.9 billion) (Copeman and Copland 2008). Overall, additional evidence on the economic cost of livestock infection is urgently needed (Cadmus and Adesokan 2009; Charlier et al. 2012; Espinoza et al. 2010).

Aquaculture production and trade have been rapidly growing over the past decades with a particularly focus in Asia, and it has become an important source of animal proteins, minerals, and essential fatty acids in many parts of the world (Keiser and Utzinger 2009; WHO 1995; Ababouch 2006; Bondad-Reantaso et al. 2005). However, in endemic FBT regions, aquaculture may expand the habitat of first (i.e. snails) and second intermediate hosts (i.e. crabs, fish, mussels, and shrimps). In combination with the lack of clean water and poor sanitation, wastewater and excreta use as nutrient sources, and inadequate aquaculture management allowing agricultural, domestic, and wild animals to access ponds, this may favour the spread of FBT (Keiser and Utzinger 2009; WHO 2006; Bondad-Reantaso et al. 2005). For instance, FBTs infected 30–50% of all fish in traditional household ponds in Vietnam (Nguyen et al. 2007; Chi et al. 2008). Hence, while the increased aquaculture production opens new domestic and international markets, potential economic losses from contaminated products may be substantial (WHO 1995; Bondad-Reantaso et al. 2005). Unfortunately, the aquaculture production loss due to FBT is still largely unknown, although most recent laboratory studies suggest that

FBT infections are associated with an increased mortality in some aquaculture fish species (Kopolrat et al. 2015).

FBT infections of domestic cats and dogs appear to be common in endemic areas. For example, in Thailand, prevalences of 36% and 0.4% have been recorded in cats and dogs, respectively (Aunpromma et al. 2012). Likewise in Vietnam, 70% of cats and 57% of dogs have been recorded as infected with *C. sinensis* and/or 11 different intestinal trematode species (Nguyen et al. 2009). *C. sinensis* has also been recovered from 42% of cats and 21% of dogs in southern People's Republic of China (Lin et al. 2011). Zoonotic intestinal trematodes appear to be common in stray cats in Korea (Chai et al. 2013a). There is very limited information on the clinical effects on domestic pets, but one report suggested that heavily infected cats suffered from lethargy, diarrhoea, and ocular and nasal discharge (Aunpromma et al. 2012). However, arguably the most important aspect of FBT in domestic pets is the potential for contamination of watercourses by faeces containing trematode eggs. This can result in the establishment or maintenance of the FBT life cycle and ultimately the contamination of food considered for human consumption. Thus, the control of FBT infection in cats and dogs is also an important aspect for human disease control and prevention (Anh et al. 2007; Clausen et al. 2012).

Besides the losses in animal production, the economic costs of human FBT infections and associated morbidity, absenteeism, reduced productivity, and health care can be considerable. In the 1990s, the annual cost due to *O. viverrini* in Thailand was estimated at US$65 million for lost wages and an additional US$19 million for direct medical care (Loaharanu and Sornmani 1991; WHO 1995). Also considering only lost wages and cost of direct medical care, a more recent opinion piece from 2008 provided an annual estimate of US$120 million due to human opisthorchiasis and opisthorchiasis-induced CCA in Thailand (Andrews et al. 2008). Of note, all these estimates include only some selected categories of the total societal costs (Buzby and Roberts 2009). Hence, to better understand the true disease and economic burden caused by FBT and to better understand, control, and prevent disease transmission, an ecosystem and one health perspective—considering both human and animal health—are inevitable.

9 Opportunities and Challenges for Mathematical Disease Modelling of Transmission Dynamics

Reducing the prevalence and burden of food-borne trematodiases requires rational planning of interventions. Mathematical modelling and analysis are well placed to clarify parasite transmission dynamics and compare the effectiveness of different control strategies. Mathematical models have been useful in planning for the control and elimination of many diseases, from providing qualitative inputs on how best to target disease life cycles (Ross 1905; Smith et al. 2012) and determining optimal vaccination strategies (Hethcote 2000) to providing quantitative predictions to disease eradication programmes (Habbema et al. 1996).

To date, the only two mathematical models of FBT transmission dynamics are a two-stage catalytic (linear ordinary differential equation with constant coefficients) model of *C. sinensis*, used to estimate the egg positive rate from age prevalence data (Song et al. 1979), and a population-based model of *O. viverrini*, calibrated to data from Lao People's Democratic Republic (Vonghachack et al. 2017), used to determine the role of reservoir hosts in maintaining transmission (Bürli et al. 2018). Interestingly, the latter simulated the mean *O. viverrini* worm burden in the definitive hosts (humans and the reservoir hosts, dogs and cats) and the prevalence in intermediate hosts (snails and fish) (Bürli et al. 2018). There are few geographical regions with comprehensive data on infection prevalence in all intermediate and definitive hosts that allow for such types of more detailed models. The study authors analytically calculated the basic reproduction number and performed sensitivity analyses on this crucial indicator to identify weak points in the parasite's life cycle. Also, they calculated the steady-state mean worm burden in humans and identified potential targets for interventions to reduce parasite burden in humans. To analyse the importance of the reservoir hosts, host-specific reproduction numbers were simulated, which describe whether those hosts can sustain transmission or not. The analysis suggested that it is likely that humans can maintain transmission and interventions only targeted at humans could interrupt transmission of the parasite in this part of Lao People's Democratic Republic (Bürli et al. 2018).

The development of these first two mathematical disease transmission models largely followed earlier efforts on schistosomiasis, a related trematodiasis. Schistosomes have a similar life cycle as FBT, with the exception that they do not have an additional stage in secondary aquatic hosts. Therefore, with additional state variables for the secondary hosts as in the model described above, schistosomiasis models could form the basis of additional modelling efforts related to FBT transmission dynamics. To get an idea and as an overview over potentially relevant advances in schistosomiasis modelling in the last 40 years, extensions of population-based models have included schistosome larval population dynamics (Woolhouse 1991), the latent period in snails (Woolhouse 1991; Barbour 1978), snail population dynamics (Woolhouse 1991), heterogeneity in human exposure (Woolhouse 1991; Barbour 1978; Woolhouse et al. 1991, 1998), human age structure (Hisakane et al. 2008; Williams et al. 2002; Woolhouse et al. 1996), acquired immunity in humans (Barbour 1978; Woolhouse et al. 1996), the existence of reservoir mammalian hosts (Woolhouse 1991; Hisakane et al. 2008; Williams et al. 2002; Allen and Victory 2003), and the effects of control interventions (Hisakane et al. 2008; Williams et al. 2002; Woolhouse 1992). Furthermore, more recently, individual-based models that simultaneously capture prevalence and intensity have grown in prominence (Hu et al. 2010).

Of note, in general, macroparasite mean burden models, such as those based on Nåsell and Hirsch (1973), are more appropriate than prevalence-based models for human FBT infection because, unlike microparasites, trematodes cannot reproduce within humans. Consequently, morbidity effects and onward infection to snails are strongly dependent on the intensity of infection within each human. However, the main drawback of these models is that they do not include prevalence of infection in humans, and additional sets of assumptions are required to estimate prevalence from model outputs on intensity of infection. Additionally, these models are inappropriate for evaluating the effectiveness of strategies that selectively target infected populations.

Individual-based models may overcome these problems because they can track the number of worms in each person at each time, thereby simultaneously capturing infection intensities and prevalences. However, they are difficult to analyse mathematically and—unlike simpler population-based models—rarely provide deeper insights into disease transmission. Individual-based models also contain more parameters and require more comprehensive data sets for model calibration.

Prevalence-based susceptible-infected dynamics as currently used in schistosomiasis snail infection models could also be applied to model FBT snail infections in the future. Essential model adaptations would have to consider infection of secondary aquatic hosts and the force of infection from these secondary hosts to human and other animal hosts. Extensions to capture more details of the secondary hosts could include (seasonal) population dynamics, a latent period of the parasites, and the relationship between parasite infection and likelihood of being eaten by humans or animals. Similar models would then need to be developed to include also infection in paratenic, reservoir, and definitive animal hosts. However, at the moment, the very limited data availability is probably still the biggest challenge for the mathematical modelling of FBT and for benefitting from opportunities that arise from such mathematical models.

10 Control and Prevention

Currently, the mainstay of human food-borne trematodiases control is drug-based morbidity control (Sithithaworn et al. 2009). However, only a few endemic countries such as Thailand run larger-scale control programmes specifically targeting FBT infections (Montresor et al. 2008; Sripa et al. 2015). Data for the WHO Western Pacific Region from 2006 indicate that a meagre 0.03% of the population at risk for FBT infections is covered by a specific preventive chemotherapy programme. And even when considering positive spillover effects from other helminth control programmes, this coverage increases only to 0.3% (Montresor et al. 2008). Furthermore, the previously described complexities in the parasites' life cycles ask for more integrated interventions as many non-human definitive hosts may maintain disease transmission in the environment (Sithithaworn et al. 2009; Mas-Coma et al. 1999; Sithithaworn and Haswell-Elkins 2003; Fried et al. 2004; Upatham and Viyanant 2003; Hotez and Ehrenberg 2010; Sripa et al. 2015). In fact, several studies found high human reinfection rates after solely drug-based interventions (Chai et al. 2000; Choi et al. 2010; Upatham et al. 1988; Belizario et al. 2004).

The non-specific clinical manifestations and diagnostic challenges further complicate FBT control and prevention as patients may present late or infections may remain completely unnoticed. As part of its response, Thailand recently initiated the Cholangiocarcinoma Screening and Care Program (CASCAP). The programme utilises ultrasonography as a tool to screen cancer risk groups. As of 2014, the programme has screened up to 40,000 high-risk individuals in Northeast Thailand and diagnosed ca. 1% as positive for CCA. Thanks to the programme, many CCA cases could be identified at an early stage with better chances for curative surgery (Chamadol et al. 2014).

In the future, more integrated control and preventive efforts may complement individual-based chemotherapy, mass deworming, and mass screening. In order to reduce or even completely interrupt disease transmission, additional interventions should adopt an ecosystem and "One Health" perspective and consider intermediate, paratenic, reservoir, and definitive host control, sanitary improvements, and food inspections (Sripa et al. 2015). The development of animal vaccines is underway to reduce disease transmission and economic losses (Fürst et al. 2012c; Sithithaworn et al. 2009; Bergquist and Lustigman 2010; Fairweather 2011). Furthermore, information, communication, and education campaigns should promote safe food processing and behaviour change (Fürst et al. 2012c; Keiser and Utzinger 2009; Blair et al. 2007; Sithithaworn et al. 2007, 2009; Mas-Coma et al. 2007; WHO 1995; Rim 2005; WHO and FAO 2004; Sripa et al. 2015). Provided that sufficient data are available, mathematical modelling may not only help to better estimate disease burden and transmission dynamics in the future but also to select optimal parasite- and location-specific interventions. In order to tackle all these formidable challenges and getting closer to sustainable food-borne trematodiases control, prevention, or even elimination, collaborations within the health sector and also with non-health sectors (e.g. environmental, agricultural, and educational sector) may be essential (Fürst et al. 2012c; WHO 1995; WHO and FAO 2004; Montresor et al. 2008; Nakagawa et al. 2015; Sripa et al. 2015).

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Leprosy in East Asia

W. Cairns S. Smith

Contents

Abstract The epidemiology of leprosy in East Asia has significantly changed over the past 100 years. There is interesting diversity between countries but the general trends have been similar. Over this period, the approach to leprosy control has changed from segregation to case detection and treatment with effective chemotherapy. The introduction of short course multidrug therapy in the 1980s and 1990s produced a dramatic fall in the number of patients registered for treatment of around 95%. Despite the introduction of effective chemotherapy, disability and discrimination due to leprosy remain a challenge often due to late diagnosis and complications of nerve injury. There has been no dramatic impact of chemotherapy on incidence of leprosy but there is a gradual decline in new case detection which in many countries predates the introduction of short course chemotherapy. This decline may be due to

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long term implementation of chemotherapy, either dapsone or multidrug therapy, use of BCG vaccine, and improving socio-economic circumstances. New targets, based on sero transmission, are now being pursued across East Asia based on novel approaches to new diagnostic tools and prophylaxis as well as early case finding and active contact management.

Keywords Chemotherapy · East Asia · Epidemiology · Leprosy · Public health · Trends

This chapter considers the changing patterns of leprosy in East Asia over a period of around 100 years and the factors that have influenced these changes up to the present time. The determinants and general pattern of these changes have been similar across many countries; however, the individual experiences within countries have been quite distinct. The chapter thus reflects both the general trends within the East Asia region and describes the details of the changes within a number of countries to demonstrate the diversity across the region.

1 Historical Aspects of Leprosy in East Asia

One of the earliest and most comprehensive reports on leprosy in East Asia was published in 1897 by James Cantlie. The report was written in response to a challenge by the National Leprosy Fund and covered China, Indo-China, Malaya, the Archipelago and Oceania in the terms used in these days. He systematically collected evidence, from key informants throughout Asia and the Pacific, which he collated and published. He was able to demonstrate that leprosy was not uniformly distributed throughout China but clustered in a number of provinces. His report also summarised the popular beliefs about leprosy, its transmission and its treatment. He explored hypotheses about the role of fish and salt consumption, the impact of segregation in the control of leprosy and possible links to other diseases such as malaria, tuberculosis and syphilis. Lastly, he explored the possible role of migrant workers in the spread of leprosy throughout the Pacific region. Cantlie concluded that overcrowding, poverty and poor nutrition were crucial conditions for the spread of leprosy and that improvements in hygiene conditions were required to eliminate the disease.

Researchers at the Leonard Wood Memorial prepared a supplement to the *International Journal of Leprosy* in 1944 to summarise the available information on the geographical distribution of leprosy and to identify omissions and errors in the data to stimulate further research (Leonard Wood Memorial 1944). This account was based on surveys and references collected between 1933 and 1943 and provided an insight into the contemporary prevalence of leprosy in East Asia, as well as worldwide at that time. The report also gave information about the care available within countries, including the number and types of settlements and hospitals for those affected by leprosy. The highest prevalence rates were reported from certain parts of Burma where 16 cases per 1000 population were counted and there were at least nine

Table 1 Estimated and registered number of leprosy cases in Asia and Oceania (Noordeen 1993)

Year	Estimated number of cases	Registered number of cases	% cases registered
1963	6,508,000	949,000	14.6
1975		1,898,000	
1985		4,019,000	
1992	4,074,000	2,007,000	49.3

colonies of more than 900 leprosy affected people. In Thailand up to 4 per 1000 population or a total number of around 62,000 people were estimated to be affected by leprosy. The report further estimated that there were around 1 million people affected by leprosy in China, provided a detailed picture of the prevalence of leprosy in each province and identified the eight provinces with the highest prevalences. The report also detailed the prevalence, number of cases and conditions in Indo-China, Japan, Korea, the Philippine islands and Malaya. The experience of people affected by leprosy in East Asia as little as 70 years ago was that of a progressive, debilitating disease with no effective cure. The prospect was limited to palliative care and perhaps segregation into one of many colonies and to be subjected to the prejudice and beliefs held about leprosy in the various communities.

2 Impact of Introduction of Chemotherapy

The introduction of dapsone therapy as an effective treatment for leprosy in the late 1940s and its widespread implementation in the 1950s and 1960s changed the picture of leprosy globally, including in East Asia. It also promoted the production of much better information on leprosy, of the number of patients registered for treatment, and thus of a strong evidence-base for estimates of the size of the problem throughout the region as well as at individual country level (Noordeen 1993).

The estimated number of leprosy cases in 1963 in the Asia and Oceania region was around 6.5 million, with only a minority registered for treatment with dapsone monotherapy (Table 1). These figures rapidly changed between the 1960s and the 1990s for two main reasons: firstly the recommendations made by the Chemotherapy Study Group meeting in Geneva for the use of multidrug therapy (MDT) in 1982 (WHO 1982) and the progressive implementation of shorter course multidrug therapy between 1963 and 1992 when almost 50% of people affected by leprosy were registered for treatment. The recommendation to implement MDT using the three drugs dapsone, clofazimine and rifampicin was primarily to combat the spread of dapsone resistance, but a major impact of this shorter regimen also was a reduction of the numbers of patients registered for treatment (Table 2). Specifically, the number of registered patients peaked in 1985 and then declined since the new MDT regimen was a shorter course of treatment (around 2 years compared with up to 10 years and sometimes lifelong treatment with dapsone), and patients completing treatment soon outnumbered new patients starting treatment.

Table 2 Estimated and registered number of leprosy cases in 1991 (Noordeen et al. 1992)

Country	Estimated number of cases	Registered number of cases	% cases registered
Myanmar	240,000	112,000	46.7
Indonesia	200,000	102,000	51.0
Thailand	54,000	13,000	24.0
Viet Nam	120,000	20,000	16.7
The Philippines	47,000	39,000	83.0
China	40,000	30,000	75.0

The improved epidemiological information on leprosy allowed better estimates of the global burden of leprosy. In the mid-1960s the global estimate was 10–12 million cases, but by 1991 this number was reduced to 5.5 million. The number of individuals with deformities was then estimated between 2 and 3 million (Noordeen et al. 1992). These improved data further provided insights into registered and estimated cases in individual countries (Table 2). The varying burden of disease between countries therefore became clearer; but the statistics did not account for the huge variability in the distribution of cases within countries. The variation in the percentage of the estimated cases actually registered for treatment represents a snap shot of the quality of the available information. The high percentage of registered cases in the Philippines reflects the early involvement of the country in pilot studies of MDT implementation and the rapid uptake of the new regimen.

3 Impact of the Global 'Elimination of Leprosy as a Public Health Problem' Strategy

The implementation of MDT in Eastern Asia was responsible for the observed fall in the number of cases registered for treatment. This was recognised at the Regional Conference on Leprosy held in Manila in 1989 where targets were proposed to reduce the prevalence of patients registered for treatment to below 1 in 10,000 by promoting 100% coverage of MDT for all patients. The proposal was then formally adopted globally by the World Health Assembly (WHA) by resolution WHA44.9 in 1991 (WHO 1993). This resolution defined the target of reducing the leprosy point prevalence, measured as patients registered for treatment, to below 1 in 10,000 by the year 2000. This target was achieved globally at the end of the year 2000 (Anonymous 2001).

The number of registered cases of leprosy and new cases at the end of the year 2000 in East Asia are presented in Table 3. The data from 2000 are very different from the 1991 data, demonstrating the radically improved situation. The prevalence in Myanmar had not reached the global target by the year 2000, but Myanmar started with the highest case load. Indonesia had the second highest case load in 1991 and the highest in 2000. Leading up to the year 2000, the target of eliminating leprosy as

Table 3 Registered leprosy prevalence and new case detection in 2000 (Anonymous 2001)

Country	Number of registered cases	Prevalence per 10,000	Number of new cases reported	Detection rate per 100,000
Cambodia	582	0.5	747	6.7
China	6384	0.0	1595	0.1
Indonesia	17,994	0.8	13,539	6.4
Lao People's Democratic Republic	286	0.5	304	5.6
Malaysia	631	0.3	207	0.9
Myanmar	11,419	2.5	10,262	22.5
The Philippines	3248	0.4	2596	3.4
Republic of Korea	535	0.1	35	0.1
Thailand	2391	0.4	1037	1.7
Vietnam	2077	0.3	1446	1.8

a public health problem had resulted in an increased level of activity, with a focus on case detection, achieving 100% MDT coverage, and also high rates of MDT completion. A number of additional activities were introduced in the 1990s to intensify the leprosy programmes such as Leprosy Elimination Campaigns (LEC) to increase leprosy awareness, training and surveys and Special Action Project for the Elimination of Leprosy (SAPEL) for hard to reach populations. Surveillance and monitoring were also strengthened in this period.

4 Leprosy in the Post-2000 Era

Prior to the year 2000, the focus of all programmes was on achieving the WHO elimination target of less than 1 case in 10,000 population by the year 2000, also known as the 'elimination of leprosy as a public health problem' target. This strategy aimed to reduce the registered prevalence, although the continuing estimation of the total number of cases recognised that not every case was registered for treatment. Thus, efforts were also made to progressively close the gap between estimated case numbers and the registered prevalence by intensifying case detection and emphasising treatment for all newly detected cases. At that time, the elimination programmes did not target new case detection. It therefore appeared as a surprise to many that the elimination programmes, which had effectively and dramatically reduced the prevalence of registered cases, did not have any impact on global new case detection (Meima et al. 2004a). Detailed analyses in a number of areas showed varying trends in case detection and that the trends were not directly related to MDT implementation (Meima et al. 1997); many other factors influenced new case detection rates including operational factors, coverage of BCG vaccination and socio-economic changes.

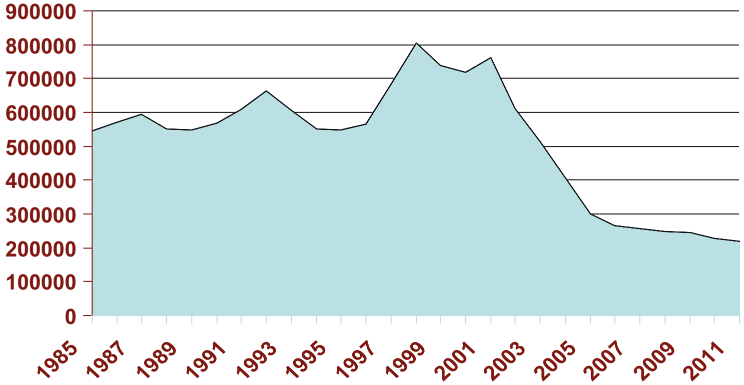

Fig. 1 Global trends in new leprosy case detection (1985–2012) (SEARO 2013)

The trends in leprosy epidemiology since the year 2000 have tended to focus on new case detection as the key indicator rather than on the registered prevalence. This was partly due to the reduction of the MDT treatment duration to 6 or 12 months which made the annual case detection figures similar to the point prevalence figures. The global trends in new case detection from 1985 up to 2013 are shown in Fig. 1. There has been a considerable fall in the number of new cases over a relatively short period of time between 2000 and 2006. This global trend is not seen in all countries and is more likely to be attributable to operational factors than to changes in transmission. Specifically, the fall has been linked to a loss of commitment to leprosy control and stagnation in activities (SEARO 2013). The recently passed Bangkok Declaration ‘Towards a leprosy-free world’ thus called for a renewed commitment to leprosy elimination.

The trend in the number of new cases reported varied between regions (Fig. 2). A sharp fall is seen in Southeast Asia, while there is a long-term steady decline in the Western Pacific Region.

5 The Current Leprosy Situation in East Asia

The most accurate picture of the current epidemiological situation of leprosy in East Asia can be derived from the information reported by the countries to WHO and published in the *Weekly Epidemiological Record* in 2014 (Anonymous 2014). The data for 12 countries in East Asia is shown in Table 4. The new case detection rate in the same countries is further shown in Fig. 3. Most countries have maintained the downward trend in the registered prevalence although the decreases are not as dramatic as those between 1991 and 2001. Indonesia has reported an increase in both the registered prevalence and the number of new cases detected, and Malaysia has shown an increase in new cases but a fall in the registered prevalence. The

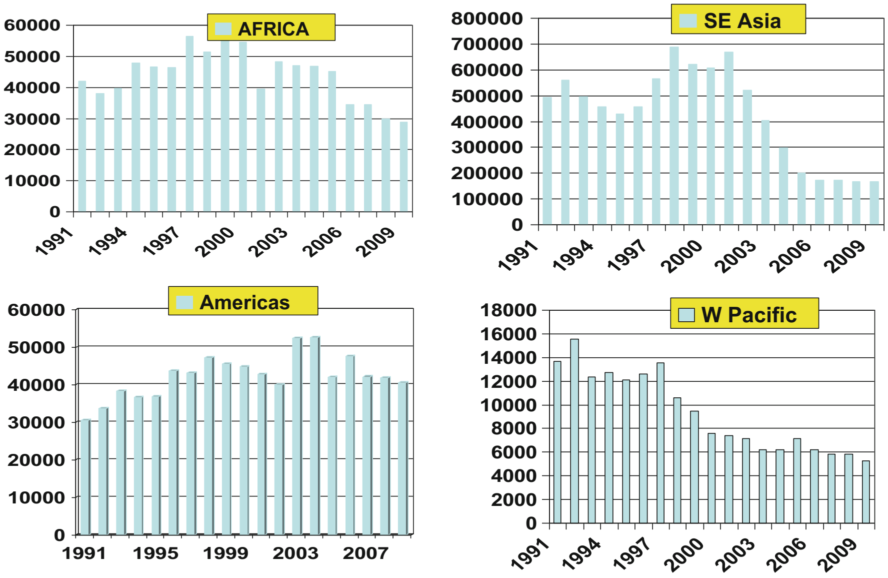

Fig. 2 Trends in new leprosy case detection by region (SEARO 2013)

Table 4 Current leprosy situation in East Asia (Anonymous 2014)

Country	Registered prevalence	Number of new cases detected	Number of female new cases	Number of new cases in children	Number of new cases with disability	Relapses
Cambodia	282	373	115	32	17	0
China	1908	924	308	14	188	6
Indonesia	19,730	16,856	6021	2002	1694	187
Japan	2	3	1	0	0	2
Republic of Korea	210	7	2	0	3	1
Lao People's Democratic Republic	67	84	35	3	28	0
Malaysia	353	306	87	26	8	6
Micronesia	188	195	75	77	1	0
Myanmar	2721	2950	997	134	423	11
The Philippines	2963	1729	523	117	72	53
Thailand	560	188	72	8	18	10
Vietnam	224	260	82	14	43	14

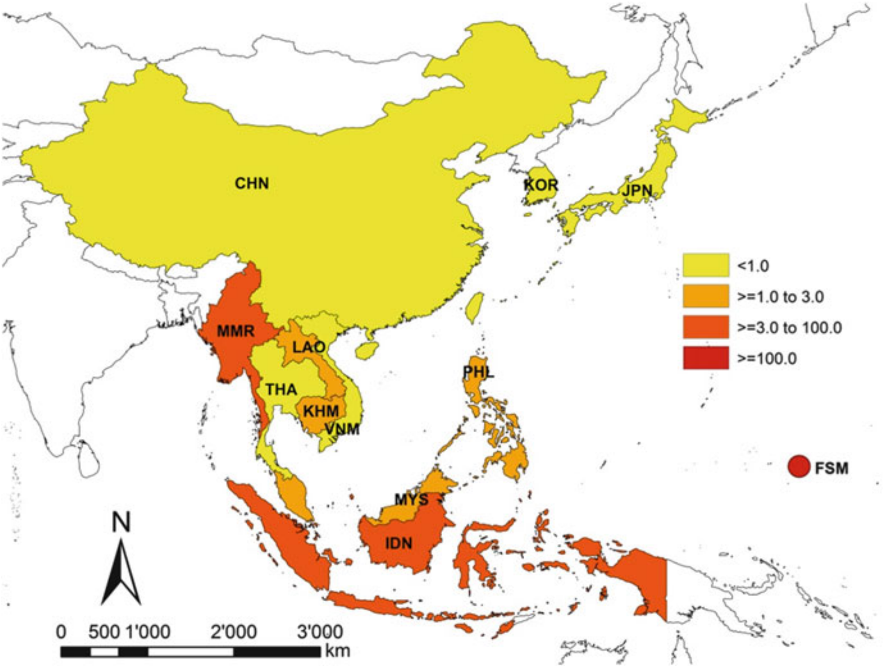

Fig. 3 New leprosy case detection rates in East Asia, expressed as rates per 100,000 population. *CHN* China; *KOR* Republic of Korea (South Korea); *JPN* Japan; *MMR* Myanmar; *LAO* Lao People's Democratic Republic; *THA* Thailand; *KHM* Cambodia; *VNM* Vietnam; *PHL* the Philippines; *MYS* Malaysia; *IDN* Indonesia; *FSM* Federated States of Micronesia (Anonymous 2014)

changes in the Philippines are more modest than those in other countries such as Thailand, Lao People's Democratic Republic (Lao PDR) and Vietnam. The countries with the largest numbers of new cases tend to be those with the largest number of cases in the previous decades. The patterns and trends are therefore different between individual countries, and it is important to consider specific countries in more detail.

The proportion of women among new cases is an important indicator as it potentially reflects issues of access to health care since there are no systematic differences in the natural prevalence among women and men; this proportion in some countries was less than 30%. The proportion of child cases is important as a reflection of continuing transmission; in some countries this indicator is very low, while it is high in others such as the Federated States of Micronesia where it stands at almost 40% of all new cases. The presence of visible deformity (grade 2 disability) in new cases is regarded as an indicator of delay in diagnosis. In the East Asia region, visible deformities are often present in more than 10% of the new cases with particularly high rates in China, Vietnam and Lao People's Democratic Republic. The current WHO enhanced global strategy (SEARO 2011) targets a reduction in grade 2 disability among new cases as an indicator of early case detection, which is clearly a challenge in East Asia. It also gives priority to issues of human rights and discrimination. The relapse numbers can be difficult to assess as many reported relapses may be relapses after dapsone monotherapy rather than relapses after MDT, and some countries have attempted to re-treat previously dapsone-treated patients with MDT.

The overall picture of leprosy in East Asia in 2014 is that of a dramatic improvement compared to 1991. A reduction of over 90% in the number of registered cases has been achieved. The progress between 2001 and 2013 has been less dramatic compared to the period 1991–2001, and some countries have even seen an increase in case numbers. There are a number of areas of concern including the low rate of leprosy detection seen in women in certain countries, the high proportion of children in others and the high rates of disability indicating delays in diagnosis.

One issue that does not appear clearly in the annual leprosy statistics is that of residual morbidity. Patients who had disability at the time of detection, along with others who may have developed disability during or after MDT, will continue to experience lifelong disability as MDT effectively stops the progress of leprosy and prevents disability but does not reverse existing disability. Noordeen et al. (1992) estimated the total number of people disabled due to leprosy at 2–3 million. They represent an ongoing challenge for health services. Many live in settlements and hospitals, while others remain in their community, and it is important that they are included and recognised within programmes. They may well experience discrimination by society and often have limited access to health and social care. Comprehensive leprosy programmes need to address these issues of continuing morbidity as vigorously as the challenges of early detection and effective chemotherapy for new cases.

6 Factors Influencing the Epidemiology of Leprosy in East Asia

Chemotherapy, initially with dapsone and later with MDT, has had a major impact on the reduction of the number of leprosy cases in East Asia since 1944 (Leonard Wood Memorial 1944). Much of this effect is due to the progressive shortening of the treatment duration, increased treatment coverage now typically approaching 100% and minimal relapse rates. The current picture is in stark contrast to that described by Cantlie (1897) and the Leonard Wood Memorial team (1944). The greatest impact was achieved in the 1991–2001 period where the ‘elimination of leprosy as a public health problem’ strategy was adopted, leading to an intensified international commitment.

The impact of the elimination effort on the new case detection indicator, used as a proxy measure of incidence and transmission, is less dramatic and more difficult to assess. Initial analyses suggested that MDT may not directly impact on new case detection rates (Meima et al. 1997). Operational factors can have a substantial impact on new case detection as active case finding, such as population surveys and school surveys, increases new case detection, while cessation of such activities will result in a reduction. Increased community awareness and improved health service capacity can also result in increased new case detection. It is thus important to report changes in case finding activities when assessing changes in new case detection rates.

A number of other factors can also affect the observed incidence of leprosy. The widespread use of the BCG vaccine at birth is likely to have an impact on the incidence of leprosy as trial evidence has shown its effectiveness in preventing the onset of leprosy disease (Setia et al. 2006). Chemoprophylaxis for contacts (Reveiz et al. 2009) is another method to reduce the number of new cases among those chronically exposed to untreated leprosy cases. However, chemoprophylaxis with single-dose rifampicin currently is only at a pilot stage and has not yet been rolled out at national level in any country. Socio-economic development is widely held to have an important impact on the incidence of leprosy. There are studies (Saikawa 1981) examining this, but it has been difficult to attribute changes in leprosy to any specific socio-economic improvement. The East Asia region has experienced rapid economic development and an improvement in leprosy concurrently. Improved housing resulting in less overcrowding, better nutrition, improved sanitation and better availability and quality of health services are all likely to contribute to a reduction in the transmission of leprosy.

7 Experiences of Leprosy Control in Specific Countries

A number of countries from throughout East Asia have been selected to illustrate the heterogeneity of the local epidemiology and the variation in health service responses to the challenge of leprosy. Generalisations can be made about East Asia as a region; however, the complexities of the issues at country level need to be understood to fully appreciate the situation. The countries are presented in alphabetic order.

7.1 Cambodia

The fight against leprosy in Cambodia experienced a major setback due to the devastation brought about the country by the reign of the Khmer Rouge (1975–1979) and the difficult years that followed that period. Before the takeover of the Khmer Rouge in 1975, leprosy patients, as in other countries, were condemned to isolation. In Cambodia, they were sent to the village of Troeung—a leprosarium—in the province of Kampong Cham. During the Pol Pot regime, leprosy patients were killed straight away as they were considered contagious and useless for the ‘new society’. After 1979, the leprosarium was officially abandoned and the survivors returned to their home provinces. At that time, no treatment was available as the fight against leprosy was far from being a priority for the authorities.

It was not until 1984 that the Cambodian Ministry of Health, supported by the Order of Malta, established the National Programme for Leprosy Control. MDT was then introduced in Phnom Penh and provinces in close proximity to the capital: Kampong Speu, Kampong Cham and Kampong Chhnang. Despite the civil war that continued until 1997, between 1993 and 1995, Malteser International began to support the National Programme for Leprosy Control in five provinces: Battambang, Siem Reap, Kampong Chhnang, Banteay Meanchey and Pursat.

Since 1996, CIOMAL—the International Committee of the Order of Malta Against Leprosy—supported the National Programme for Leprosy Control which was incorporated in 1997 into the National Center for Tuberculosis and Leprosy Control (NCTLC). It consists of 5 national leprosy supervisors and 24 provincial leprosy supervisors, 1 for each province. In 2000, the Kien Khleang Leprosy Rehabilitation Center (KKLRC) in Phnom Penh was opened, marking a turning point in the fight against leprosy in Cambodia. Till today, KKLRC—which has a capacity of 50 beds—is the reference hospital for leprosy patients in the country. It has become a centre of competence for the treatment of leprosy, offering free medical, including surgical, care. Patients come from across the country for treatment, mostly related to disability care. In 2013, 2155 people were receiving care, 148 surgeries were performed and 262 patients were hosted in the centre. With the team of KKLRC, which includes doctors, physiotherapists, nurses and social workers, a multidisciplinary approach in line with the reality of leprosy in the country has been developed: physical rehabilitation, socio-economic rehabilitation, early case detection, awareness raising, training and prevention. Knowledge transfer and training are key initiatives to strengthen local capacity: medical students, dermatologists, physiotherapists, experts in prosthesis-orthotics and in reconstructive surgery and national health staff are trained. The programme is also developing outreach awareness-raising activities (radio, TV, local theatre performance, information-education-communication (IEC) advertisement) targeted to various audiences including villagers and workers in garment factories. The National Leprosy Elimination Programme (NLEP) together with CIOMAL and with the support and technical guidance of the Novartis Foundation has developed active screening and early detection campaigns based on retrospective contact tracing. These campaigns have allowed the detection of hundreds of cases of leprosy among contacts of previously detected cases, showing that the disease continues to be present in the country.

Specifically, since 2011, ‘drives’ in Cambodia have visited 66 districts where 32,760 household members and neighbours of 2324 leprosy cases were examined. These efforts resulted in the detection of over 600 new cases of active leprosy by the end of 2014, including over 70 child cases and 568 patients identified at an early stage disease so that disability could be avoided. The commitment of these and other partners (WHO, NLR, the Order of Malta France and Raoul Follerau) allowed for a new dynamic partnership to be built around the fight against leprosy in Cambodia.

The number of new leprosy cases detected in Cambodia varied greatly over time. In 1991, there were 415 new cases reported, rising to 2219 new cases in 1995 and again declining to 634 cases in 2001 and 373 in 2013. The trends between 1991 and 2013

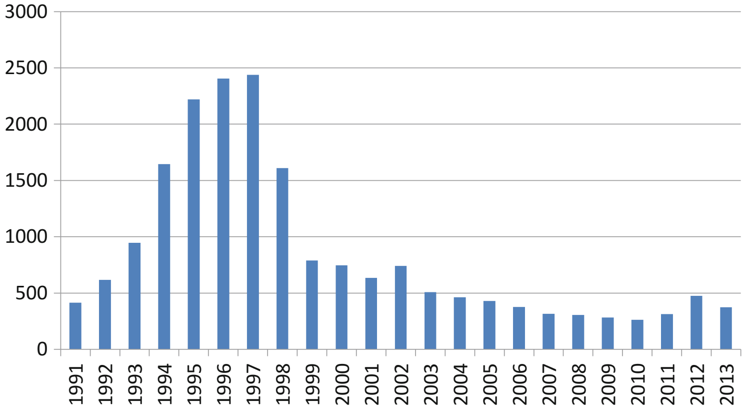

Fig. 4 New leprosy case detection trends 1991–2013 in Cambodia (Anonymous 2014)

(WHO 2003) are shown in Fig. 4. The increased case detection in the 1990s reflects the LEC and SAPEL activities which were conducted in Cambodia (Anonymous 2003a, b).

7.2 *China*

Cantlie (1897) recognised, over 100 years ago, that there was considerable geographical variation in the prevalence of leprosy across China. In 1944 the estimated number of cases was up to 1 million (Leonard Wood Memorial 1944). A major review of leprosy from 1949 to 1998 confirmed these estimates and reported that almost half a million patients had been detected within that 50-year period (Chen et al. 2001). This analysis was based on the computerised national leprosy recording and reporting system covering the whole of China which was established in 1990. The majority of these patients were male (75.2%) but the proportion of male patients has decreased over time. Only 5.1% were children and this proportion, too, has decreased over time. The trends in new case detection per 100,000 over this period are shown in Fig. 5. A long-term decline in new case detection rates follows the peak in 1957/1958, a fall that predates the introduction of MDT. The closer analysis of this trend revealed a reduction in the delay from the onset of signs to detection from 5 years in the 1950s to less than 2 years in the 1990s. Consequently, the disability rates in new cases fell from over 50% in the 1950s to around 20% in the 1990s.

The registered prevalence of leprosy reached a peak in the 1960s and then fell progressively until the 1990s. China reached the WHO elimination of leprosy as a public health problem target of less than 1 case in 10,000 population in 1981 (WHO 1993) at national level, 10 years before the target was even set. At provincial level, the target was reached in 1992 and at county level in 1996 when the country adopted a new target of 1 in 100,000.

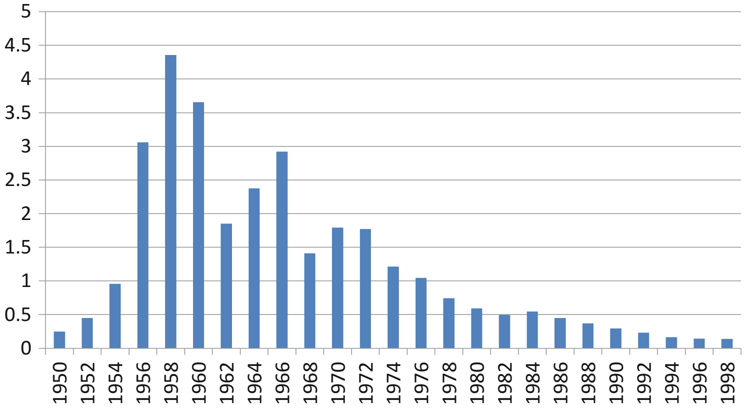

Fig. 5 New leprosy case detection trends per 100,000 in China (1949–1998) (Chen et al. 2001)

The distribution of leprosy in China is uneven and detailed analyses have been conducted in certain provinces. The trends in Shandong province from 1955 to 1983 have been examined using age-specific cohorts (Li et al. 1985). This analysis found a decrease in incidence (new case detection) using repeated surveys from 5.1 to 0.46 per 100,000 over 25 years. The analysis further showed an increasing age of onset and a decreasing incidence in successive age cohorts, an observation that has also been made in other countries as leprosy was slowly disappearing. The trends in Sichuan province has also been described in detail. The local epidemiology was found to resemble that of the country and Shandong province, although the rates of leprosy were higher (Wu et al. 2000). The other interesting observation is the increasing proportion of new cases that are household contacts of already known cases; this rate increased from 16.8% in the 1950s to over 30% in the 1990s.

New case detection rates in China have continued to fall and ‘in 2013’ the number fell below 1000 (Anonymous 2014). Factors for the decline in new case detection rates in China suggest that MDT was not decisive as it may not be greatly superior to dapsone in preventing transmission (Meima et al. 2004b). Active surveys, school surveys and contact surveillance promoting early case detection as indicated by the decreased delay in detection and the higher proportion of new cases arising from contacts are likely to have had an impact on transmission. General socio-economic improvements in China and the use of BCG since the late 1980s probably also contributed.

7.3 *Indonesia*

In 2013, Indonesia reported the third largest number of new leprosy cases in the world, after India and Brazil. The new case detection rate in Indonesia has remained

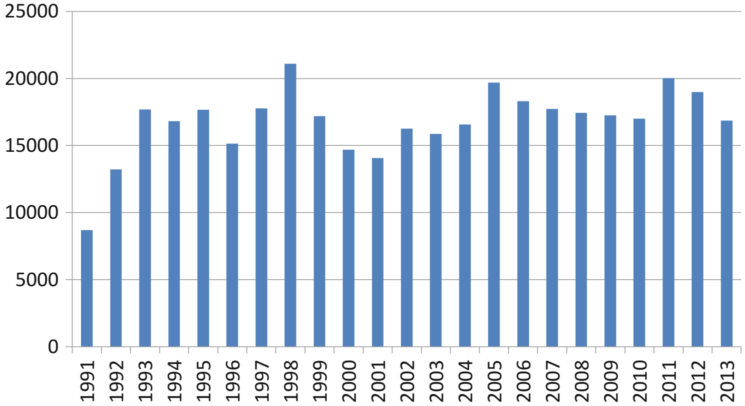

Fig. 6 New leprosy case detection trends 1991–2013 in Indonesia (Anonymous 2014)

remarkably stable over the last few decades. Random sample surveys in the past have suggested a much higher true prevalence of leprosy than the official figures suggested. Case surveys in 1977 identified many untreated patients with a long history of leprosy (Louhenapessy and Zuiderhoek 1997), and social stigma was seen as a major contributing factor.

Indonesia adopted MDT in the 1980s and case finding was accelerated in the 1990s through LEC activities. The registered prevalence fell from 126,221 (4.9 per 10,000) in 1985 to 17,539 (0.86 per 10,000) in 2000, a fall of 86%. Active partnerships with WHO and international non-governmental organisations (NGOs) were important contributors to this achievement. The programme has been sustained since 2001 but with less support. A detailed analysis (Fig. 6) of the new case detection trends in Indonesia has been conducted (Anonymous 2010). The number of new cases detected increased from 8691 in 1991 to 21,095 in 1998, an increase that was interpreted as a result of the expansion of MDT services and the detection of many previously undetected cases. However, new case detection numbers have not declined since 2000 and have been sustained up to 2013. Validation of the diagnosis of these new cases showed only minimal misdiagnosis (Anonymous 2010).

The proportion with MB leprosy has increased from 53% to 82%, but changes in classification make this shift difficult to interpret. The proportion of cases with grade 2 disability declined from 23% in 1991 to 10% in 2000 but has since then remained at that level. The proportion of female patients in 2008 was 36% but showed a marked geographical variation across Indonesia, ranging from 11% to 49%. This geographical variation is taken into account in the planning and implementation of the national programme, which is divided into 14 high burden and 19 low burden provinces.

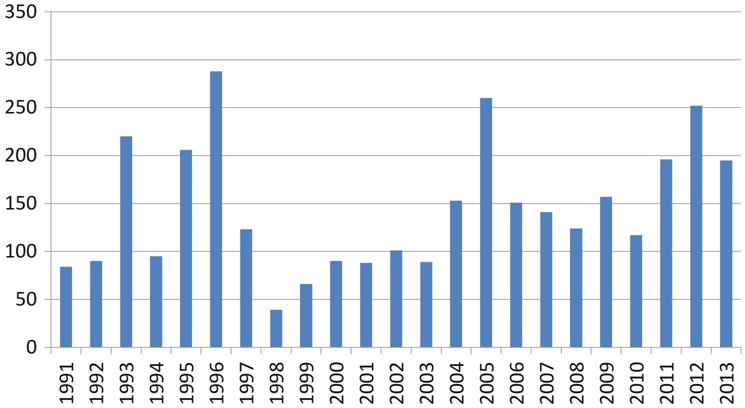

Fig. 7 New leprosy case detection trends 1991–2013 in the Federated States of Micronesia (Anonymous 2014)

7.4 Federated States of Micronesia

The epidemiology of leprosy in the islands of the Federated States of Micronesia is extraordinary but also reflective of many island communities in the Pacific. In the 1990s these islands reported a new case detection rate of around 20 per 10,000. The case detection rates had been known to be very high, and previous local initiatives for chemoprophylaxis had been deployed using long-acting dapsone (DADDS). Active case finding in 1995 in 10% of the population resulted in a case detection rate of 65 per 10,000 with the majority of cases being in children. In 1996/1997, a total population survey was implemented, and chemoprophylaxis was administered using rifampicin, ofloxacin and minocycline (Diletto 1999). Of the total population of 105,506, 72% were examined and 322 new cases were detected. Of the screened, 70% received chemoprophylaxis. A year later, a second round of screening and chemoprophylaxis was conducted with 80 new cases detected, and a further 72% received chemoprophylaxis. The pattern of new case detection between 1991 and 2013 is shown in Fig. 7. The population screening in 1996/1997 is reflected in the increased numbers of new cases, followed by an obviously lower number in the next 5 years before the numbers increased to the pre-intervention levels. This may reflect the chemoprophylaxis effect waning over time and being most effect immediately after administration.

It is difficult to attribute the reduction in the new case detection to the population screening, chemoprophylaxis or the combination of both without any control population. A further round of chemoprophylaxis after 5 years has been suggested. Today, the new case detection rates per 100,000 population remain extremely high with a high child proportion but a very low number of grade 2 disabilities. The low rate of disabilities in leprosy found in Micronesia is intriguing and may be related to host factors. In 2013 a total of 195 new cases were reported, 38% of them female and 39% children with only one new case with grade 2 disability.

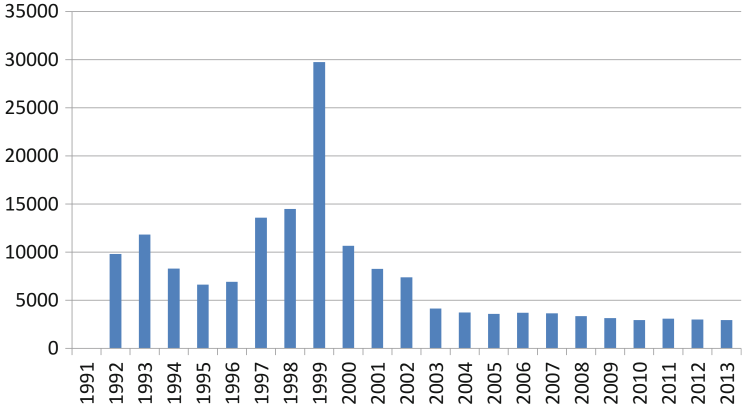

Fig. 8 New leprosy case detection trends 1991–2013 in Myanmar (Anonymous 2014)

7.5 Myanmar

Early surveys in Myanmar had estimated a prevalence of 200,000–590,000 people affected by leprosy, one of the highest leprosy disease burdens in East Asia (Lwin et al. 2005). In 1952 a control programme was launched based on early case finding and dapsone treatment. The programme was progressively developed and integrated with primary health care in 1978. The peak prevalence was recorded between 1973 and 1977 when 262,171 patients (86.2 per 10,000) were registered for treatment, and the annual incidence was 1–3 cases per 1000 population. Surveys in the 1980s identified the increasing problem of dapsone resistance, and trials of alternative chemotherapy regimens were conducted. At that time, a trial of the effect of BCG in the prevention of leprosy was also conducted in the country. MDT was progressively introduced from 1988 onwards. In 1991 the responsibility to administer MDT was handed over to basic health service staff and township medical officers who acted as programme managers. The vertical leprosy staff were deployed as supervisors and trainers. By 1994, MDT had extended to all townships and by 1996 all registered patients were receiving MDT (Lwin et al. 2005). The prevalence fell from 6.1 per 10,000 (24,082 cases) in 1994 to 2.5 per 10,000 (11,906 cases) in 1998 when 183,731 patients had completed MDT treatment. Myanmar reached the WHO elimination target of less than 1 registered case in 10,000 population by 2003. An important component of the success of MDT in Myanmar was the involvement of trained midwives who worked at village level (Barua et al. 1999). The midwives showed commitment and reliability, especially in the supervision of MDT.

The trends in new case detection numbers from 1992 to 2013 are shown in Fig. 8. Between 1986 and 1997 (Lwin et al. 2005), around 7000–14,000 new cases were detected each year. Over the same period, the proportion of children among new cases fell from 17.9% to 9.5%, and that of grade 2 disability fell from 27.6% to 10.9%. LECs were also used to increase community awareness, strengthen capacity and improve case finding (Anonymous 2003a). These campaigns along with six Special Action Projects (Anonymous 2003b) helped boost case detection as seen in the late 1990s (see Fig. 8). The new case detection rates slowly decreased after 2003, and in 2013 there were 2950 new cases detected including 34% female, 4.2% children and 14% with grade 2 disability (Anonymous 2014).

7.6 *The Philippines*

Over a hundred years ago, the leprosy control policy in the Philippines as elsewhere was segregation. In 1906, a leprosarium was established on the island of Culion in Palawan Province, and people affected by leprosy were shipped to this settlement from all over the country. This policy continued until the introduction of dapsone chemotherapy in the 1950s. In the 1980s, MDT was introduced and then rolled out nationally. By 1994 the registered prevalence was reduced to 2.5 per 10,000 (16,486 cases) with an annual case detection rate of 6.9 per 100,000. The prevalence steadily fell from 1982 onwards and reached the elimination goal of less than one case per 10,000 population in 1998 with 7005 registered cases. The prevalence continued to fall and by 2000 there were 2041 cases registered. However, the new case detection rate remained relatively stable (WHO 2003). The national control programme was largely based on passive case finding and supported by a number of national and international NGOs. The leprosy elimination campaigns implemented in at least one province (Anonymous 1998) and three Special Action Projects (Anonymous 2003b) played a part in the programme in the 1990s. Since 2000 the focus has been on high prevalence areas and hard to access populations, including areas with security concerns.

The new case detection trend has shown a consistent downward trend (see Fig. 9) but not as dramatic as the prevalence trend. A peak in 1997 reflects intensified

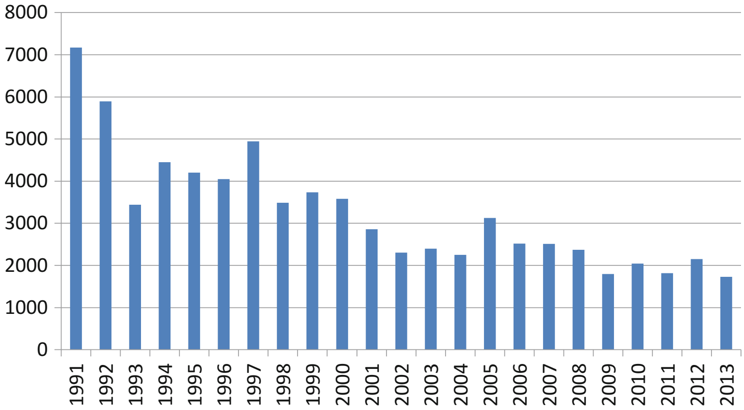

Fig. 9 New leprosy case detection trends 1991–2013 in the Philippines (Anonymous 2014)

activities prior to achieving the elimination target. In 2013 there were 1729 new cases reported in the Philippines, 30% of them female, 6.8% children and 72 with grade 2 disability representing 4.2% of all new cases (Anonymous 2014).

7.7 Thailand

In 1953 it was estimated that there were 140,000 people affected by leprosy in Thailand with an overall prevalence of 5 per 1000 (Montreewasuwat and Peerapakorn 1988). In 1956, a leprosy control strategy based on early case detection, treatment and health education was launched which was expanded to cover the whole of Thailand by 1972. The leprosy control strategy was then integrated into the primary health-care system, a change that involved extensive staff training between 1972 and 1976 (Anonymous 2007). The number of new cases detected each year increased as the programme expanded, and the point prevalence fell to 0.54 per 1000 by 1987 due to effective case finding and the implementation of MDT which reached 100% coverage by 1989. The estimated prevalence based on random surveys was twice the number of registered cases. However, as in most countries, the geographical distribution was found to be uneven, and two provinces in the northeast had a prevalence higher than 1 per 1000. About 60% of the registered cases were found in the north-eastern region.

The annual new case detection trends have been analysed in detail from 1965 to 2005, with additional details on individual cases available since 1984 (Anonymous 2007). In 1965, a total of 4951 new cases were reported (15.4 per 100,000). The numbers of new cases then declined due to changes in the programme, but after the integration and training of basic health-care staff, there was a greater focus on new case detection, resulting in increased numbers of new cases being detected annually up to a peak of 4463 cases (9.5 per 100,000) in 1981. The numbers of new cases detected annually then progressively fell to 638 (1.03 per 100,000) in 2005 and then to 188 in 2013 (Anonymous 2014). The trends in new case detection in Thailand between 1965 and 2005 are shown in Fig. 10.

The proportion of MB cases among all new cases detected has varied over the period, reflecting changes in disease classification (Anonymous 2007). In 1984, 10% of all new cases were children. The rate of child cases fell to 5.5% in 1994 and stood at 4.3% in 2013 (Anonymous 2014). The proportion of children with grade 2 disability varies from 0% to 6%. The proportion of female cases among the new cases varied between 36% and 40% during 1992–2005. Grade 2 disability in new cases between 1995 and 2005 ranged between 10.3% and 14.1%. The absolute number fell from 169 to 77 in 2005 and to 18 in 2013. The absolute fall, or the rate per population rather than as a percentage of new cases, is the current target of the WHO enhanced global programme (SEARO 2011). This clearly shows that Thailand is achieving the target of reducing disability in new cases through early case detection.

The early variation in new case detection methods demonstrates the importance of operational factors for the numbers of new cases detected. The long-term declining trend of leprosy in Thailand is attributed to general access to diagnosis and

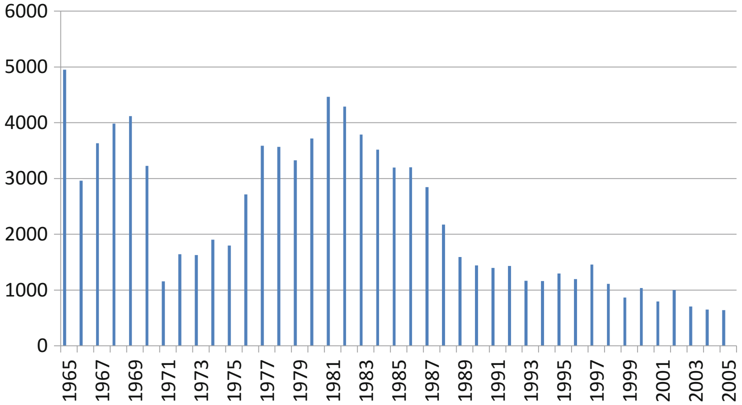

Fig. 10 New leprosy case detection trends 1965–2005 in Thailand (Anonymous 2007)

treatment, as well as socio-economic development and the high BCG vaccination coverage. Despite the progress, Thailand remains committed to sustaining access to detection and treatment and to prevention of disability and rehabilitation of those affected by leprosy (SEARO 2013).

7.8 Vietnam

Leprosy has long been a major public health problem in Vietnam and has a history of strong stigma associated with the disease. Traditionally, this has resulted in many people affected by leprosy being segregated into leprosy villages and colonies. In 1982, the government established a national leprosy control programme and instigated pilot studies of MDT in 1983. Detailed records have been maintained since 1983 (Anonymous 2008). The national programme was associated with the National Institute of Dermatology and Venereology, which maintained a Dermatology and Venereology Center in each province and staff at district and commune levels. MDT coverage in 1985 was 50% and increased to 100% by 1991.

In 1983 there were 38,652 registered cases (6.78 per 10,000). Many patients previously treated with dapsone were registered for retreatment with MDT, and MB patients were treated for 24 months or until they became smear negative. The prevalence rates later rapidly fell, and Vietnam reached the WHO elimination as a public health problem target rate of less than 1 per 10,000 at the national level in 1995 and at provincial level by the end of 2000. By 2006, the total number of cases was 572 (0.1 per 10,000), a reduction of 98% compared to 1983. The rapid reduction in prevalence was attributed to high MDT coverage, shortening of the duration of treatment, and updating of the treatment registers. The national programme was

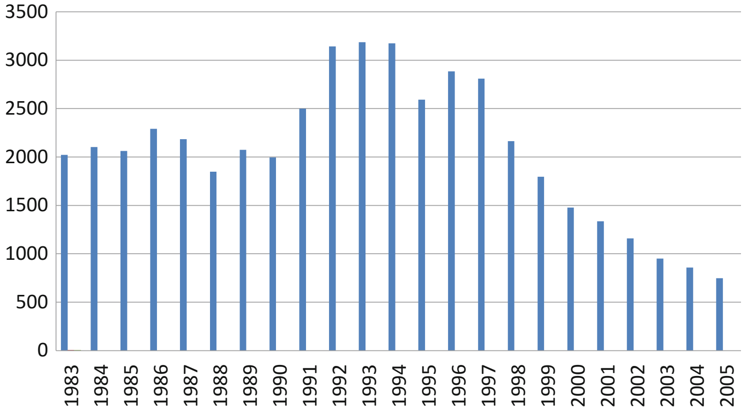

Fig. 11 New leprosy case detection trends 1983–2006 in Vietnam (Anonymous 2008)

supported by health education campaigns, six SAPELs and eight LECs conducted between 1991 and 1997 and covering over 3 million people.

The new case detection trends are shown in Fig. 11. The number of new cases detected between 1983 and 1990 remained basically stable, but from 1991 to 1997, the numbers increased, reflecting the intensified case finding activities and the backlog of undetected cases.

Since 1997 the number of new cases detected each year has steadily declined until it reached 666 in 2006 (0.75 per 100,000). In 2013, a total of 260 new cases were reported of which 32% were female, 43 had grade 2 disability and 14 were children. Traditionally, the proportion of new cases with grade 2 disability in Vietnam has been high, in 1983 it was 41%, in 1993 it was 18%, and in 2006 it was still 16%. This is interpreted as reflecting delays in diagnosis and is related to the level of stigma towards leprosy in the community. The absolute number of new patients with grade 2 disability has substantially declined from over 800 in 1983 to 108 in 2006 and to 43 in 2013. This is an important achievement under the current WHO Enhanced Strategy (SEARO 2011) which aims at a reduction in the rate per population rather than as a percentage of all new cases detected. The proportion of females among the new cases detected has remained almost stable, slowly rising from 30% to 37%, and the proportion of children has always been under 10%, falling to 5.3% in 2006.

8 Discussion

The last 70 years have seen dramatic changes in the epidemiology of leprosy in East Asia, evolving from policies of segregation to the generalised implementation of effective chemotherapy. The changes are particularly striking in terms of the prevalence of patients registered for treatment which declined from as many as 6.5 million in 1963 (Noordeen 1993) to around 50,000 in 2013 (Anonymous 2014).

This dramatic impact of MDT on the registered prevalence was first noted in this region in 1989 and become formalised as a resolution of the WHA in 1991 (WHO 1993) which set a target point prevalence of patients registered for treatment of less than 1 in 10,000 population at a global level by the year 2000. However, there remain millions of individuals in East Asia who are affected by disability and discrimination due to leprosy after MDT, and some of the colonies still exist but with much reduced numbers and ageing residents. The focus of attention since the year 2000 has moved from the registered prevalence to case detection trends as the key epidemiological indicator. The case detection rates, like the earlier registered prevalence rates, show considerable geographical variation between and within countries across East Asia. The trends in new case detection rates are less influenced by MDT as compared to the trends in registered prevalence. Specifically, new case detection is influenced by operational factors as well as socio-economic development, use of BCG, among others factors.

The call of the 1991 WHA resolution to eliminate leprosy as a public health problem by the year 2000 (WHO 1993) stimulated increased support and greater focus on leprosy control, both globally and in endemic countries. This ‘elimination as a public health problem’ strategy was based on early case detection and treatment with MDT. It resulted in increased political commitment as well as increased resources to implement and roll out MDT to achieve 100% coverage. Leprosy control activities were intensified following the resolution in terms of case detection activities, staff training, community awareness and the introduction of specific activities such as LECs (Anonymous 2003a) and SAPELs (Anonymous 2003b). The global programme also proposed progressive simplifications, which facilitated the implementation of the strategy, particularly in areas with weak health-care infrastructure. Important simplifications concerned diagnosis, which could now be based on cardinal signs without reliance on skin slit smears, disease classification based on skin lesion counts, the delivery of MDT in blister packs free at the point of care and the shortening of the duration of treatment. In 1982, WHO recommended that MB patients be treated for at least 2 years or until they became skin smear negative (WHO 1982). This duration of MB treatment was changed to 24 months in 1994 and then to 12 months in 1998. The fixed duration treatment of PB leprosy was also reduced from 12 to 6 months in 1998, and the option of single-dose ROM (rifampicin, ofloxacin and minocycline) was introduced in 1997 for patients with single skin lesions, a treatment option which is today not commonly used.

Much of the impact of MDT on the point prevalence of registered cases can be attributed to the shortening of the treatment duration and to better management and updating of disease registers. The point prevalence was commonly measured on December 31 of each year. The elimination strategy thus was a highly focussed programme with a clear and measurable target which attracted support at all levels. It was also framed in a tight time bound target to be achieved by the year 2000. There is no doubt that the strategy was highly effective in extending the use of MDT treatment to all people affected by leprosy, with minimal relapses. One of the downsides of the strategy became apparent after 2000 or when the target had been achieved and elimination could be declared. The challenge was maintaining support, momentum and expertise for leprosy programmes when elimination of leprosy as a public health problem was often misunderstood as eradication. The impact of this is clearly seen in Fig. 1 where a sudden and dramatic fall in new case detection numbers occurring over the 5 years after 2000 is apparent. The other important fact was that MDT although effective in arresting disease progression, especially when the disease was diagnosed early, did not appear to have a direct impact on new case detection (Meima et al. 1997, 2004a). A number of countries in East Asia have registered long-term declines in new case detection, which started before MDT was introduced, e.g. China and Thailand. Other countries continued to report high levels of new case detection after the introduction of MDT, despite substantial falls in the registered prevalence such as Indonesia and Micronesia. New case detection was more vulnerable to changes in operational factors as is seen with the impact of LEC and SAPELs in the 1990s across East Asia.

The epidemiology of leprosy is commonly described by both the registered point prevalence and the new case detection rate as measures of disease, along with indicators based on age, sex and disability. These measures fail to recognise people affected by leprosy before diagnosis although earlier attempts were made to make estimates of undetected cases (Noordeen 1993; Noordeen et al. 1992). Community surveys can be used to estimate the numbers of people with leprosy in the community who are undetected and untreated, however these can be technically challenging and require very large sample sizes. The number of hidden cases is often considered as a reflection of the delay between onset of signs and symptoms of leprosy and diagnosis.

The epidemiological measures used in leprosy also fail to recognise people affected by leprosy after completion of MDT, despite the fact that they may have significant physical impairments, disability and experience discrimination in society. Over the past 25 years, the number of leprosy patients globally who have completed a course of MDT is around 15 million. Many of these people had significant disability at the time of diagnosis as assessed by the grade 2 disability measure; others will have developed new disability during and after completing MDT due to reactions and the progressive consequences of nerve function impairment. Few countries maintain registers or have estimates of the size of this residual morbidity as the focus of programmes has been on new case detection, and it is often ignored in assessments of the burden of disease. Noordeen et al. (1992) estimated the extent of this problem at a global level as being between 2 and 3 million people. Many still remain in settlements, colonies and villages, but the majority live in the community, supported by families or living alone.

The size of this residual morbidity and the nature of their medical, physical and social problems need to be investigated and defined. Most national leprosy programmes include prevention of disability (POD) activities based on self-care, footwear and adapted tools, as well as programmes of community based as well as socio-economic and physical rehabilitation. These are important components of current leprosy programmes.

The focus of leprosy control since the year 2000 has been on new case detection rates. The quality and completeness of data on new case detection is much improved, and analysis reveals some interesting issues. It is clear that operational factors such as programme activities have a great effect on new case detection. The country examples of new case detection trends during the 1990s elimination as a public health problem efforts show the impact of intensification of case finding activities. Increased community awareness, staff training and surveys in the community and schools all increase new case detection and shorten the period of delay between onset and diagnosis. The limited of impact of MDT on new case detection is an interesting observation. It has been suggested that MDT may not have a greatly increased impact on transmission compared to dapsone. This is due to the difference in the duration of the viability of *M. leprae* which, after dapsone as well as after MDT, may be relatively short compared to the lengthy periods of transmission before treatment is commenced, which may extend to months and years (Meima et al. 2004b). This may partly explain the apparent lack of observed impact on transmission after MDT was introduced. Models suggest that early detection and treatment are more important in reducing transmission than the type of chemotherapy that is used (Meima et al. 2004b).

There are other factors which are likely to have an impact on transmission and incidence but they are difficult to quantify. Trial and systematic review evidence suggests that BCG vaccination, which is widely given at birth in East Asia, is likely to have an impact on transmission and incidence (Setia et al. 2006). East Asia is a region which has experienced considerable socio-economic development over the past decades with improved housing, nutrition, education and sanitation. All of these developments are likely to improve the environmental circumstances that are thought to sustain the transmission of leprosy. It is difficult to attribute changes in leprosy directly to specific changes, but it is important to recognise the potential impact of general socio-economic development.

The London Declaration (Uniting to Combat NTDs 2013) and the WHO road map for neglected tropical diseases (WHO 2012a, 2013) have set new elimination targets for leprosy, to be achieved by 2020. These elimination targets are the global interruption of transmission (WHO 2012a), with elimination (interruption of transmission) defined as 'the reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area as a result of deliberate efforts' (WHO 2013). The reintroduction of the term 'elimination' is confusing for the leprosy community familiar with a very different definition of elimination as that of a registered prevalence of leprosy of less than in 1 in 10,000 population. The further challenge is that in leprosy there is no accepted measure of transmission or of infection. The assumption in leprosy is that transmission of infection follows exposure to *M. leprae* but that not all those infected develop disease. It is unclear what the relationship is between infection with *M. leprae* and the onset of clinical disease, and there may be considerable self-healing particularly in children. The gold standard definition for the leprosy epidemiology is a clinical diagnosis, based on three cardinal signs (WHO 2012b). New detection is used as a proxy for incidence but it does not reflect transmission of the pathogen.

The elimination of leprosy defined as the cessation of transmission in a defined geographical area has occurred repeatedly throughout East Asia, for example, in Japan, in the Republic of Korea and in many provinces of China. However, this has typically not been achieved through deliberate efforts. As the trends in new case detection decline further in many countries and in areas within countries in East Asia, there may be a future role for more specifically targeting localised elimination. There also is a need for significant investment in developing new diagnostic tools for infection and disease for leprosy to realistically engage with the new definition of elimination based on a reduction of transmission. The development of contact management and the roll-out of chemoprophylaxis to contacts is an intervention which is specifically designed to reduce transmission. The development of a diagnostic test and a test for infection used with chemoprophylaxis, perhaps combined with immunoprophylaxis (Richardus and Oskam 2015), has the potential for a strategy of elimination to reduce transmission, but they will need a longer timeframe than 2020.

The road map for neglected tropical diseases (WHO 2012a, 2013) sets a second target for leprosy for the year 2020, namely, reducing grade 2 disability in new cases to less than one in a million population. This target was proposed by the WHO Expert Committee on Leprosy in 2012 (WHO 2012b) and represents a development of the target of the current enhanced global strategy (SEARO 2011), which targets a 35% reduction in the rate per population of grade 2 disability in new cases. This target is aimed at promoting improved early case detection which would not only prevent disability but would also impact on transmission through reduced exposure.

9 Conclusion

There has been a step change in leprosy in East Asia over the past 70 years from segregation policies to roll out of effective chemotherapy for all those affected by leprosy. The short course MDT has produced a dramatic fall of over 95% in the registered prevalence of leprosy in East Asia. It is important to recognise that those with disability at the time of diagnosis will continue to experience the physical and social effects of leprosy after completing MDT and this residual morbidity must be quantified and addressed within leprosy programmes.

The introduction of MDT has had no discernible impact on new case detection; however, increased leprosy activities have produced increases in case detection. The overall trend in new case detection is on a decline, which in many countries began before MDT was introduced. However, some countries have yet to see any substantial decline. The declines in new case detection may be due to long-term implementation of chemotherapy, either dapsone or MDT, due to BCG and due to economic development. New targets, based on elimination defined as zero transmission within a certain geographical area, are now proposed, but new diagnostic tools for prevention need to be developed before the targets can be achieved and monitored.

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Dengue: An Expanding Neglected Tropical Disease

Annelies Wilder-Smith, Tanu Chawla, and Eng Eong Ooi

Contents

Abstract The World Health Origanization has classified dengue as a major international public health concern. The reasons for the resurgence are complex, and are likely a combination of multiple factors, including population growth associated with rapid uncontrolled urbanization, increased movement of viruses in people among countries and regions via international travel, demographic changes, poor vector control, genetic changes in circulating or introduced viruses, and modulating climatic factors. The past decade has seen more investment in vaccine development and novel vector control measures than ever before. Three dengue vaccine candidates are far advanced in development, with CYD-TDV being the first licensed dengue vaccine. However, this vaccine showed serostatus dependent performance. The two other dengue vaccines are currently in Phase 3 efficacy trials.

Keywords Dengue · Severe dengue · Dengue vaccines · Vector control · *Aedes* mosquitoes

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1 Introduction

Dengue is an acute arthropod-borne viral (arboviral) infection that places a considerable socio-economic and disease burden on many tropical and subtropical regions of the world. With an estimated 50–100 million cases annually, dengue is regarded as the most prevalent arboviral disease globally. Modelling and cartographic estimates even put the estimated annual number of dengue infections as high as 390 million infections, of which 96 million had clinically apparent infections (Bhatt et al. 2013). Approximately 50% of the world's population resides in dengue-endemic countries (Murray et al. 2013). Dengue infections are thought to have increased 50-fold in the past five decades (Guzman et al. 2010). Dengue viruses belong to the genus *Flavivirus*, family *Flaviviridae*, and there are four serologically distinct dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) (Simmons et al. 2012). All four virus serotypes cause a spectrum of illness ranging from asymptomatic or a mild febrile illness to classical dengue fever and to more severe disease manifestations. Dengue viruses are transmitted by mosquitoes of the genus *Aedes* (such as *Aedes aegypti* and *Ae. albopictus*). *Aedes aegypti* is the principal vector, found widespread in the tropics and subtropics.

For decades, arboviral diseases were considered to be only minor contributors to global mortality and disability. As a result, low priority was given to arbovirus research investment and related public health infrastructure. The past five decades, however, have seen an unprecedented emergence of epidemic arboviral diseases. In response, there have been ever-louder calls for a concerted effort to improve prevention and control (Wilder-Smith et al. 2017). Although dengue is still listed as a neglected tropical disease (NTD), the past 10 years have seen more investment in vaccine development and novel vector control measures than ever before (Horstick et al. 2015).

2 Disease Manifestations

The incubation period lasts usually 3–7 days, although asymptomatic periods up to 14 days have also been reported. Dengue has a wide range of clinical manifestations. The most common presentation is the sudden onset of fever accompanied by headache, pain behind the eyes, generalized myalgia and arthralgia, flushing of the face, abdominal pain, and nausea. Rash is frequently seen and can be macular, maculopapular, morbilliform, and scarlatiniform, sometimes with characteristic "island-sparing". For the purpose of clinical management, the World Health Origanization classifies dengue illness as (i) dengue with or without warning signs for progression towards severe dengue and (ii) severe dengue. Warning signs of severe dengue include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement of >2 cm, or an increase in haematocrit concurrent with a rapid decrease in platelet count. Severe dengue signs include severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding or severe organ impairment. A detailed clinical case classification of dengue is provided in the WHO Dengue Guidelines.

Infection by one serotype is thought to provide lifelong immunity against that particular serotype (homotypic immunity) and transient cross-immunity to the other serotypes. There is a small risk of severe disease after any dengue infection, but a second infection by a different serotype to the first is thought to be associated with the highest risk of severe dengue, while the third and fourth infections are usually associated with a milder clinical course (Halstead and O'Rourke 1977a, b). Following recovery from a second infection, broadly neutralizing antibodies are induced (multitypic protection), such that severe disease with tertiary and quaternary infections is considered rare. Severe disease is thought to be due to cross-reactive antibodies that opsonize DENV to enhance infection in monocytes, macrophages, and dendritic cells through Fc gamma receptor (FcγR)-mediated entry (Halstead et al. 2005; Halstead 1988). This hypothetical process is more commonly referred to as antibody-dependent enhancement (ADE) of dengue; however, other hypotheses such as cross-reactive T cells have also been postulated (Wilder-Smith et al. 2010).

For those patients who develop more severe disease, fluid loss through vascular leakage will lead to hypovolemic shock associated with high mortality rates (Gubler 1998). Since there is no specific antiviral treatment available, clinical management depends on early recognition of the development of capillary leakage and prompt institution of intravenous fluid treatment. With appropriate fluid therapy, most patients survive the 24–48 h of the critical phase of illness and enter the recovery phase where they gradually revert to normal with reabsorption of fluids. However, a small proportion of patients experience prolonged lethargy and malaise, which can last for weeks after the acute illness (Simmons et al. 2012).

Despite promising in vitro and animal studies, no specific antiviral treatment has proven to be efficacious in clinical human trials (Wilder-Smith et al. 2010; Low et al. 2014).

3 Factors Responsible for the Expansion of Dengue

Based on the Global Burden of Disease (GBD) study estimates, dengue is increasing at a higher rate than any other communicable disease, with a 400% increase over 13 years (Global Burden of Disease Cancer et al. 2017). The current *Aedes* distribution is the widest ever recorded; the mosquito breeds extensively in all continents, including North America and Europe, with over three billion people living in *Aedes*-infested countries or areas. *Ae. aegypti*, the principal vector, mainly found in the tropics and subtropics, is efficient because it is highly susceptible to the virus, feeds preferentially on humans, is active during the daytime, thrives in peri-domestic environments close to humans, and is capable of biting several people in a short period of time. As a peridomicillary mosquito, it is hence well adapted to urban areas where it typically breeds in a wide variety of man-made containers such as tires, tin cans, pots, and buckets that collect rainwater. The rise of urbanization with increasing population sizes in endemic countries facilitates the availability of waste and water containers, thus driving the proliferation of vectors. The proximity of humans in highly urbanized areas, combined with the capacity of *Aedes* mosquitoes to bite several people for one blood meal, drives urban outbreaks (Gubler 2011). Using a mathematical model, Cummings et al. studied the impact of urbanization and population growth on the occurrence of dengue in Thailand. The study included 72 provinces of Thailand and found that the three yearly waves of outbreaks mainly originated from Bangkok (Cummings et al. 2004). Bangkok has the highest volume of trade and travel within the country as well as with other neighbouring countries. Similarly in Singapore, Poisson regression models identified population growth as the main driver for the increasing frequency and magnitude of dengue outbreaks (Struchiner et al. 2015). Significant geographic expansion of both the vector and virus has been coupled with exponential increases in cases, epidemics and co-circulation of all four serotypes, leading to the more severe forms of disease (Wilder-Smith and Gubler 2008).

Ae. albopictus is also continuing its geographic expansion into tropical and temperate climates. Although a less efficient vector compared to *Ae. aegypti*, dengue epidemics have been recorded in places where *Ae. albopictus* is the only vector (Effler et al. 2005). The global spread of *Ae. albopictus*, fuelled by global trade and travel (Reiter 1998), and its hardiness in more temperate climates (Kraemer et al. 2015), puts selected areas of North America and Europe, where *Ae. aegypti* cannot survive cold winters, at risk for transmission for *Aede*s-borne viruses. Modelling studies predict that climate change, including extreme weather, with large daily temperature fluctuations will increase dengue-epidemic potential in temperate regions, potentially flattening the differences between tropical and temperate zones (Rocklov et al. 2016).

Dengue outbreaks are occurring at an increasing frequency and magnitude of outbreaks, with epidemics occurring every 3–5 years (Wilder-Smith and Macary 2014). The underlying reason for this cyclical trend is poorly understood but is perhaps best explained by demographic, immunologic, and environmental changes combined with ineffective public health measures (Ooi and Gubler 2009a; Wilder-Smith and Gubler 2008; Cheng et al. 1998; Egger et al. 2008). Climatic influences, such as the El Niño-Southern Oscillation (ENSO) and global warming, have been suggested as other factors contributing to the cyclical pattern of dengue activity (Hales et al. 1999).

International transport of cargo and goods, especially via commercial sea shipment, can export and import dengue's primary and secondary vectors *Ae. aegypti* and *Ae. albopictus* (Banu et al. 2011). Transatlantic transport of used car tires has been linked with the introduction of *Ae. albopictus* from Asia to North America and from North America into Europe (Reiter 1998). Given the vectors' suitability to breed and survive sea travel within water collected in a tire, their transport has contributed a major public health threat in the last few decades, and this will only increase as more automobiles are used globally (Reiter 1998). However, the main reason for the rapid geographic spread of dengue viruses globally is the movement of people via modern means of transportation (Wilder-Smith and Gubler 2008). Air travel connectivity between dengue-endemic countries and from dengue-endemic countries to dengue-nonendemic (but still vulnerable) regions has increased exponentially (Glaesser et al. 2017). International travellers are increasingly at risk of acquiring dengue, and international travel contributes to the global spread of dengue (Wilder-Smith and Schwartz 2005). Importation of dengue into Europe, Northern America, and Australia has increased exponentially, and dengue is now the leading cause of fever in returning travellers from Asia (Wilson et al. 2007; Schwartz et al. 2008, 2013; Leder et al. 2013). While imported dengue cases to the USA have resulted in small but contained dengue clusters for many years (Effler et al. 2005; Centers for Disease Control and Prevention (CDC) 1996; Adalja et al. 2012; Hafkin et al. 1982; Gubler 1998), the first autochthonous cases in Europe were only reported starting in 2010, with the first two cases in southern France, followed by a case in Croatia (La Ruche et al. 2010; Gjenero-Margan et al. 2011). In 2012, the first major outbreak of dengue occurred in Europe since the outbreak in Greece between 1926 and 1928 (WHO 2012; Sousa et al. 2012). This rapidly evolving outbreak occurred in the autonomous region of Madeira, Portugal. Madeira is an archipelago in the Atlantic on the same latitude as the African north coast (Frank et al. 2013). The main vector for dengue, *Ae. aegypti*, was introduced to Madeira in 2005 (Alves et al. 2013), and because of Madeira's subtropical climate, this vector has been able to establish itself.

Information on air traffic can be used to predict the risks of vector-borne disease importation (Tatem et al. 2012). A project known as BioDiaspora (now renamed to BlueDot) was developed to evaluate the probable pathways of international dissemination of infectious diseases via the global airline transportation network, and there are increasing modelling activities to predict the future spread of dengue into naïve countries (Massad et al. 2013; Quam et al. 2015; Quam and Wilder-Smith 2015; Sessions et al. 2013).

Messina et al. traced the global pattern of concurrent or sequential emergence of all four DENV serotypes from 1943 to 2013 indicating the increasing co-circulation of all four serotypes and hyperendemicity (Messina et al. 2014) which predisposes to more severe disease due to more frequent secondary infections.

Furthermore, the evolution of dengue viruses has had a major impact on their virulence for humans and on the epidemiology of dengue disease around the world. The RNA genome of the virus is susceptible to random mutations due to the lack of proofreading capacity of the RNA-dependent RNA polymerase, which could thus give rise to more virulent strains following increased levels of infection in a population (Gubler and Trent 1993). Dengue viruses can be classified as being of epidemiologically low, medium or high impact (Rico-Hesse 2003). Subtypes within the American genotype of DENV-2 and genotype IV of DENV-3, for example, are less virulent with a reduced ability to grow in cell cultures and mosquitoes compared to the Asian genotypes of DENV-2 and DENV-3. Analysis of envelope protein amino acid changes predicted to have accompanied endemic/epidemic emergence suggested a role for domain III in adaptation to new mosquito and/or human hosts

(Wang 2000). Phylogenetic and epidemiological analyses suggest that the genotypes and subtypes with greater epidemic potential are now displacing those that have lower epidemiological impact (Wilder-Smith and Gubler 2008).

In a hyperendemicity situation, the fluctuation in serotype predominance is driven by herd cross-reactive immunity levels combined with the importation of new serotypes. A cohort study in Kamphaeng Phet in northern Thailand demonstrated that a higher incidence of dengue infection in the previous year resulted in milder disease in subsequent years (Endy et al. 2011). Anderson et al. showed that shorter time intervals between first and second infection are associated with protection but as the antibodies wane from protective to enhancing levels, it leads to severe forms of dengue disease (Anderson et al. 2014). Hyperendemicity thus provides the necessary mix of virus serotypes that is able to take advantage of increasing susceptible population each time heterotypic immunity levels wane following a preceding epidemic. Hyperendemic transmission also increases the likelihood of emergence of DENV strains with greater virulence or epidemic potential (Gubler and Trent 1993).

In summary, as a consequence of the expanding geographical distribution of both the virus and the mosquito vector, increased frequency of epidemics and the emergence of dengue haemorrhagic fever in new areas, WHO has classified dengue as a major international public health concern. The reasons for the resurgence are complex and are likely a combination of multiple factors, including population growth associated with rapid uncontrolled urbanization, increased movement of viruses in people among countries and regions via international travel, demographic changes, poor vector control, genetic changes in circulating or introduced viruses, and modulating climatic factors (Wilder-Smith and Gubler 2008). A large number of unknown factors, including effective entomological predictors, genetic diversity of circulating viruses, population serological profile and human mobility, continue to pose challenges and to limit the ability to produce accurate and effective risk maps, thereby failing to support the development of effective early warning systems (Louis et al. 2014).

4 Dengue in Asia

Asia accounts for 75% of the dengue disease burden according to WHO (Bhatt et al. 2013). Within Southeast and East Asia, dengue has been hyperendemic in Cambodia, Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Vietnam for many decades. The countries with more temperate climates such as Taiwan, Japan, South Korea and the People's Republic of China initially recorded only imported cases due to travellers (Wu et al. 2010) but now experience seasonal epidemics (Fig. 1). South Korea reported 324 imported dengue fever cases from 2006 to 2010 (Park and Lee 2012), and a similar trend was observed in Japan (Takasaki 2011). In the past decade, the southern coast of the People's Republic of China (Guangdong, Guangxi, and Hainan) and Taiwan have reported dengue epidemics (Sang et al. 2014; Shang et al. 2010). Dengue is also reported in southern coastal regions towards eastern (Fujian and

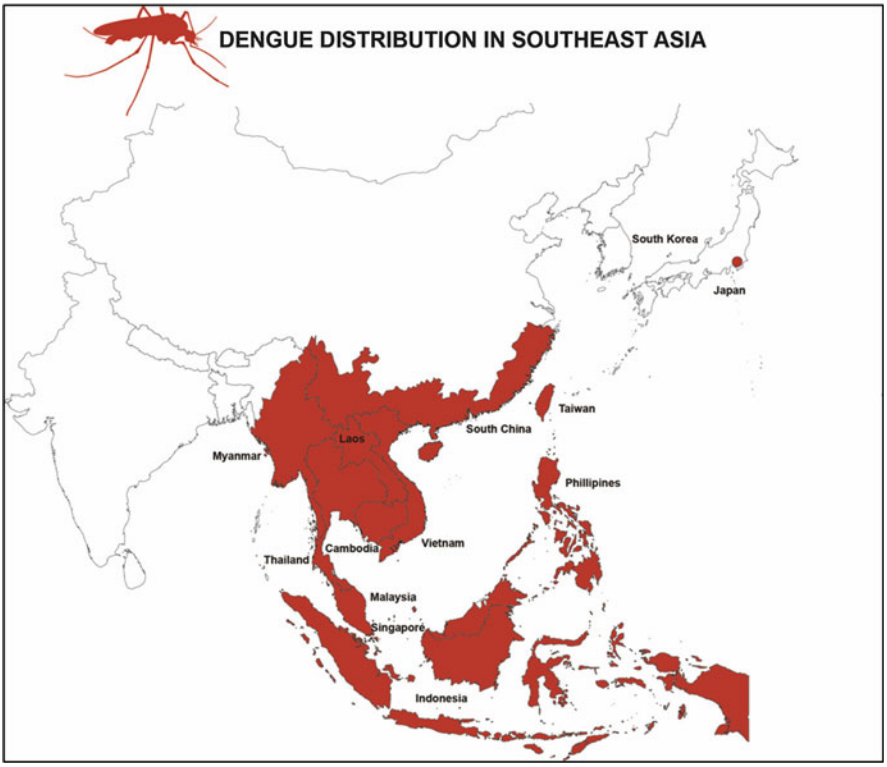

Fig. 1 Southeast Asian countries and regions with dengue epidemics, 2014

Zhejiang) and south-western (Yunnan) regions of The People's Republic of China (Zhang et al. 2014; Wu et al. 2010). In Taiwan, the southern half of the island has a more tropical climate, and the presence of *Ae. aegypti* has caused repeated epidemics in cities like Kaohsiung and Tainan (Lin et al. 2010; Wu et al. 2013). In the northern half of the island, the cooler climates favour *Ae. albopictus*, and outbreaks are not as intense as those in the south (Yang et al. 2013). Despite Japan's temperate climate, an autochthonous dengue outbreak occurred in Tokyo for the first time in over 70 years in 2014 (Quam et al. 2016). Based on phylogenetic analysis, the dengue virus might have been imported to Japan from The People's Republic of China, Indonesia, Singapore or Vietnam (Quam et al. 2016). The largest travel volumes into Japan were from The People's Republic of China; hence, Guangzhou may have been the source of DENV introduction, given that Guangzhou also reported a large-scale dengue outbreak at the same time. Coinciding with the 2014 outbreak, Tokyo's climate conditions permitted the amplification of *Aedes* vectors and the annual peak of vectorial capacity (Quam et al. 2016).

An interesting case study is the island-city state of Singapore, a modern wealthy country in Southeast Asia. Intensive vector surveillance and control in Singapore resulted in an approximately 15-year period of low dengue incidence from the mid-1970s to the late 1980s (Ooi et al. 2006). Since then, however, Singapore has experienced repeated cyclical epidemics. The largest on record occurred in 2013 with over 22,000 dengue cases and 8 deaths. This epidemic occurred despite the continued investment in vector control that costs Singapore an estimated US$50 million annually (Carrasco et al. 2011). Singapore's status as a transportation and financial hub likely contributes to the repeated importation of the virus from other endemic countries (Ooi and Gubler 2009b). Interestingly, dengue epidemics in Malaysia, a neighbouring country, show a similar pattern of periodicity as Singapore, possibly due to similar climatic factors and sharing of the same virus strains due to the high interconnectivity between the two countries (Fig. 2d, f). A related trend is also seen in Lao People's Democratic Republic and Thailand which all had an especially high number of cases in 2013 (Fig. 2c, g).

South Asia also has an increasing dengue burden. In Sri Lanka, dengue increasingly poses a significant socio-economic and public health burden. The geographic spread, incidence, and severity of disease are of major concern ever since the first dengue haemorrhagic fever epidemic occurred in 1989. Periodic epidemics have become progressively larger, peaking with the 2009–2014 epidemic with 28,000–40,000 cases reported each year (44,461 cases in 2012), which may be partly due to the increasing awareness and diagnosis, but is more likely a true reflection of dengue emergence in this country, as also observed in the Asia Pacific region (Tissera et al. 2014, 2016). During that same period, the disease dramatically expanded to the whole island. Internet-based media coverage to explore the extent of awareness of the disease and perceived severity of an outbreak at a national level can be used for early outbreak detection. Between 2007 and 2015, a rapid rise in hits was registered in 2009 and followed by a rising trend ever since. These hits were highly correlated with the national epidemiological trend of dengue. The volume of digital media coverage of dengue was much higher than of influenza and malaria (Wilder-Smith et al. 2016a). In India, the true dengue burden remains unknown. A study from India suggested that the true number of dengue cases between 2006 and 2012 was 282 times greater than what was officially reported (Shepard et al. 2014).

5 Economic Impact of Dengue

The morbidity, high incidence, and the unpredictability of dengue outbreaks pose a considerable economic burden on dengue-endemic countries. Patients will not only need to seek medical care, but parents of diseased children will also have to take time off work to tend to their sick children. During epidemics, hospitalization of a large number of dengue cases can lead to acute bed shortages and postponement of elective procedures. Furthermore, many dengue-endemic countries are also reporting increasing dengue burden in young adults, thereby resulting in days lost to work. Estimation of the economic and disease burden is critical for policy-makers to establish intervention strategies and disease control methods. A cost evaluation for reported ambulatory and hospitalized dengue cases from 2001 to 2005, including clinical diagnosis and treatment in Cambodia, Malaysia, and Thailand was

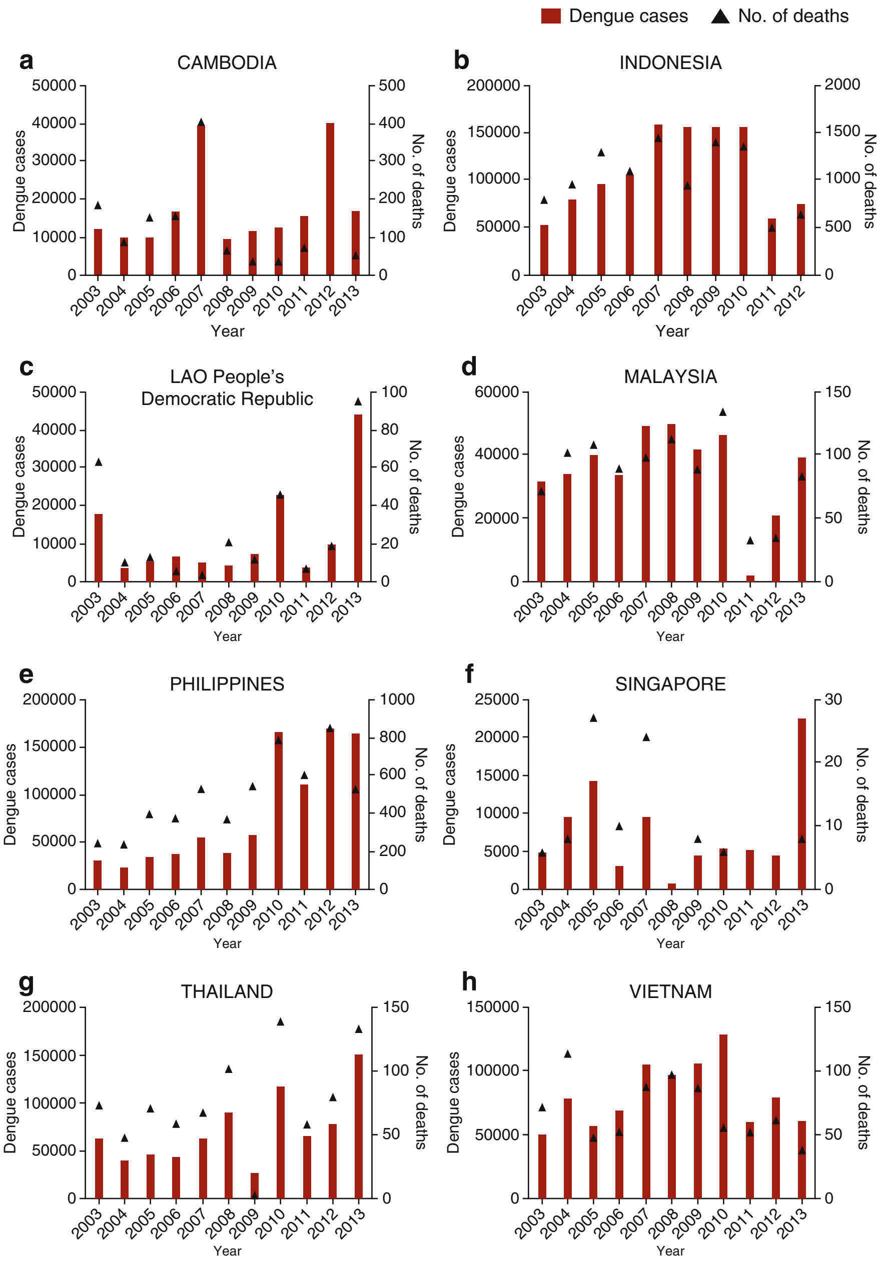

Fig. 2 Dengue cases reported from 2003 to 2013 in hyperendemic Southeast Asian countries (http://www.wpro.who.int/emerging_diseases/DengueSituationUpdates/en/)

approximately US$2.8 million, US$38.2 million and US$47.8 million, respectively (Suaya et al. 2009). The annual cost in Cambodia from 2006 to 2008 was estimated at US$8.0 million (Beaute and Vong 2010). Costs of dengue illness in Malaysia (2002–2007) and Thailand (2000–2005) were reported at US$54.9 million and US$66.2 million, respectively (Lee Han et al. 2010). Carrasco et al. estimated the annual dengue disease and vector control costs as US$41.5 million and US$50.0 million, respectively, for Singapore from 2000 to 2009 (Carrasco et al. 2011). The first attempt to assess the economic burden of dengue response in the public health sector in Sri Lanka (e.g. public sector costs of dengue control activities and the direct costs of hospitalizations) in Colombo was done during the epidemic year of 2012 from the Ministry of Health's perspective (Thalagala et al. 2016). The total cost of dengue control and reported hospitalizations was estimated at US$3.45 million in Colombo district in 2012. Personnel costs accounted for the largest shares of the total costs of dengue control activities (79%), followed by hospitalizations (46%). The results indicated a per capita cost of US$0.42 for dengue control activities. The average costs per hospitalization ranged between US$216 and US$609 for paediatric cases and between US$196 and US$866 for adult cases, according to disease severity and treatment setting.

To standardize the estimation of the cost of dengue for South and East Asian countries, Shepard et al. applied a consistent methodology to analyse data from 12 countries: Bhutan, Brunei, Cambodia, East Timor, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. The total annual cost of dengue in all these 12 countries was estimated at US$950 million of which Indonesia bore the highest dengue economic burden, followed by Thailand (Shepard et al. 2013). The extensive medical and economic burden of dengue on endemic countries calls for increased attention and effective public health measures to prevent the disease.

6 Dengue Prevention and Control

All dengue-endemic countries need an effective surveillance system to guide disease prevention and control efforts (Wilder-Smith et al. 2012; Peeling et al. 2010; Ooi and Gubler 2009b). Historically, surveillance is often just passive with mandatory dengue notifications based on illness clinically compatible with dengue and only limited laboratory confirmation. Adding active surveillance elements to a well-functioning passive surveillance system improves sensitivity; adding laboratory elements to the system improves specificity (Runge-Ranzinger et al. 2008). Passive surveillance providing the baseline for outbreak alert systems should be strengthened and appropriate threshold levels for outbreak alerts investigated. Appropriate alert signals need to be identified and integrated into a risk assessment tool (Runge-Ranzinger et al. 2014). Shifts in dengue serotypes/genotype or electronic event-based surveillance have also considerable potential as indicator in dengue surveillance. Further research on evidence-based response strategies and cost-effectiveness is needed. Most countries do not have comprehensive, detailed contingency plans for dengue outbreaks. Countries tend to rely on intensified vector control as their outbreak response, with minimal focus on integrated management of clinical care; epidemiological, laboratory, and vector surveillance; and risk communication (Runge-Ranzinger et al. 2016).

7 Vector Control

Effective vector control methods are an essential component of the strategic direction to reduce dengue mortality and morbidity by 2020. “Integrated vector management” (IVM) is the strategic approach promoted to countries by the WHO as a rational, cost-effective, and optimal decision-making process for vector control programmes. This involves using a combination of approaches incorporating key elements of social mobilization, integration of chemical and non-chemical control methods targeting areas of high human-vector contact, evidence-based decision-making guiding research and policy as well as capacity building. Utilizing an effective, IVM strategy will aid in the reduction of dengue transmission and the resulting disease burden.

The use of source reduction has been shown to be effective in Singapore (Ooi et al. 2006) and Cuba (Bonet et al. 2007). However, source reduction is costly (Carrasco et al. 2011), and few countries in dengue-hyperendemic regions can afford to sustain the intensive vector control programmes deployed in Singapore and Cuba. Insecticides such as pyrethroid deltamethrin or metofluthrin have been a common tool for controlling mosquito populations for many years (Ritchie and Devine 2013). However, there are problems related to the usage of insecticides such as dosage, method of delivery, and the emergence of insecticide resistance in mosquitoes (Maciel-de-Freitas et al. 2014). Most importantly, the use of insecticides involves high costs, and the evidence that they reduce the mosquito population density remains scarce (Gubler 1989; Eisen et al. 2009).

Evidence for epidemiological efficacy from well-designed field trials of mosquito control is urgently needed to guide application and evaluation (Bowman et al. 2016). As control of *Ae. aegypti* is challenging, effective interventions must be expedient, comprehensive and sustained (Achee et al. 2015). Community mobilization and participation to reduce *Aedes* larval habitats have shown variable success (Louis et al. 2016). However, a recent multicentre randomized controlled trial provided evidence that community mobilization can enhance dengue vector control (Andersson et al. 2015). There is evidence that cyclopoid copepods (*Mesocyclops* spp.) could potentially be an effective vector control option, as shown in five community effectiveness studies in Vietnam. This includes long-term effectiveness for larval and adult control of *Ae. aegypti*, as well as dengue incidence. However, this success has so far not been replicated elsewhere (six studies, three community effectiveness studies in Costa Rica, Mexico, and the USA and three studies analysing both efficacy and community effectiveness in Honduras, Lao People’s

Democratic Republic and the USA), probably due to community participation and environmental and/or biological factors (Lazaro et al. 2015).

Personal protective measures include repellents, wearing protective clothing, insecticide treatment, spatial repellents, traps, etc. Applying repellents on a daily basis is impractical, and will not be scalable on a population basis. Improving home construction, including use of screens with or without insecticide treatment, may be a long-term solution for decreasing contact between *Aedes* vectors and humans. Developing technologies that can be applied during the daytime to protect against mosquito bites should similarly be a priority. Safe technologies for long-lasting insecticide-treated clothing materials that can be used for school and workplace uniforms and maternity clothing should become an urgent area of research (DeRaedt Banks et al. 2015; Orsborne et al. 2016). First results of a community-based trial in 10 schools in Thailand using permethrin-impregnated school uniforms did, however, not show an impact (Kittayapong et al. 2017).

A variety of new approaches show promise for enhanced disease prevention, for example, methods to either decrease the capacity of *Aedes* mosquitoes to transmit the dengue viruses or reduce mosquito populations, genetically engineered or irradiated male mosquitoes that are sterile (the wild females with which they mate producing infertile eggs, thus reducing populations), spatial repellents, and vapour-active insecticides to remove mosquitoes from homes where they bite and infect human hosts and insecticide-treated screening of homes (Ritchie and Devine 2013). WHO has expressed its support for developing and upscaling three novel approaches to controlling the *Ae. aegypti* mosquito: the sterile insect technique (SIT), the release of insects carrying dominant lethal genes (RIDL), and the release of *Wolbachia*-infected mosquitoes (Yakob et al. 2017). Whereas the former two approaches are temporary insect population suppression strategies, *Wolbachia* infection is a self-sustaining, invasive strategy that uses inherited endosymbiotic bacteria to render natural mosquito populations arbovirus resistant. *Wolbachia* is found naturally in 60% of all insects including fruit flies, moths, butterflies, and dragonflies but not in *Ae. aegypti* (Sinkins et al. 1995). Strains of the bacterium *Wolbachia*, deliberately introduced into *Ae. aegypti* mosquitoes, have been shown to be able to spread to high frequencies in mosquito populations in release trials, and mosquitoes infected with these strains show markedly reduced vector competence. Thus, *Wolbachia* represents an exciting potential new form of biocontrol of dengue (Dorigatti et al. 2017). A crucial next step for *Wolbachia*-based vector control is to assess the efficacy of *Wolbachia* in reducing dengue virus transmission. However, a cluster randomized trial is at this time premature because the choice of *Wolbachia* strain for release and deployment strategies is still being optimized (Lambrechts et al. 2015). The other approach to eliminate *Aedes* mosquitoes is to use genetically modified (GM) mosquitoes (Alphey 2014). The most advanced of such an approach is the one developed by Oxitec. Termed “release of insects containing a dominant lethal” (RIDL), this approach uses the insertion of a lethal gene, under the control of a chemically inducible promoter, into the *Ae. aegypti* genome using a transposon-based system (Alphey and Alphey 2014). As the GM male mosquito with a lethal gene mates with wild-type females, the lethality trait is passed on to the offspring.

Field trials in Brazil and Panama are in progress. Advances in genetic engineering technology (CRISPR-Cas9) that allows highly efficient, targeted transformation and gene drive systems in mosquitoes are being explored as ways to block transmission or reduce vector populations (Gantz et al. 2015). Like existing tools, these novel approaches will need to have demonstrated epidemiologic impact and be scalable across the vast geographic areas in which *Ae. aegypti*-borne diseases increasingly persist.

Based on the growing consensus that no single intervention will be sufficient to effectively reduce disease from the expanding number of *Ae. aegypti*-borne viruses, there is increasing interest in combining mosquito interventions with vaccination (Reiner et al. 2016). Conceptually, a vaccine can increase herd immunity, making it easier to sustain reduced virus transmission with limited vector control. Vice versa, vector control can complement a vaccine by lowering the risk of infection, making vaccine delivery goals easier to achieve.

8 Vaccine

In late 2015, after decades of research, the world's first dengue vaccine was licenced: CYD-TDV vaccine (Dengvaxia®) (Wilder-Smith et al. 2016b). Dengvaxia® is a recombinant live-attenuated, tetravalent dengue vaccine based on the yellow fever 17D backbone. The structural genes (prM-E) of the YF17D virus vector are replaced by the structural genes of each the four DENV serotypes. CYD-TDV is now registered in 19 countries, typically with an indication for individuals aged 9–45 years living in endemic areas. Data generated by a large Phase 3 trial in 10 endemic countries in Asia and Latin America (Capeding et al. 2014; Villar et al. 2015) showed an unpredicted complexity of vaccine performance with efficacy dependent on serotype, baseline serostatus, and age. Vaccine efficacy varied significantly by prior DENV infection status (Capeding et al. 2014; Hadinegoro et al. 2015). In a post hoc, pooled analysis of the two Phase 3 trials, vaccine efficacy was 78.2% (95% confidence interval (CI) 65.4%, 86.3%) in trial participants who were DENV-seropositive at baseline (hereafter referred to as "seropositive") and 38.1% (95% CI, 3.4%, 62.9%) in trial participants who were DENV-seronegative at baseline (hereafter referred to "seronegative") (Hadinegoro et al. 2015), based on the limited immunogenicity subset. In participants 9–16 years of age, vaccine efficacy in seronegatives was 52.5% (95% CI 5.9%, 76.1%). In the 12–24-month period after the last vaccine dose (year 3 of the trial), participants aged 2–5 years old in the Phase 3 trial in Asia were at increased risk of hospitalized dengue with a relative risk (RR) of 7.5 (95% CI 1.2, 313.8). The reason for this elevated risk in the 2–5 year age group has not yet been fully elucidated. One hypothesis proposed is that in seronegative individuals, the vaccine acts like an asymptomatic primary infection, priming vaccinees to experience a "secondary-like" clinical presentation upon a first natural exposure to DENV (Organization). Based on the difference in performance of Dengvaxia® in seropositive and seronegative individuals, WHO proposed seroprevalence thresholds as the best approach to define target populations for vaccination. Therefore, WHO published a conditional recommendation on the use of the vaccine for areas in which dengue is highly endemic as defined by seroprevalence (Organization). Trial results and mathematical modelling suggested optimal benefits of vaccination if seroprevalence in the age group targeted for vaccination was in the range of $\geq 70\%$.

On 29 November 2017, Sanofi Pasteur made a press release announcing that they had completed additional analyses based on a novel NS1 assay in blood samples taken at month 13 during the Phase 3 trials, thus enabling to retrospectively stratify all subjects into baseline seropositive and seronegatives. Based on these additional analyses, Sanofi Pasteur announced that the subset of trial participants who were inferred to be seronegative at the time of first vaccination had a significantly higher risk of more severe dengue and hospitalizations from dengue compared to unvaccinated participants, regardless of age. The risk was highest in year 3 following the first dose, declined in the following years but persisted over the trial follow-up period of about 5 years after the first dose. The Global Advisory Committee on Vaccine Safety subsequently published a statement not to vaccinate seronegative subjects. On 6–7 December 2017, the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed the data and subsequently published a statement related to the safety of the product. WHO acknowledges that in high seroprevalence settings, the vaccine can have significant population-level benefits. However, until a full review has been conducted, WHO recommends vaccination only in seropositive individuals (http://www.who.int/immunization/diseases/dengue/q_and_a_dengue_vaccine_dengvaxia_use/en/).

Besides CYD-TDV, other chimeric live-attenuated dengue vaccines are now in Phase 3 trials (Wilder-Smith 2017; Whitehead 2016). Furthermore, various other dengue vaccine candidates with different platforms are in development (Vannice et al. 2015).

9 Conclusion

The dramatic spread of dengue over recent decades and the increased frequency and magnitude of dengue epidemics underscore the critical need for more effective tools for the surveillance, prevention, treatment, and control of this disease. Dengue vaccine introduction will not be the only strategy to combat dengue but needs to be combined with novel vector control approaches, with community-based interventions to reduce the number of breeding sites and with improved clinical case management to reduce the case fatality rates.

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Yaws in Southeast Asia: Towards Elimination

Michael Marks and Oriol Mitjà

Contents

Abstract Yaws is a chronic infectious disease caused by *Treponema pallidum* subsp. *pertenue*, which causes disease of the skin, bones, and joints. Most cases are seen in young children living in remote communities in warm humid environments. Yaws is endemic in several countries in Asia, including the Philippines, Indonesia, and Timor-Lester. Azithromycin is now the first line treatment for yaws and community mass treatment with azithromycin is the central component of the World Health Organization yaws eradication strategy.

Keywords Yaws · *Treponema pallidum* · Elimination · Eradication · Southeast Asia

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1 Introduction

Yaws is one of the human treponematoses, which comprise venereal syphilis and the three non-venereal endemic treponematoses: yaws, bejel (endemic syphilis), and pinta. Yaws is a chronic infectious disease, caused by *Treponema pallidum* subsp. *pertenue*, which is spread by skin-to-skin contact in warm and humid environments, mainly among children. The disease progresses from a primary phase to a secondary and then a tertiary phase. The first sign of infection is a localized papilloma or a solitary yellow-brown crusted ulcer. Secondary lesions consist of smaller multiple skin excrescences or scaly plaques and osteoperiostitis of long bones. In some untreated individuals, the tertiary stage of yaws develops with inflammation leading to severe deforming bone lesions. The aim of treatment for yaws is to halt the progression of disease by clearing the infection and to stop transmission to uninfected individuals. Although the tissue injury occurring during the early stages of infection resolves completely following adequate therapy, tissue damage occurring during the late stages of infection is irreversible (Mitjà et al. 2013).

There have been recent advances in the diagnostic tools available for yaws and the use of azithromycin which is a viable oral agent for the treatment of yaws. Despite these advances the management of patients with yaws remains challenging. Ongoing research has led to updated recommendations for clinical decision-making, particularly in the areas of both rapid diagnostic serological tests and molecular diagnostics. These developments have particular importance in the light of increasing numbers of yaws cases reported from remote areas of Africa, Asia, and the Western Pacific and in the context of the World Health Organization (WHO) announcement of a new eradication campaign based on mass drug administration (MDA) with azithromycin. This so-called Morges strategy aims to eradicate yaws by 2020 (WHO 2012).

Yaws is endemic in two countries of the Southeast Asia (SEA) region, as defined by WHO: Indonesia and Timor-Leste. India was formerly endemic but has been certified to have eliminated yaws in 2016. In addition to the global Morges strategy, the WHO SEA Regional Office has also set a target for regional yaws elimination by 2020. Yaws elimination is at various stages in these two countries. In Indonesia, the yaws elimination programme is in an advanced stage, while in Timor-Leste the programme is in its infancy. If lessons are learned from the yaws elimination programme in India and an externally funded, technically supported programme is started immediately in Indonesia and Timor-Leste, the target should be possible to accomplish.

In this chapter, we review (i) the microbiology and molecular biology of the causative agent; (ii) the latest epidemiological data of the disease; and (iii) the clinical presentation and differential diagnosis, and we draw attention to advances; (iv) in new laboratory tests for yaws; (v) the new azithromycin treatment for patients with yaws; and (vi) new MDA strategies for yaws eradication.

2 Bacteriology and Genetics

Microbiology All human treponematoses are caused by gram-negative, spiral-shaped bacteria, which are members of the *Spirochaetaceae* family. This group includes *T. pallidum* subsp. *pallidum*, the causative agent of venereal syphilis; *T. pallidum* subsp. *pertenue*, the causative organism of yaws; *T. pallidum* subsp. *endemicum*, the causative agent of bejel; and *T. carateum*, the causative agent of pinta. The organisms all have a length ranging from 10 to 15 μm and a diameter of 0.2 μm, rendering them invisible to light microscopy except under dark-field illumination (Ovcinnikov and Delektorskij 1970). Electron microscope studies have shown that there are no significant differences in morphology or structure between *T. pallidum* subspecies and with *T. carateum* (Angulo et al. 1951).

The bacteria are easily killed by drying, elevated temperature and exposure to oxygen. The organisms multiply slowly (once every 30–33 h) (Magnuson et al. 1948) and cannot survive outside the mammalian host. Since *T. pallidum* species cannot be grown in culture, testing for antibiotic resistance is difficult and can be done only by experimental infection of animals, typically golden hamsters or rabbits, or indirect molecular methods, most frequently the detection of point mutations in the 23s rRNA gene (Stamm 2010).

In vitro susceptibility assays utilizing cultivation of treponemes in rabbit testis have been used to assess the effect of antibiotics on treponemal protein synthesis. The method consists of measuring active protein synthesis via quantitative incorporation of radiolabeled ^{35}S-methionine, while freshly isolated treponemes are incubated with and without test antibiotics. These assays have demonstrated sensitivity of *T. pallidum* subsp. *pallidum* and *T. p. pertenue* to penicillin, tetracycline, and erythromycin (Stamm et al. 1988). The same in vitro system demonstrated a lack of sensitivity to streptomycin (up to 500 mcg/mL), rifampicin (up to 100 mcg/mL), or quinolones (up to 10 mcg/mL).

Laboratory in vivo studies with animal models have been consistent with the in vitro susceptibility findings. Penicillin and several macrolides have also shown curative results in animal models (Alder et al. 1993). Tests on experimentally infected animals and infected patients showed that benzylpenicillin levels >0.03 units/mL of serum maintained for at least 7 days were treponemicidal. These levels can be achieved either by giving repeated doses of short-acting benzylpenicillin preparations (i.e., aqueous benzylpenicillin) or a single intramuscular injection of slowly absorbed, repository benzylpenicillin preparations. Clarithromycin was also shown to be curative in *T. p. pertenue* infections in animal models with concentrations of the drug in serum similar to those achieved in humans.

Genetics Whole-genome analysis of several pathogenic treponemes has been performed, and several genetic differences between *T. p. pallidum*, *T. p. pertenue*, and *T. p. endemicum* have been identified. The regions of sequence divergence could be used for the molecular detection and discrimination of syphilis, yaws, and bejel strains, which are not possible with the currently available serological or molecular diagnostic tests.

The overall genetic sequence identity between *T. p. pallidum* and *T. p. pertenue* is 99.8% (Mikalová et al. 2010). In all strains, no major rearrangement is found and the gene order is nearly identical, further establishing the close genetic relationship. Analyses of sequences between nonhuman primate and human treponemal infections revealed a closer relationship between the Fribourg-Blanc simian treponemes and *T. p. pertenue* strains and showed that *T. p. endemicum* (Bosnia A strain) also clustered with *T. p. pertenue* strains, though more distantly than that of the Fribourg-Blanc isolate.

3 Global Epidemiology

Historic Perspective The worldwide prevalence of yaws was significantly reduced from an estimated 50 million cases in 1952 to 2.5 million in 1964; this was achieved as a result of mass treatment with long-acting injectable penicillin campaigns led by the WHO and the United Nations International Children's Emergency Fund (UNICEF) in 46 countries. Over 300 million individuals were screened, and 50 million individuals were treated as a result of this campaign. Although yaws was not eradicated country-level elimination was achieved in several countries, including Malaysia and Brazil (Lo 1985; Muniz 2012).

Following this initial success, yaws slipped down the public health agenda, and the disease began to re-emerge in the late 1970s. A World Health Assembly (WHA) resolution called for renewed efforts to eradicate yaws in 1978 (WHA 31.58). However, yaws control was not prioritized in many regions, and surveillance and reporting have been sporadic. From 2010 to 2013, a total of 240,000 yaws cases were reported to WHO from 12 countries and territories.

Geographic Distribution Yaws is predominantly found in rural areas among communities living in overcrowded conditions with poor hygiene. Data available from a number of endemic countries demonstrate that yaws is endemic mainly in warm, humid regions of Africa, SEA, and the Pacific (Fig. 1) (Perine et al. 1984; Capuano and Ozaki 2011). SEA and the Pacific thus represent a major focus of yaws cases worldwide. Of the 12 endemic countries, Papua New Guinea (PNG) (17,560 cases in 2012) and the Solomon Islands (12,372 in 2012) consistently report the most cases in the world, alongside Ghana in West Africa (8980 in 2012). Together, these three countries currently report more than 85% of all cases worldwide. Other countries in SEA and the Pacific are also affected by yaws, including Indonesia (3746 cases in 2012) and Vanuatu (2514 in 2012). Reporting of yaws is not mandatory, and these figures likely underestimate the true burden of disease in these countries. The number of active infections is below 300 cases per year in Benin, Cameroon, Central African Republic (CAR), Republic of Congo, Democratic Republic of the Congo (DRC), and Togo, but, again, it is likely that there is

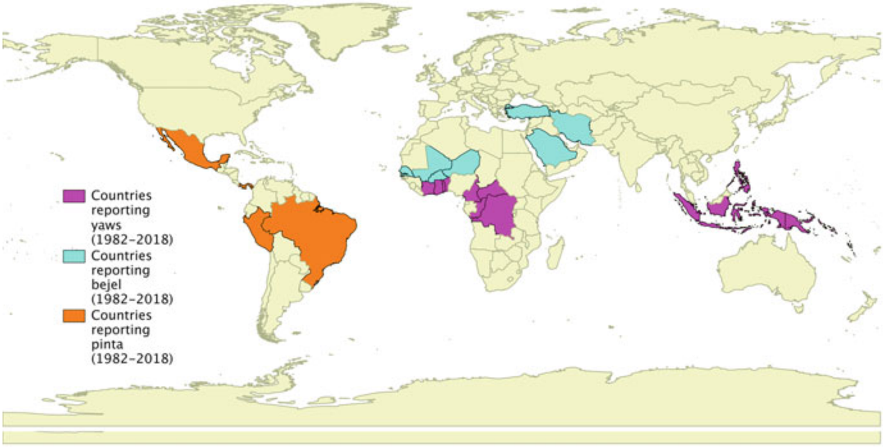

Fig. 1 Geographic distribution of yaws, bejel, and pinta. Shading indicates countries where cases of endemic treponematoses have been reported between 1982 and 2018. In some countries the transmission may be restricted to small areas

underreporting from all of these countries. Finally in recent years, both Ecuador (Anselmi et al. 2003) and India (WHO 2008) have reported elimination of yaws.

A total of 87 million people are estimated to live in yaws-endemic districts and are therefore at risk of infection. In the small islands, states of Solomon Islands and Vanuatu, and in PNG, almost 100% of the population is assumed at risk. However, there is uncertainty about the actual size of populations at risk in some countries such as Côte d'Ivoire, Ghana, and Indonesia where there are often only few endemic communities in endemic districts.

4 Epidemiology in Asia

Yaws has been either currently or previously reported to be endemic in 11 countries in Asia (Table 1). Of these countries, India was certified by WHO in 2016 as having interrupted transmission (see below), while Indonesia and Timor-Leste are considered to still be endemic for yaws. For the remaining eight countries, there is limited recent information on the current epidemiological status of yaws. It is likely that yaws has been eliminated in many of these countries through a combination of earlier elimination programs and improvements in the living conditions. Validation of the presumed elimination will be necessary in these countries as part of the WHO yaws eradication efforts.

Table 1 Countries in Asia where yaws is or was previously endemic

Country	Current status
WHO Southeast Asia region	
India	Interrupted transmission
Indonesia	Currently endemic
Myanmar	Previously endemic—current status unknown
Sri Lanka	Previously endemic—current status unknown
Thailand	Previously endemic—current status unknown
Timor-Leste	Currently endemic
WHO Western Pacific region	
Cambodia	Previously endemic—current status unknown
Lao People's Democratic Republic	Previously endemic—current status unknown
Malaysia	Previously endemic—current status unknown
Philippines	Currently endemic
Vietnam	Previously endemic—current status unknown

4.1 India

Yaws in India affected people living in tribal communities from hilly and inaccessible areas in the states of Madhya Pradesh, Maharashtra, Orissa, and Uttar Pradesh (WHO 2008). Between 1952 and 1964, about 200,000 individuals were treated using penicillin as part of the WHO and UNICEF yaws eradication efforts. It is believed this reduced the prevalence of yaws in affected communities from 14% to <0.1%. Cases of yaws subsequently rebounded in the previously endemic districts during the 1970s. The National Institute of Communicable Diseases conducted a number of activities during the 1980s, culminating in 1995 with the development of the Indian Yaws Elimination Programme. Following a successful pilot in Orissa, in 1999, the programme was expanded to 49 districts of all the 10 previously endemic states (Andhra Pradesh and Telangana, Assam, Chhattisgarh, Jharkhand, Gujarat, Madhya Pradesh, Maharashtra, Odisha, Tamil Nadu, and Uttar Pradesh) (WHO 2008). A health volunteer programme in the form of the Accredited Social Health Activist (ASHA) became a critical link between the community and the formal health system in improving access to health-related information.

The Indian Yaws Elimination Programme combined 6-monthly active case-finding surveys during which all cases and contacts were treated with penicillin and awareness-raising activities in endemic communities to promote health-seeking behavior for suspected cases of yaws. Following implementation of this strategy, the number of cases fell rapidly from 3571 in 1996 to 735 in 1997 and subsequently to 0 cases in 2004. Serological surveys conducted over the following period indicated an absence of ongoing transmission of yaws in previously endemic states, and the Ministry of Health declared elimination of yaws in 2006. WHO formally certified elimination of yaws in India in 2016.

There are many lessons for other countries in the region and worldwide to learn from the success of the Indian Yaws Elimination Programme. The programme was built on a platform of sustained political support, community mobilization, and a prolonged period of case finding. Similar structures will be vital to support elimination efforts in other yaws-endemic countries.

4.2 Indonesia and Timor-Leste

Indonesia has reported between 2000 and 7000 cases per year in the period 2008–2013, with the number of cases currently appearing to be decreasing. More than 98% of the current cases of yaws are found in the provinces of East Nusa Tenggara, Southeast Sulawesi, Papua, and Maluku (Capuano and Ozaki 2011). A prevalence survey in West Sumatra conducted in 1991 found a prevalence of yaws-like lesions of 0.3%, but no more recent population-based data is available.

Yaws had been reported from at least 6 of the 13 provinces of Timor-Leste with between 500 and 1000 clinical cases of yaws reported per year (Capuano and Ozaki 2011). In 2007, a cross-sectional convenience survey found a prevalence of yaws-like lesions of 0.4%.

There is a need for larger population-based prevalence surveys, supported by diagnostics, to help guide yaws elimination efforts in both Indonesia and Timor-Leste.

4.3 Philippines

A small number of cases of yaws have been reported in rural villages in the Philippines but data remain limited. There is need for large-scale surveys to better inform our understanding of the epidemiology and extent of the disease in the country.

5 Nonhuman Primates

Treponemal infections have been found throughout the nonhuman primate population of Africa in countries where yaws is currently, or has previously been, endemic (Knauf et al. 2013). Sequencing of nonhuman primate strains has demonstrated a high degree of sequence homology with human strains of *T. pallidum* subsp. *pertenue*. In experimental models, primate strains are capable of infecting humans, and human strains are capable of giving rise to symptomatic infection in primates, suggesting that zoonotic transmission may be possible. A recent small study has also demonstrated evidence of *T. pallidum* infection of nonhuman primate species in Asia (Klegarth et al. 2017). The possible epidemiological significance of these findings in Asia and worldwide remains an important research question.

6 Clinical Presentation and Differential Diagnosis

The clinical features of yaws have been classified into a primary, secondary, and tertiary stage. As in other human treponematoses, untreated infection may become latent at any time, with only serologic evidence of infection. Relapses can occur up to 5–10 years following initial infection (Mitjà et al. 2013).

The primary lesion ("mother yaw") appears at the site of initial infection. It is usually a localized papule, which may develop into a large papilloma 2–5 cm in diameter, or a solitary nontender ulcer with a red, moist base reminiscent of a raspberry (hence yaws is also referred to as "framboesia" in some parts of the world) (Fig. 2). Ulcerated areas often become crusted. Lesions of primary yaws are most frequently found on the legs and ankles (65–85% of cases) (Mitjà et al. 2011a, b, c) but can also occur on the buttocks, arms, hands, or in the face. In the absence of treatment, primary lesions usually heal after 3–6 months, regressing into a depigmented pitted scar with dark margins (Sehgal 1990). In a small proportion of patients (9–15%), the primary lesion is still present at the onset of the secondary stage.

Secondary lesions are the result of lymphatic and hematogenous dissemination of the bacteria and typically occur a few weeks to 2 years after the primary lesion.

Fig. 2 Yaws primary ulcer. Early-stage papilloma, round in shape with raised margins and reddish, friable bed. Courtesy of Oriol Mitjà

Fig. 3 Yaws secondary skin lesion. Scaly patches on the skin of a patient with secondary yaws. Courtesy of Oriol Mitjà

Polyarthralgia is probably the most common, albeit nonspecific, symptom of secondary yaws. Secondary skin lesions consist of multiple smaller excrescences, sometimes resembling the primary lesion ("daughter yaws") that may ulcerate. Multiple scaly patches or plaques with discoid or irregular shapes may also develop (Fig. 3). Other manifestations of secondary yaws include regional lymphadenopathy, palmar and plantar hyperkeratotic plaques (Gip 1989), and nocturnal bone pain due to osteoperiostitis of the proximal phalanges of the fingers (dactylitis) or long bones (forearm, tibia, or fibula) (Fig. 4) (Mitjà et al. 2011a, b, c). If left untreated, relapse of latent infection may occur at any time and may present with any of the manifestations of secondary yaws.

Tertiary yaws is now reported infrequently but was historically reported to occur in approximately 10% of untreated patients. It consists of late lesions that develop after 5 or more years of infection. This stage is characterized by gummatous lesions of the skin, bones, and overlying tissues. Massive necrotic tissue destruction can occur, followed by debilitating scarring.

Fig. 4 Yaws secondary periostitis. Radiograph of the forearms and hands showing dactylitis of the second digit of the right hand and periosteal reaction of the ulna and radius. Courtesy of Oriol Mitjà

Differential Diagnosis Yaws shares clinical features with a number of other conditions that are common in the tropics. The primary lesion of yaws may be mistaken for cutaneous leishmaniasis, tropical ulcer (a typically painful and malodorous ulcer caused by anaerobic fusobacteria and *Treponema vincentii*), or pyoderma. There is also epidemiological overlap in the distribution of yaws and Buruli ulcer in a number of countries, although the features of the two diseases allow clinical differentiation. The papulosquamous secondary lesions of yaws must be distinguished from common skin disorders such as psoriasis, dermatophytosis, and scabies, which are also extremely common in the settings where yaws is endemic.

An important recent finding has been the emergence of *Haemophilus ducreyi* as a common cause of chronic skin ulceration in yaws-endemic communities (Mitja et al. 2014). Lesions caused by *H. ducreyi* are extremely difficult to distinguish clinically from yaws lesions and may be found in patients who are both sero-positive and sero-negative for yaws (Marks et al. 2014a, b). *H. ducreyi* DNA has been found in isolation or alongside *T. p. pertenue* in yaws-like lesions. In a prospective cohort study in PNG during a yaws elimination campaign, polymerase chain reaction (PCR) on lesional exudate was performed to determine the causative organism. *H. ducreyi* was the most common pathogen, with *H. ducreyi* DNA found in 54 of 73 individuals (74%). This finding has added difficulty in diagnosing yaws on clinical grounds alone and highlights the need for improved access to diagnostic testing to support yaws eradication efforts.

H. ducreyi is sensitive to treatment with azithromycin, and there is evidence that MDA campaigns to control yaws may also be effective in reducing the community prevalence of skin lesions caused by *H. ducreyi* (Mitjà et al. 2015). Further work to delineate the epidemiology, clinical features, and treatment responsiveness of this emerging pathogen is urgently needed to better understand the role of *H. ducreyi* in chronic skin ulceration.

7 New Laboratory Tests for Yaws

In the absence of laboratory facilities, the diagnosis of yaws has traditionally been based upon a combination of both the patient's symptoms and signs and knowledge of the epidemiological context of human treponematoses. As noted above, recent findings that *H. ducreyi* may cause clinically similar lesions have highlighted the need for expanded access to diagnostic testing. In the laboratory, serological testing is the mainstay of yaws diagnosis, though direct PCR techniques have shown useful for the confirmation of infection. In recent years, a point-of-care rapid diagnostic test (RDT) kit has been assessed. The kit can potentially be used to support yaws surveillance and control programmes in remote communities where serological and PCR testing are limited (see below).

Differentiation of yaws and syphilis is currently limited to molecular methods that target genetic signatures thought to be specific for each subspecies. At present, these tests are only available at research laboratories, which limit their utility in the routine management of suspected yaws cases.

Serological Tests The serological tests used to diagnose yaws are identical to those used in the diagnosis of venereal syphilis (Menke et al. 1979). Testing traditionally involves the combination of a nonspecific, nontreponemal antibody test, followed by a more specific treponemal test for diagnostic confirmation. At present, there are no available serological assays that can distinguish between the different subspecies of *T. pallidum*, which can create diagnostic quandaries in settings where the two diseases are co-endemic.

Nontreponemal agglutination tests [rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL)] use an antigen of cardiolipin, cholesterol, and lecithin and detect antibodies against lipids in the cell surface of *T. pallidum*. These tests are positive in untreated patients and can also be used as a test of cure since they usually revert to negative after successful treatment. A fourfold decrease in titer following treatment is considered evidence of cure. The RPR can be read with the naked eye, whereas the VDRL requires a microscope. The nontreponemal tests may give rise to false-positive results in patients with other conditions, including malaria, leprosy, and rheumatological diseases (Garner and Backhouse 1972). They are often performed on serial serum dilutions to give a quantitative titer, defined as the highest dilution that yields a positive result.

Treponemal agglutination tests [*T. pallidum* hemagglutination assay (TPHA), *T. pallidum* particle agglutination assay (TPPA), and the fluorescent treponemal antibody absorption (FTA-Abs)] (Garner et al. 1972) are more specific than nontreponemal tests. However, these assays remain positive even after successful treatment and are therefore not recommended to evaluate the response to a therapy.

Point-of-Care RDT As yaws is serologically indistinguishable from syphilis, point-of-care RDTs originally developed for syphilis also support yaws diagnosis, although differentiation from syphilis remains an issue in countries where the diseases are co-endemic. A large number of rapid treponemal tests based on immunochromatographic strips are now available. These kits can be used with whole blood and can be reliably performed outside a laboratory setting with minimal training (Herring et al. 2006). Most of the RDTs for syphilis only contain a *Treponema*-specific antibody that cannot be used to distinguish between active (untreated) and past (treated) infections, limiting their value in the field. For serodiagnosis of active yaws infections, detection of antibodies to both nontreponemal and treponemal components is needed.

A Combined Point-of-Care Test The Dual Path Platform (DPP) Syphilis Screen and Confirm test (Chembio Diagnostic Systems; Medford, NY, USA) detects treponemal (T1) and nontreponemal (T2) antibodies simultaneously. The DPP was evaluated in the diagnosis of yaws in both PNG (Ayove et al. 2014) and the Solomon Islands (Marks et al. 2014a, b) in 2014.

In the evaluation conducted in remote communities of PNG, the test showed excellent performance in confirming the diagnosis of yaws in patients with suspected clinical lesions. When compared with TPHA, the DPP T1 test had a sensitivity of 88.4% and specificity of 95.2%. By comparison with the RPR test, the DPP T2 test had a sensitivity of 87.9% and specificity of 92.5%. In the evaluation conducted in the Solomon Islands, the DPP was used as a tool for community surveillance. The sensitivity of the test kit was lower than the value reported from PNG, but it should be noted that this probably mainly reflects the on average lower antibody titers found when screening exposed and asymptomatically infected individuals.

The key value of the DPP test resides in the nontreponemal T2 element, which provides rapid and accurate results for the field diagnosis of active untreated yaws infections based on only finger-prick blood. Increased use of the DPP RDT will allow improvements in the accuracy and validity of national yaws surveillance data and facilitate an improved understanding of the epidemiology of yaws worldwide.

Polymerase Chain Reaction PCR assays have been developed over the last two decades for detection of *T. p. pallidum* nucleic acids. These tests generally employ qualitative or quantitative PCR alone or PCR followed by amplicon detection with a labeled probe to increase the sensitivity and specificity of the assay. Although designed to diagnose syphilis infection, the analysis of the available *T. p. pallidum* and non-*T. p. pallidum* strain genomes confirmed that these methods could also be applied to detect but not differentiate nucleic acids from all other treponemal strains found in humans. Examples of molecular tests include the amplification of the tmpA (TP0768), the 4D [also known as tpf-1 (TP1038)], the bmp (TP1016), and the polA gene (TP0105).

In addition, PCR assays to distinguish nonvenereal *T. pallidum* subspecies have also been evaluated as *T. p. pertenue* and *T. p. endemicum* genetic signatures have been identified (Centurion-Lara et al. 1998; Cameron et al. 1999, 2000; Chi et al. 2015). Different assays exist, but all rely on the analysis of a combination of genetic regions including the tpr family of genes [e.g., tprC (TP0117), tprI (TP0620)], the tp0858 gene, sequencing of the intergenic region 19 (IGR19), and sequence variation in the arp gene (TP0433). Performing these molecular identification assays is limited to laboratories equipped with the appropriate equipment, resources, and trained personnel. An additional limitation of molecular diagnosis of treponematoses is that the sensitivity of DNA detection in a biological sample varies with the type of sample analyzed (e.g., lesion exudates versus blood samples) and, likely, the fluctuations in the bacterial burden in the host that characterize these multistage diseases.

A molecular test of pivotal importance for those involved in the diagnosis and treatment of human treponemal infections is represented by the assay to detect the point mutations in the 23S rRNA genes known to confer resistance to azithromycin (and macrolides in general), the antibiotic that WHO is planning to use in the new eradication campaign for yaws and endemic treponematoses (discussed in more detail below). Investments in laboratory capacity building will be required to support the roll out of assays for both diagnosis and drug-resistance monitoring to all yaws-endemic countries.

8 Antibiotics to Treat Patients with Yaws

Antibiotics with activity against *T. pallidum* include penicillin, azithromycin, erythromycin, doxycycline, and tetracycline. The efficacy of injectable benzathine benzylpenicillin and oral azithromycin is comparable for treatment of yaws, and the WHO favors use of either regimen (WHO 2012). Treatment with azithromycin avoids the need for injection and could enable yaws eradication through MDA programs. Pilot studies in Ghana, PNG, and Vanuatu have demonstrated the potential of this approach (Mitja 2015). Current recommendations are that the contacts of any confirmed case of yaws (e.g., household residents, friends, schoolmates, playmates) should be treated with the same regimen as the index case. How best to define the contacts of an index case and therefore who requires treatment is an important research question that yaws eradication efforts are facing.

Penicillin G Benzathine Long-acting penicillin (single intramuscular dose) has been the mainstay of yaws treatment for the past 60 years. Therapeutic levels of penicillin can be achieved by giving repeated doses of short-acting benzylpenicillin preparations (i.e., aqueous benzylpenicillin) or by a single intramuscular injection of slowly absorbed, repository benzylpenicillin preparations (i.e., benzathine benzylpenicillin or penicillin aluminum monostearate). The WHO-recommended regimen consists of 1.2 million units for adults and 0.6 million units for children (WHO Scientific Group 1982), the dosing being lower than for syphilis. However, there is no definite knowledge about the total dosage of penicillin required for the satisfactory treatment of nonvenereal treponemal diseases, and many clinical guidelines continue to recommend the higher dosage of 2.4 and 1.2 million units, respectively. Clinical and serological results of a randomized trial involving a cohort of 1200 adults with yaws in Haiti showed that 92% of adults treated with 1.2 million units of benzathine penicillin were cured compared with 94% of those receiving 2.4 million units (Rein 1949). No significant variation was noted when four different penicillin aluminum monostearate dosages were compared in Java (Li 1955).

Azithromycin The clinical efficacy of both oral azithromycin (30 mg/kg; maximum 2 g) and injectable benzathine benzylpenicillin is high and similar for the treatment of yaws. In a randomized trial of children in PNG, clinical and serological cure rates of children treated with azithromycin were 96% (Mitjà et al. 2012). Efficacy of azithromycin was 91% for patients with primary stage lesions, and 100% for patients with secondary stage disease, including polyarthralgia or bone pain and swelling. Similar findings were reported from a study involving 500 patients with confirmed primary yaws skin lesions in Ghana (Kwakye-Maclean et al. 2017). Clinical outcomes were similar for patients in all groups, and serologic response at 6 months was superior in the azithromycin group, confirming the results of the earlier publication in a different geographic region. A single 2 g dose of azithromycin is generally well tolerated; the most commonly observed adverse events in 10–15% of cases are related to the gastrointestinal tract, and these are all transient and short-lived.

Substituting a painful injection of penicillin with a single dose of an oral antibiotic represents a significant improvement, as no trained staff are needed to treat cases in remote areas, infection and anaphylactic shock control measures and other logistical problems and equipment needs linked to penicillin use are overcome, and therefore acceptability of treatment is likely to be improved. In 2018, a small number of cases of azithromycin resistant yaws were reported in PNG. Investment in surveillance and monitoring for drug resistance will be critical to support yaws eradication efforts (Mitjà et al. 2018).

Second-Line Agents Although a number of agents have been suggested to be effective based on evidence from either case series or their known effectiveness in the treatment of syphilis, there are no second-line agents for the treatment of yaws which have been shown to be effective in randomized control trials.

For patients over the age of 8 years who are allergic to drugs of choice, oral tetracycline (500 mg q6h) or doxycycline (100 mg q12h) for 15 days is considered the best substitute. This is based upon small series of yaws patients treated with tetracycline derivatives (aureomycin, terramycin, or oxytetracycline) in Africa, Haiti, and Jamaica. These studies, done some 40 years ago, demonstrated cure rates from 83% to 100%. Tetracyclines are not recommended for pregnant and breastfeeding women and for children under the age of 8 years because of their association with staining of developing teeth.

Oral erythromycin (8–10 mg/kg, q6h for 15 days) was used as an alternative for penicillin-allergic children under 8 years and pregnant women before the discovery of azithromycin. However, now, azithromycin is the preferred macrolide antibiotic for yaws because of the superior pharmacokinetic profile.

Oral penicillin V is rarely used due to inadequate levels in the blood, despite one report describing the successful clinical use of oral phenoxymethylpenicillin for 7–10 days (12.5 mg/kg q6h; maximum dose 300 mg q6h) given to children <14 years with active yaws lesions in rural Guyana (Scolnik et al. 2003). Regimens requiring the administration of multiple oral doses over a number of days raise, however, concerns with patient compliance.

Ceftriaxone, a broad-spectrum cephalosporin with a long half-life in serum (7 h), has demonstrated activity against *T. p. pallidum* in a rabbit model. The long half-life allows for daily dosing and has been used by some experts as an alternative to penicillin for the treatment of syphilis. However, clinical data for its use to treat yaws are lacking.

Treatment Failure Failure of an early-stage yaws lesion to heal within 4 weeks is considered evidence for treatment failure. Patients with clinical treatment failure should be treated with an alternative agent. Microbiologic studies may help to distinguish whether the non-healing lesion is due to an infection by another pathogen.

Serological treatment failure is defined as $\geq$ fourfold increase in the RPR titer, titer persistently $\geq$1:64, or $\leq$ fourfold decrease in titer over 12 months. Patients who do not have an appropriate decline in serological titer should be managed with another course of treatment. Most serologically defined treatment failures are thought to be caused by either reinfection following treatment or slow decline in nontreponemal test titers, rather than by a relapse or true antibiotic resistance. This again highlights the importance to ensure that all household and community contacts are treated as well, thus decreasing the risk of reinfection.

9 Mass Treatment for Yaws Elimination

Yaws is a potentially eradicable disease since the diagnosis and treatment are relatively straightforward and there is no significant animal reservoir. It was the first disease slated for eradication by WHO in 1948 (Rein 1949). However, despite a reduction of cases by 95% in the 1950s, yaws has not been eradicated. It is thought that a failure to adequately treat all latent cases of diseases and a lack of integration of yaws surveillance into primary health care systems were major contributors to the eventual resurgence in yaws cases.

In 2007, experts and delegates from endemic countries agreed on a renewed effort to assess the yaws burden and restart activities for disease control (WHO 2012) with an ultimate aim of yaws eradication. In 2012, WHO officially launched the road map for implementation of the programme to accelerate the work to overcome the global impact of neglected tropical diseases, including a new effort to eradicate yaws. This was ignited by the potential use of azithromycin to fight the disease. WHO set a target of 2020 for yaws eradication (WHO 2012).

The approach to eradication, called the "Morges strategy," is centered on community mass treatment with a single dose of oral azithromycin (30 mg/kg, maximum 2 g). Following an initial round of mass treatment, the strategy proposes undertaking surveys every 6 months to detect and treat remaining cases. The strategy defines the extent of the community flexibly; in the initial round of mass treatment, it covers the entire endemic region of a country, while subsequent case-finding activities may be carried out at the district or village level. Benzathine penicillin may be used as an alternative for individuals who cannot be treated with azithromycin or for mass treatment in places where azithromycin is not available.

The efficacy of the "Morges approach" was demonstrated in a study of mass treatment performed in rural villages on Lihir Island, PNG (Mitjà et al. 2015). Of 16,092 residents, 84% received mass treatment with single-dose azithromycin and were monitored. One year after mass treatment, the prevalence of active yaws decreased from 2.4% to 0.3% in the total population and from 7% to 0.6% in children 5–15 years of age. No evidence of macrolide resistance was observed.

Another pilot study was conducted in Ghana in a community that was geographically contiguous with neighboring areas where the disease is also endemic. The study reported a coverage of 96% and a reduction from 3% to 0.0% 1 year after the intervention. The Ghanaian study confirmed that provision of MDA of azithromycin was highly effective at reducing the community prevalence of both clinical and latent yaws even in areas adjoining other endemic communities (Kwayke C, personal communication).

In all the yaws pilot projects, a significant proportion of skin lesions clinically diagnosed as yaws were found not to be *T. p. pertenue*-PCR positive but rather associated either with detection of *H. ducreyi*- specific DNA sequences by PCR or caused by as yet unknown pathogens. Although isolates of *H. ducreyi* obtained from skin lesions from children are fully sensitive to azithromycin in vitro, it is clear that community mass treatment with azithromycin has less impact on lesions caused by this bacterium than those caused by *T. p. pertenue*.

The Morges strategy has several advantages over previous campaigns, including oral versus parenteral administration of the drug and mass treatment versus selective treatment of active cases which inevitably omits treatment of latent cases, which can relapse with infectious yaws lesions. The eradication of yaws will be declared when no new active cases are reported over 3 successive years, supported by evidence of no transmission among children younger than 5 years.

At present roll out of the Morges strategy has been limited to small pilot studies. Significant financial support will be required to enable endemic countries in Asia and elsewhere to adopt the strategy and achieve disease eradication.

10 Challenges for Yaws Eradication

There are a number of challenges facing the yaws eradication campaign. Although pilot data have demonstrated promising results from community mass treatment with azithromycin, the coverage and number of rounds of mass treatment that will be required to interrupt transmission and achieve yaws eradication in areas with different endemicity remain unknown.

There is incomplete epidemiological data on the geographic scope, distribution, and burden of the disease. Both Timor-Leste and Indonesia are considered endemic for yaws, but there is a lack of up-to-date epidemiological data from either country to support the implementation of the WHO eradication strategy. A number of countries in Asia also previously reported cases of yaws, including Cambodia, Lao People's Democratic Republic, and Vietnam, but recent surveillance data is lacking. Innovative approaches to disease mapping, combining mapping for yaws with other neglected tropical disease programmes, should be considered. In addition, the majority of the affected populations live in remote and difficult to reach communities, creating logistical barriers both to surveillance and treatment.

The potential for synergies between yaws and trachoma control programmes, both relying on azithromycin MDA, is an area of active research. In the Pacific there are regions where both trachoma and yaws are thought to co-exist, notably the Solomon Islands, Vanuatu, and possibly PNG.

The discovery that *H. ducreyi* is responsible for a substantial number of skin ulcers in yaws-endemic communities is also a cause for concern. The current WHO strategy is based around clinical case detection, but this approach may need to be revisited in the light of our increasing understanding of the complex and diverse causes of clinically similar lesions in yaws-affected communities. In particular it may become necessary to integrate molecular diagnostics into surveillance strategies.

Finally, integration of molecular techniques will be necessary to facilitate monitoring for the emergence of macrolide-resistant strains of *T. p. pertenue.* Surveillance for treatment failure and resistance to azithromycin is important because there is biological evidence that antibiotic pressure can select for resistant strains of venereal syphilis (Lukehart et al. 2004). Macrolide resistance in *T. pallidum* is associated with a single A-to-G mutation occurring at position 2058 or 2059 of the 23S ribosomal RNA gene (Chen et al. 2013). A real-time PCR assay for the detection of the above-mentioned mutations has been developed that would enable molecular surveillance for rapid identification of macrolide resistance in *T. p. pertenue* (Chen et al. 2013).

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Rabies in East and Southeast Asia: A Mirror of the Global Situation

Monique Léchenne, Tenzin Tenzin, Mary Elizabeth Miranda, and Jakob Zinsstag

Contents

Abstract Despite the availability of efficacious and safe vaccines for human and animal use, rabies takes tens of thousands of human lives annually worldwide. The vast majority of human rabies cases are due to exposure through a rabid dog and subsequent lack of access to post-exposure prophylaxis (PEP) in remote and poor communities around the globe. Therefore, low- and middle-income countries and rural settings are highly affected by this deadly zoonotic disease, while rabies is eliminated from the domestic reservoir in most of the economically strong countries

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and areas. Although rabies reservoirs in wildlife remain a danger almost all around the world, human cases due to exposure to sylvatic and bat rabies is marginal. Recently momentum, fuelled by the World Health Organization and partners, has been gaining to achieve global elimination of dog-mediated human rabies. Main objectives are increasing efficiency of surveillance, wide scale vaccination of dog population together with dog population management and worldwide coverage for affordable PEP. Advances on the agenda to this global goal vary from country to country. Whereas surveillance and intervention in animals and humans remain patchy and inefficient in some countries, others are focussing on interventions in humans. Those most advanced in the control of rabies have implemented surveillance and prevention measures in the animal reservoir, which is the most cost-effective approach. The South and Southeast Asian region mirrors the described global situation comprising the whole spectrum from rabies-free countries, to countries with only sylvatic rabies and finally the largest group of those with endemic dog rabies. Within the latter, distinctions are made between those that focus on prevention in humans and those with a One Health approach including intervention in animals. Some areas have even adopted an integrative community participation approach including educational programmes. The different sections of this chapter describe the detailed rabies situation in South and Southeast Asian countries grouped by epidemiological context and implemented prevention measures. It highlights the need for holistic control programmes coordinated across the whole region to achieve sustainable elimination of rabies.

Keywords Rabies elimination · Asia · Post-exposure prophylaxis · Rabies vaccination · Rabies surveillance

1 Introduction

The history of rabies is closely intertwined with the Asian region. One possible scenario for the evolution of rabies suggests the Indian sub-continent as the birth place for all dog-related rabies viruses about 700 years ago. From there, it putatively spread to Europe with emerging global trade and from there to Africa during the colonial era, again mediated by human movement (Bourhy et al. 2008; Troupin et al. 2016). This theory, however, can be disputed because a disease very similar to rabies was already described in ancient Greece (King 2004).

The first overseas Pasteur Institute was founded by Albert Calmette in Saigon, former French Indochina, today Vietnam, in 1891 (Hawgood 1999). Soon after, and exactly 10 years from the first administration of the newly invented rabies vaccine by Joseph Meister, the second Asian Pasteur Institute was established in 1895 by Alexandre Yersin in Nah Trang, Vietnam (Hawgood 2008). Both Calmette and Yersin must have administered the vaccine to numerous victims of rabid dogs during their stay in these former French colonies. The vaccine was far from being safe in those days, but the alternative was to take one's chances in the face of probable death. Louis Pasteur was confident in the final years of his life that the methods of modern science would one day eliminate rabies in domestic animals (Rosset 1985), and there was hope to overcome a disease most feared by humans since ancient times. But from his time till now, domestic dogs remain the most important source for transmission of rabies to humans.

Despite the fact that Pasteur's pioneer work translated over time into efficacious and safe vaccines, for both animals and humans, more than 59,000 people still die from rabies every year (Hampson et al. 2015). The disease affects mainly underprivileged communities in low- and middle-income countries, which have limited healthcare access (Meslin and Briggs 2013). The post-exposure prophylaxis (PEP) that should be administered after a bite from a rabies-suspect animal is usually too expensive or not available (Wilde et al. 2016). Also, many bite victims are not sufficiently informed about this crucial treatment and rely on ineffective traditional methods. Not all countries list rabies as a notifiable disease (Taylor et al. 2015), and even where rabies reporting is compulsory, inadequate surveillance is common in remote areas. Furthermore, diagnostic possibilities are limited, misdiagnosis is frequent, and people often die at home (Banyard et al. 2013; Taylor et al. 2017). All these factors lead to a continual state of neglect at every level of disease control: missing perception of the true burden worldwide, absent international and governmental commitment, and low public awareness (Bourhy et al. 2010; Banyard et al. 2013).

East and Southeast Asia are no exception in this vicious cycle of neglect. Asia carries the biggest continental burden associated with the disease, accounting for 59.6% of all worldwide human rabies deaths and more than 80% of the global monetary expenses (Anderson and Shwiff 2013; Hampson et al. 2015). The detailed picture for East and Southeast Asian countries is very heterogeneous and reflects the worldwide situation. Timor Leste and Singapore, similar to New Zealand and Australia, have been historically free of canine rabies (Tenzin and Ward 2012). Other countries have successfully eliminated the disease and implemented strict control measures to prevent reintroductions, for instance, Japan and Taiwan which mirror several European countries such as the United Kingdom and Switzerland (Rupprecht et al. 2004; Takahashi-Omoe et al. 2008; Liu 2013). Another continued prevention effort even for rabies-free countries is the sensitization of travellers to rabies-endemic areas to prevent infection in the destination country and subsequent importation of a human case. In South Korea, rabies remains prevalent in racoon dog populations near the border with North Korea, and challenges for control are similar to the ones in the United States of America, where rabies research is driven by prevention of wildlife rabies (Rupprecht et al. 2004; Cheong et al. 2014).

Among the regions that still face endemic rabies in domestic animals and, consequently, considerable numbers of human rabies fatalities, different priorities between the known measures to prevent animal-to-human transmission can be observed. Cambodia, Lao People's Democratic Republic, and Myanmar are the countries farthest from elimination. They are in a similar situation as many countries on the African continent where accessibility to PEP, adequate surveillance and sustainable dog rabies control plans are yet to be established nationally

(Nel 2013). In many countries like the People's Republic of China and Vietnam, the focus is on PEP administration to bite victims. This is reflected in the large amount of funds allocated to human vaccination compared to other prevention measures. Over 80% of the expenses are allocated to PEP, with much less to dog vaccination (15%) and diagnostics (0.03%) (Shwiff et al. 2013). In consequence, the number of reported PEP administrations exceeds the number of confirmed animal rabies cases a 1000-fold in many countries (Ly et al. 2009; Tenzin et al. 2012; Song et al. 2014), while dog rabies control remains insufficient to interrupt transmission. Despite dog vaccination campaigns being undertaken in many areas, they remain patchy and often do not reach a sufficient coverage or have the impact evaluated (Davlin and Vonville 2012). Unsustainable culling interventions to control stray dog populations are utilized less often, being replaced by the Animal Birth Control Approach (ABC) (Reece 2007). Shifting resources from the human to the diagnostic and animal sector could effectively reduce overall costs from rabies and is the only way to fight the disease at its source. PEP, dog vaccination and population control jointly implemented and balanced in a One Health framework (Box 1) can successfully lead to the elimination of dog rabies, as demonstrated in Latin America (Vigilato et al. 2013). This approach has also been proven to be cost-effective in several different settings (Lavan et al. 2017; Mindekem et al. 2017; Tenzin et al. 2012; Fitzpatrick et al. 2014).

Disease management tools to formulate and implement One Health strategies for successful rabies control are available, and momentum has increased in recent years towards integrated rabies control targeting elimination. The Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and the World Health Organization (WHO) have established a tripartite coordination mechanism to harmonize technical cooperation at the regional and country level for prevention and control of zoonoses, including rabies (OIE, WHO, FAO 2010). The member states of the Association for Southeast Asian Nations (ASEAN) and the South Asian Association for Regional Cooperation (SAARC) have also identified rabies as a priority public health problem and have set a target of elimination of canine-mediated rabies by 2020 (OIE 2013; WHO 2012). The goal of this road map is to control and eliminate dog-mediated rabies and protect and maintain rabies-free areas in South and Southeast Asia. The objective is to strengthen the regional and national coordination as well as technical and institutional capacities to manage dog rabies elimination programmes.

While One Health is becoming established at national levels, many communities have not yet been integrated in the One Health framework. By implementing community-based activities, these populations will also have access to other public health and veterinary services. Local examples of community-integrated One Health rabies elimination are the programmes in Bohol, Philippines, and in Bali, Indonesia (Lapiz et al. 2012; Townsend et al. 2013). We will introduce these programmes in this chapter as well as highlight all other stages of rabies control in East and Southeast Asia which, when combined, mirror the global rabies situation.

In December 2015, the WHO and partners have defined a goal for global elimination of dog-mediated human rabies by 2030 (WHO 2015). The Asian 2020 agenda will therefore have a cutting edge role for the worldwide 2030 agenda.

Box 1
The One Health framework is an integrated approach of cooperation between human and animal health using the synergistic potential. Thereby public and animal health create an added value by establishing close communication, coordination, and action plans for joint surveillance and control of dog rabies (Zinsstag et al. 2015).

2 Challenging Neglect: Lack of Surveillance and Effective Control

Rabies, a zoonosis with a companion animal reservoir, often falls between the gap of public health interventions for human diseases and animal disease control programmes, which target the economically important livestock sector. In addition, it predominantly affects poor people in remote areas who have limited access to healthcare, with the result that most human and animal rabies cases go unnoticed, so the burden of the disease is significantly underestimated. Taylor et al. (2015) illustrate the lack of surveillance, particularly in Asia and Africa. In Asia, five countries do not list rabies as a notifiable disease: India, Pakistan, Indonesia, Myanmar, and Bangladesh. Even in countries where rabies is notifiable, the surveillance system is ineffective or non-existent nationwide, as, for example, in Cambodia and Malaysia (Taylor et al. 2015). This also reflects the situation in Africa, where rabies is notifiable in about half of the countries, but only a handful of these countries have an effective surveillance system in place. The identified shortcomings include lack of case definition, specific legislation, and dissemination of data. These facts highlight the need for enforcement of legislation and guidance on national levels, including training of laboratory and health personnel. In Vietnam, a survey among human and animal health workers showed that knowledge of rabies reservoirs, wound management and guidance on PEP was unsatisfactory (Nguyen et al. 2016). Despite the fact that rabies is feared by many and generally known to be deadly, the knowledge about prevention measures which should be taken following an animal bite or control measures for disease prevention in dogs has been shown to be limited in several local knowledge, attitude, and practice (KAP) surveys, e.g. in Cambodia (Lunney et al. 2012); Bohol, Philippines (Davlin et al. 2014); and India (Ichhpujani et al. 2006). This lack of awareness, together with misconceptions, leads to delayed or inadequate health-seeking behaviour after a dog bite. Too often, traditional health practices are preferred or even the only option available (Sudarshan et al. 2006).

The problems facing rabies control are symptomatic of the general problem of access to healthcare for marginalized, poor communities in predominantly rural settings (Obrist et al. 2007). The goal of any rabies control programme must, therefore, aim to strengthen the overall access to healthcare rather than focus solely on elimination of rabies. Interventions vertically targeting rabies should also be transferable to a horizontal approach within the local health system and conducted with local support to guarantee sustainability (Ollila 2005). As a zoonotic disease requiring close collaboration between human and animal health services for effective control, rabies has great potential to build up One Health thinking and partnerships. One Health is an answer to the neglect described above, from which other zoonosis would also benefit; however, only a few countries have taken specific action, even though this approach has been discussed often. In theory, cooperation between the Ministry of Health (MoH) and the Ministry of Agriculture (MoA) and joint technical working groups for the prevention and control of zoonoses is in place for avian influenza, rabies, anthrax, and leptospirosis in several Asian countries, including Vietnam, Indonesia, Cambodia and the Philippines. The need for practical implementation persists, particularly in Cambodia, Lao People's Democratic Republic and Myanmar. Although joint regional disease control activities are already ongoing in the larger Mekong River area, rabies has not yet been prioritized. The rabies control programmes of the Mekong countries are striving to keep up with the pace of the regional efforts for disease elimination, although no comprehensive national rabies programmes have yet been established.

Control measures are currently being implemented in Lao People's Democratic Republic with increased animal rabies surveillance and dog vaccination (Douangngeun et al. 2017). However, both coverage of surveillance and vaccination are not yet nationwide.

The disease is thought to be widespread in Cambodia, though surveillance is limited and PEP is available only at the Pasteur Institute in Phnom Penh and Angkor Hospital for Children in Siem Reap (Ly et al. 2009). Consequently, access to PEP and compliance to the treatment schedules are reduced in remote villages and provinces (Ly et al. 2009; Tarantola et al. 2017). In 2012, 27,500 rabies vaccine doses (0.5 mL) and 591 equine rabies immunoglobulin (eRIG) doses were used to provide intradermal PEP to 20,610 persons at Rabies Prevention Center at Pasteur Institute of Cambodia following animal bites. Another 53,400 rabies vaccine doses and 200 eRIG doses were used outside Pasteur Institute in Phnom Penh, Cambodia. The wholesale cost of full rabies PEP was estimated at 50–100% of a Cambodian farmer's monthly wage (Tarantola et al. 2015). This illustrates that local populations and travellers cannot access to adequate and timely PEP due to high costs and low access to RIG.

On the basis of incidence numbers in the Phnom Penh area, Ly et al. (2009) modelled the overall human rabies incidence for the whole country to be 5.8 per 100,000 people. This figure is 15 times higher than the official national reports and one of the highest rates in Asia. Reasons are the striking lack of nationwide access to PEP and a high dog ownership rate, with a dog to human ratio of 1:3 particularly in rural areas. A prospective community-based survey on dog bite incidence documented an extremely high number of dog attacks in a Cambodian rural context, with approximately 5 dog bites per 100 person-years (95% confidence interval (CI), 3.6–6.8).

Over 80% of the wounds were WHO Category III, and nearly 60% of victims with severe dog bites are in children aged below 17 years. The most at-risk age group are children aged 1–5 years, with an overall attack incidence of around 12 per 100 person-year (95% CI 5.4–22.5) (Ponsich et al. 2016).

For Myanmar, the MoH estimates over 600,000 dog bites and 1000 human deaths due to rabies per year (Gongal and Wright 2011). These numbers remain putative as rabies is not notifiable, and no national programme for prevention and control has been implemented (AREB 2011).

When vaccinations are undertaken, they often fail to reach the set target of 70% coverage necessary to interrupt disease transmission (Coleman and Dye 1996). There is a strong need for interventional research in Asian countries, including dog demography and best vaccination strategy to achieve sufficient coverage. Average dog to human ratios in Asia are similar to those in Europe and are estimated to be 1:7.5 in urban and 1:14 in rural areas (Knobel et al. 2005). Therefore, it is not the overall dog number but rather the characteristics of the dog populations, which make them well suited as rabies reservoirs (Kitala et al. 2001; Morters et al. 2013). On one hand, the poor health status of many dogs in poverty-affected settings leads to a high population turnover, making it difficult to maintain stable vaccination coverage. On the other hand, dog owners with little means do not feed their animals regularly, and thus, these animals tend to scavenge food in the streets leading to high contact rates. Cultural and religious backgrounds have also been identified as influencing dog populations and accessibility of dogs to vaccination. In Muslim communities, dog to human ratios are very low, but the animals are less likely to be brought to fixed vaccination posts because dogs are viewed as unclean. In contrast, in Hindu and Buddhist communities, dogs are more likely to be straying or community owned and are fed in the streets, but access for parenteral vaccination might be more adequate (Bogel and Joshi 1990; Totton et al. 2010; Massei et al. 2017).

Such factors require thorough investigation and must be taken into account in planning interventions in dogs, but until the problem of rabies in dogs is addressed, even countries with good access to PEP will continue to invest considerable resources into prevention of human rabies fatalities.

3 Control Without Elimination: The Focus on PEP

The People's Republic of China administers the highest numbers of vaccine doses worldwide (12–15 million/year) at an estimated cost of US$1 billion. Nonetheless, from 1960 to 2014, the People's Republic of China reported 120,913 human rabies cases with an annual average of 2198, including 23,932 (19.8%) cases being reported from 2004 to 2014 (Yin et al. 2013; Song et al. 2014; Zhou et al. 2016). More than 50% of these cases occurred in rural areas of the southern part of the People's Republic of China (e.g. Guizhou, Guangxi, Hunan, Guangdong, and Yunnan) (Si et al. 2008; Wu et al. 2009; Tu 2011; Guo et al. 2013; Zhou et al. 2016). In 2005, a national rabies surveillance programme was introduced to investigate the situation in terms of vaccination coverage, PEP treatment, and geographic and social composition. Although the number of human rabies cases decreased by 65% from 2004 to 2014, the geographic distribution of cases has paradoxically expanded from 162 prefectures to 200 prefectures and from southern to the central and northern provinces of the People's Republic of China (Guo et al. 2013; Zhou et al. 2016). The failure to receive PEP is attributed to the fiscal decentralization and privatization of the healthcare system, leading to lower access to healthcare services for many poor and rural families. Also the replacement of concentrated vaccines with more expensive purified cell culture vaccines contributed to a lower accessibility to PEP among marginalized communities (Si et al. 2008; Hu et al. 2009). Another cause for the re-emergence of rabies in the People's Republic of China is believed to be the high dog population growth and low vaccination coverage (Zhang et al. 2011). In addition, the development of the transportation network increased the movement of people with their dogs, particularly in rural areas and also across borders (Zhang et al. 2011).

As with access to PEP, dog vaccination coverage also shows a striking disparity between wealthy and rural provinces. Over 90% of dogs are vaccinated against rabies in Shanghai, as opposed to less than 10% in neglected rural areas. In southern part of the People's Republic of China, half of all cities register vaccination rates below 70% (Song et al. 2009).

After the re-emergence of rabies in the People's Republic of China, thousands of dogs were killed in an effort to control the rabies epidemic (Associated Press 2006; Chinadaily 2009; WeirdAsiaNews 2009). Mass elimination of dogs is no longer recommended to reduce populations and control rabies because it increases population turnover, while decreasing herd immunity, and the public opposition to dog removal can lead to the failure of rabies control programmes (Morters et al. 2013). Recently, the approach has shifted focus towards dog registration and compulsory vaccination (Xinhuanet 2009; Tu 2011; Wang et al. 2011). The interdisciplinary Rabies Advisory and Technical Board is meeting twice a year to move forward rabies prevention and control in the People's Republic of China. Rabies research from Chinese scientists has also increased in the last decade, but Yin et al. (2013) identified a lack of studies regarding intervention, policies, and surveillance compared to laboratory-based publications. Such a gap is also observed on the international level (Zinsstag 2013).

A similar picture to the People's Republic of China can be observed in Vietnam. Most rabies cases are reported in rural areas where about 80% of the overall 7 million dogs are found (WHO 1996; Hanh 2011). The majority of rabies cases occur in the northern mountainous provinces which do not have adequate access to information and health services. In 1987, a vaccine card and rabies vaccination register were introduced in all provinces/cities in the northern part of Vietnam to measure vaccine usage and record the number of deaths from rabies. During 1992 and 1995, Vietnam recorded 414 human rabies deaths, and 345,000 people received PEP per year (WHO 1996).

Rabies prevention and control programmes included both mass dog vaccination and intensified human PEP. With the increased rate of PEP, reaching as high as 790 per 100,000 population in 2004, the rabies death rate in humans has decreased drastically from 0.71 per 100,000 population in 1994 to 0.1 per 100,000 population in 2011 (Xuyen 2008; Hien 2009; OIE 2013). However, in 2007 a temporal peak of 131 deaths (12 per 100,000 population) was observed (Thanhniennews 2010; Hanh 2011). The slack management by the provincial health authorities, public ignorance of the threat, and large number of free-range breeding of dogs with poor vaccination coverage are believed to be reasons for the temporal rise in rabies cases (Thanhniennews 2010). Overall, expanded access to rabies biologics throughout the country has achieved reduction of canine-mediated human rabies deaths by 82%, from 505 cases in 1994 to only 91 cases in 2016 (Nguyen 2017).

Besides dog bites, butchering of dogs and cats for human consumption has been identified to account for 1.6% of human rabies deaths (Hanh 2011). Currently the country spends at least US$66 million on PEP against rabies annually due to the high commitment of the Vietnamese government for rabies prevention and control programmes (Nguyen 2017). Vietnam has 936 rabies vaccination posts in the whole country for rabies consultation and prophylaxis, and about 400,000 and 32,000 people received rabies vaccine and equine rabies immunoglobulin (eRIG) each year, respectively (Hanh 2011; Nguyen 2017). Nationwide rabies vaccination campaigns were conducted for dogs and cats, but the coverage was low, at approximately 35−50% (Hien 2009; Hanh 2011). In light of this fundamental problem, the Ministry of Agriculture and Rural Development (MARD) endorsed a US$7.5 million project to implement the national programme on rabies control and elimination within the period 2011–2015. In the same year, the MoH also allocated US$15 million for communication, training, workshops, vaccination, and monitoring of rabies control and prevention activities (OIE 2013). Recently, the MoH and MARD jointly signed the Circular 16, dated May 27, 2013, providing guidelines for coordinated prevention and control of key zoonotic diseases including rabies through a One Health approach (Xinhuanet 2013). In December 2012, Vietnam also received 200,000 doses of animal rabies vaccine from the OIE Rabies Regional Vaccine Bank funded by the European Union (HPED programme) (OIE 2013). These coordinated approaches represent a big step towards eliminating rabies by 2020.

4 The Advantage of Dog Rabies Vaccination

People's Republic of China and Vietnam have in recent years made an important turnaround and are thriving with their policy decisions pointed in the right direction. Vaccination of dogs is the best way to eliminate rabies in the animal reservoir and to prevent infection in humans (Bogel and Meslin 1990; Cleaveland et al. 2006; Zinsstag et al. 2017). There are many field examples in which vaccination coverage ranging from 60% to 87% resulted in significant decrease in incidence of dog rabies and human exposures. The oldest examples date as far back as the 1950s, such as in Memphis, Tennessee in the USA (Steele and Tierkel 1949). With the success in Latin America, an entire continent previously endemic for dog rabies has nearly succeeded in elimination (Vigilato et al. 2013). In Asia, the Phetchabun province in Thailand (Kamoltham et al. 2003), the cities of Jaipur and Jodhpur in India (Reece and Chawla 2006) and the Bohol and Ilocos Norte provinces in the Philippines (Lapiz et al. 2012; Valenzuela et al. 2017) have, among others, set a successful example. The recent incursion of rabies in Bali in Indonesia was first targeted with mass elimination of dogs, which failed to control the disease, and later a mass dog vaccination campaign was initiated. Following the dog vaccination campaign, the incidence of rabies declined significantly in both dogs and humans (Putra et al. 2013).

Regions and countries that are free from canine rabies enjoy long-term cost savings by discontinuing animal and human rabies prevention and control programmes (Fishbein et al. 1991; Cleaveland et al. 2006; Mindekem et al. 2017; Shwiff et al. 2013). The average cost of dog vaccination varies in a range of different rural and urban settings depending on the accessibility of dogs and the level of community participation during the campaigns. Direct costs per dog vaccinated were estimated to be on average US$1.30 in Asia and Africa (Bogel and Meslin 1990; Knobel et al. 2005). In contrast, the cost of human PEP is very high, with an average estimated cost (both direct and indirect) of US$40–55 per person (Bogel and Meslin 1990; Knobel et al. 2005). In addition, the human diploid cell vaccine (HDCV) or equine rabies immunoglobulin (eRIG) would cost about US$110 or US$25 per person, respectively (Knobel et al. 2005). In Africa and Asia, the current estimated annual cost of rabies is above US$500 million, excluding the cost of years of life lost (YLL) (Shwiff et al. 2013).

Detailed field studies confirm broadscale economic evaluations and the concept of advantageous One Health interventions in Asia and Africa (Sambo et al. 2013). A study using the Bali rabies control programme data indicates that a comprehensive high dog vaccination coverage campaign would likely result in elimination, saving 550 human lives and US$15 million in human rabies prophylaxis costs over the next 10 years (Townsend et al. 2013). Similarly, a cost estimation of rabies control in Flores Island, Indonesia, also indicated that providing PEP for humans is costly for government and cannot provide a permanent solution to prevent rabies (Wera et al. 2013). Dog mass vaccination, in contrast, is promising with regard to its potential for elimination of rabies. Yet, because dog populations in low- and middle-income countries are highly dynamic and not closely supervised, vaccination intervention must go hand in hand with dog population control and promotion of responsible dog ownership in order to become sustainable. The island of Bohol and the Phetchabun Province in Thailand have implemented control programmes with a holistic systems approach, which integrates many different aspects of rabies control, and their interdependencies serve as an example for other control projects. Another good example of a control programme is Ilocos Norte in the Philippines, where dog vaccination has led to the elimination of animal and human rabies (Valenzuela et al. 2017). PEP numbers meanwhile have increased due to higher awareness triggered by the programme. Therefore even higher cost-efficiency can be achieved through a close collaboration between the animal and human health sector to distinguish real rabies exposures in need of PEP from unsuspicious bite cases (Mindekem et al. 2017).

5 Community Empowerment: Integrated One Health Elimination Programmes

In 2007, the National Rabies Law was enacted in the Philippines, and a national rabies elimination strategy was developed to implement local rabies elimination activities and to establish and maintain rabies-free zones. The 'Bohol model' initiated in the same year has proven that, with the leadership and commitment of the local government and adequate funding and approaches, human rabies will decrease and eventually disappear. In addition to dog rabies vaccination, education of children, improvement of surveillance, and empowerment of the local community have been included in the programme. This was done through motivating communities to establish their own rabies control programme. Giving communities the key role ensured their full awareness on the rabies situation and prevention measures as well as the participation of the public during the intervention. The community-based approach fostered empowerment and integrated the One Health approach to expand ownership of the programme by involving other sectors beyond animal and human health staff. The education sector, with teachers and students, led the integration of rabies prevention and responsible pet ownership into the primary and secondary school curriculum. Police and customs officials, women's cooperatives, religious and other civil society leaders, rural development agencies, and business groups were also partners. The establishment of rabies-free zones contributed to safe tourism activities bringing more income to the communities. With committed, but limited, local resources, the local government was keen to sustain the programmes and advance towards dog rabies elimination.

A similar programme was implemented in Phetchabun Province, Thailand, to prevent human deaths from rabies. This 5-year rabies control project was initiated in March 1993, with the specific aim of eliminating human rabies throughout the province by 2000. The programme had several strategies including increasing the accessibility and coverage of PEP in humans exposed to animals potentially or confirmed as rabid; increasing awareness of rabies through advocacy in provincial schools, television programmes and newspapers; reducing canine rabies by monitoring the dog population and implementing vaccination and sterilization programmes; increasing cooperation between the MoH, MoA, and the Ministry of Education (MoE) on a provincial level; and finally assessing the impact of the programme through intensified follow-up of patients exposed to both suspected and laboratory-confirmed rabid animals. Increased use of PEP in humans was achieved by expanding the use of the intradermal Thai Red Cross regimen that reduces the cost of PEP by at least 60% (Hampson et al. 2011). By the third year of the programme, no further human rabies death was reported, which proved the success of the chosen approach (Kamoltham et al. 2003).

Many people, and especially disadvantaged groups, lack knowledge about rabies and may engage in high-risk practices, e.g. having stray dogs in their villages, eating dog meat and preferring traditional healers for bite wound treatment. Therefore, a risk communication campaign adapted for a given local background and a well-designed information, education, and communication (IEC) plan is important for any such integrated approach. A KAP study undertaken after the implementation of the Bohol control programme indicates that the Bohol population today have a good knowledge of the danger of rabies and understand the importance of responsible pet ownership, registration and vaccination of dogs (Davlin et al. 2014). Investigations into the dog vaccination coverage on the household level showed that over 60% of dogs had been vaccinated by the programme although the vaccination and registration were not free of charge (Davlin et al. 2013).

The majority of dog bite victims are children (Knobel et al. 2005; Sriaroon et al. 2006; Hampson et al. 2015). Education targeting children has proven to be very successful and sustainable in pilot areas in Thailand, the Philippines, Indonesia, and India (Auplish et al. 2016). Finally, most local government units have limited funds to conduct the needed community-based activities, and they have limited number of staff to carry out field activities. Therefore many local programmes in a limited geographic area depend on non-governmental organisations (NGO) or private funding.

6 On Constant Watch: Dog Rabies-Free Countries and Areas

There are only very few historically rabies-free countries in East and Southeast Asia. Brunei and Timor-Leste have not reported any occurrence of animal rabies and have specific surveillance, vaccination, quarantine, and precautions instituted at borders. Other countries have successfully eliminated rabies over the past 70 years and stayed rabies-free for over 2 years. These countries are therefore eligible to qualify for disease freedom in accordance with the provisions of the OIE Terrestrial Animal Health Code (OIE 2017). After the development of the first rabies vaccine in 1885 by Louis Pasteur, Japan initiated the first urban dog vaccination programme in the world in 1921 and eliminated rabies in 1954 through vaccinating dogs and reducing the urban dog population (Tamashiro et al. 2007; Takahashi-Omoe et al. 2008). Also in the 1950s, several other Asian countries and areas carried out rabies elimination programmes through mass dog vaccination and killing of dogs, with canine rabies being eliminated from Malaysia in 1954 (Wells 1954; WHO 1987), Taiwan in 1961 (Weng et al. 2010; Liu 2013) and Singapore in 1953 (OIE 2013). Of those cited countries, Malaysia is one of the best examples of the risk of reintroduction. Sarawak province of Malaysia that borders rabies-endemic Indonesia did not detect any human rabies cases from 1999 onward, but rabies was reintroduced in July 2017 resulting in human deaths (Desmond 2017). South Korea eliminated rabies in domestic dogs in 1985 and stayed rabies-free until 1993, when cases re-emerged in the form of wildlife rabies (Kim et al. 2006; Joo et al. 2011). The cycle seems to be maintained in raccoon dogs with spillovers to cattle and domestic dogs (Kim et al. 2005). The problem is believed to have emerged from the demilitarized zone bordering North Korea, and efforts are undertaken to understand transmission dynamics and to control the disease via oral vaccination of wildlife and dog vaccination (Kim et al. 2006; Oem et al. 2013). The problem of rabies in wildlife also exists in the People's Republic of China where rabies in ferret badgers has become an increasing concern (Yu et al. 2012). This shows that after elimination of rabies in domestic dogs, persistent wildlife rabies cycles will remain as a risk for reintroduction of the disease into dog populations and for direct transmission from wildlife to humans. Direct transmission from wild animals to humans becomes more apparent after elimination of rabies in domestic animals, as observed for skunks and raccoons in the USA (Rupprecht et al. 1995) and vampire bats in Latin America (Schneider et al. 2009). However, wildlife rabies is currently contributing very little to the overall burden of rabies on public health in Asia and worldwide.

Rabies-free countries need a strict quarantine and regulatory system for the import of dogs and cats from rabies-endemic countries. Some are also carrying out risk assessment for reintroduction of rabies through the importation of dogs and cats from overseas and making policy changes to reduce the risk (Wilsmore et al. 2006; Tamashiro et al. 2007; McQuiston et al. 2008; Kamakawa et al. 2009; Weng et al. 2010; Sparkes et al. 2014; Brookes et al. 2017). For example, with widespread rabies outbreaks and dissemination in Indonesia, the risk of rabies entering northern Australia is real (Sparkes et al. 2014; Hudson et al. 2017). Despite stringent regulations, there have been a number of well-documented cases of importation of rabid dogs recorded in rabies-free countries through failure of border controls or ignorance of importation rules (Fooks et al. 2008; Gautret et al. 2011b). Low awareness by travellers, illegal pet trade, and animal rescue organizations are potential sources for reintroduction.

In addition to imported dog rabies, 60 imported human rabies cases were recorded globally from 1990 to 2012 (Carrara et al. 2013). Such imported cases are also reported on an annual basis by the European Centre for Disease Prevention and Control (ECDC 2016). All these imported cases, both in dogs and in humans, involve financial cost. Illegal or accidental importation of rabid dogs into rabies-free countries has led in the past to resource-intensive, costly public health responses (McQuiston et al. 2008; Gautret et al. 2011a; Johnson et al. 2011; Mailles et al. 2011). Costs involved with the importation of rabid dogs include expenses for diagnostic tests, as well as disease investigation, prevention, and control, posing unnecessary strain on health systems. For example, the importation of rabid dogs from Morocco to France in 2004 and 2008 resulted in a high demand of PEP in humans (Lardon et al. 2010; Gautret et al. 2011a).

The emergence and spread of rabies from endemic foci to rabies-free areas within the same country pose an even higher risk than importation. A notable example is the rabies incursion into Bali Island in Indonesia during 2008. More than US$17 million has been spent to eliminate rabies in Bali, but the disease has not been completely eliminated (Putra et al. 2013). The re-emergence of rabies in previously free areas has also been reported in Bhutan (Tenzin et al. 2011, 2017). Nationwide intensive mass dog vaccination, as well as administration of PEP to dog bite victims, continues although only sporadic cases of rabies are reported in the South and East of the country where there are shared borders with India. Consequently, high costs for rabies control are observed in Bhutan, and the trend of PEP and the cost of the treatment are escalating each year (Tenzin et al. 2012).

The impact on global trade due to endemic rabies in Asia is unknown. Although companion animals are increasingly being imported for a thriving commercial pet trade by industrialized countries in Europe and the USA, there is scant data on the number of dogs imported from Asian countries. Nonetheless, illegal trading between Asian countries of thousands of live dogs for meat consumption is believed to be occurring and has become a concern. A ban on these movements would be beneficial for animal welfare and rabies control. The international trading of dog and cat fur from Asian countries to the USA and many European countries existed until the mid-2000s but has subsequently been banned on animal welfare grounds.

The proposed elimination of dog-mediated rabies by the year 2020 in Asia and worldwide in 2030 will also lead to financial savings in rabies-free countries. Not only would the costs of surveillance, prevention and outbreak measures due to rabies importation or re-emergence be alleviated, but the costs for prophylactic pre-exposure vaccination of veterinarians and travellers would also be avoided. Not surprisingly, the study on rabies re-incursion risk into Australia mentioned above found that the most cost-effective measure for the prevention of such incidents is investment into vaccination of Indonesia's dog population (Hudson et al. 2017). As long as dog rabies-endemic areas exist, everyone remains at risk of rabies infection in our globalized world, and awareness will have to be maintained in all countries.

7 Rabies in a Globalized World: Rabies Awareness and Risk in Travellers

Every year, millions of people travel around the world for various purposes, putting themselves at risk of being exposed to rabid animals in rabies-endemic countries. Southeast Asia is one of the most popular tourist destinations for travellers worldwide, and rabies is a recurring public health concern in this area (Wilde et al. 2005; Piyaphanee et al. 2012). A similar concern exists in North Africa for the many European visitors (Gautret et al. 2011b). Several studies have been conducted to assess the risk of rabies exposure among travellers, as well as their treatment-seeking behaviour, attitudes, and practices related to rabies. Although potential rabies exposure of travellers by bites or licking is fairly common, only a low percentage (<20%) received pre-exposure vaccination before travel (Phanuphak et al. 1993; Pandey et al. 2002; Piyaphanee et al. 2010). Advice from travel medicine guides recommends pre-exposure vaccination only when people stay in an endemic area for longer periods of time. However, a study from Thailand indicated that more than half (54%) of all exposures occurred in the first 10 days after arrival in Southeast Asia (Piyaphanee et al. 2010).

A survey conducted among foreign travellers in Thailand indicated that the risk of being bitten was 1.11 per 100 travellers per month and the risk of being licked was 3.12 per 100 travellers per month. Among those who were bitten, only 37% went to a hospital to get PEP. While almost 60% sought health information before their trip, only about one in 10 participants had completed rabies pre-exposure prophylaxis (Piyaphanee et al. 2012). The above findings corroborate with imported human rabies cases in the world (Carrara et al. 2013).

There is no clear data to indicate that endemic rabies in Asia has any negative effect on the tourism industry since millions of people travel to Asian countries each year. For example, People's Republic of China and Thailand were ranked 4th and 10th, respectively, among the top 10 international tourism destinations in 2013. People's Republic of China recorded 55.7 million international arrivals in 2012 and 2013, whereas Thailand recorded 22.4 million international arrivals in 2012 and increased to 26.5 million arrivals in 2013. The tourism industry accounts for billions of dollars in these countries (UNWTO 2014). For the whole East Asia region (northern and southern part), the international arrivals increased from 47.6 million people in 1990 to 220 million in 2013, demonstrating a significantly increasing trend of international arrivals (UNWTO 2014) apparently unaffected by the rabies-endemic state. Bali Island, for example, reported a major rabies outbreak in 2008 and continued to report rabies cases in both humans and animals until the mass dog vaccination programme described earlier controlled the outbreak and significantly reduced rabies incidence (Putra et al. 2013). Although there were reported incidences of dog bites among travellers in Bali during this time, it has not deterred the travellers nor affected the tourism industry. On the contrary, numbers of international arrivals in Bali have steadily increased from 1.96 million people in 2008 to 3.27 million in 2013 (BGTO 2013). These data indicate that neither endemic rabies nor ongoing rabies outbreaks affected the tourism industry in Asia.

A study to examine the characteristics of rabies PEP in returned travellers from France, Australia, and New Zealand who were victims of an animal-related injury in Africa, Southeast Asia, or the Pacific region highlighted important deficiencies in rabies PEP for travellers in rabies-endemic countries, with the majority not receiving adequate PEP or experiencing substantial delay before treatment (Gautret et al. 2008). The rabies risk perception among the travellers was shown to be largely lacking. A most recent survey among adolescent travellers departing from Athens, Greece, to Africa and Asia observed that this age group is particularly unaware of the overall health risks to which they are potentially exposed during such travels (Maltezou et al. 2017). Travel-associated rabies risk awareness needs to be improved, particularly regarding the prevention of animal bites, post-bite measures, and the urgency for obtaining PEP (Hamer and Connor 2004; Toovey et al. 2004; Wilder-Smith et al. 2004; Altmann et al. 2009). This is due to the general public from rabies-free countries having little knowledge about rabies, even when living in proximity to an endemic country. For instance, a study among tour leaders in Taiwan showed that they had a positive attitude towards rabies vaccination but a relatively low level of knowledge about rabies regarding clinical manifestations, rabies-endemic areas, prevention, and management (Huang et al. 2014).

As a sad consequence of the lack of awareness and inadequate use of pretravel immunization and access to PEP, cases do occur where travellers are bitten by rabid dogs in rabies-endemic countries and later diagnosed with rabies after returning home (Carrara et al. 2013). Among them, people travelling for tourism, business, or expatriates from high-income countries accounted for 57% of the cases, while migrants originating from low-income countries accounted for 43% of cases. The vast majority (85%) of the cases resulted from exposure to rabid dogs and were due to failure to seek PEP or inadequate treatment (Gautret et al. 2011b; Malerczyk et al. 2011; Carrara et al. 2013). This reinforces the point that travellers should be adequately counselled about animal-associated injuries and rabies risk when visiting rabies-infected countries.

8 The Way Forward to Rabies Elimination by 2020

Rabies is one of the few communicable diseases which can possibly be eliminated using the currently available tools for veterinary and public health interventions. Still, more than a billion people in Asia are at potential risk of contracting rabies. While the burden of rabies is primarily on human health, the disease control has to target the animal source. Cost-effectiveness studies of rabies control have demonstrated that dog rabies vaccination is more economical and ethical than the intensified use of PEP in humans alone. The OIE has stated that just 10% of the costs currently used to treat people bitten by potentially rabid dogs would be sufficient to eradicate dog rabies worldwide and thereby prevent almost all human rabies cases (Vallat 2011).

Asian nations have set a regional goal to control and eliminate dog-mediated rabies by 2020 and protect and maintain existing and future rabies-free areas. With the objective to strengthen regional and national coordination as well as the technical and institutional capacities to manage dog rabies elimination programmes, a regional road map is being developed that aims to integrate country level rabies elimination efforts. There are many challenges that need to be addressed to reach elimination in Asia and worldwide. More work is needed to improve diagnosis and increase the coverage of laboratory-based surveillance to break the cycle of neglect. Especially in rural areas, rabies awareness, access to timely PEP, sufficient dog vaccination coverage, and effective implementation of dog population control have yet to be established. Priority has to be given to physical, financial, and human resource to build more capacity. There is also the constant need to assess the epidemiologic situation, considering the ongoing rabies control activities. There are many possible risk factors that may further amplify and disseminate the disease in the at-risk areas.

South–South collaboration should be encouraged by twinning countries with successful local programmes currently undertaking community-based action against rabies. Such programmes use a highly successful bottom-up approach that entails collaboration across various sectors—animal and human health, education, trade, local media, community-based NGOs, and local government units at provincial, commune, and village levels. The partnerships established from avian influenza experience could be extended to work on rabies using the One Health approach. These partnerships will encourage an exchange of best practices and joint training.

With a comprehensive and integrated approach, it is expected that dog rabies will be eliminated and there will be eventual decline and disappearance of human rabies cases. Countries that are still endemic for dog rabies, as well as those that are rabies-free, will gain from elimination, and the resilience of communities in confronting the threat of other zoonotic diseases will be strengthened.

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Coinfection with Helminths and HIV-1 in East Asia

Katarina Stete, Xiao-Nong Zhou, Li-Guang Tian, and Matthias C. Mueller

Contents

Abstract As geographic distributions of human immunodeficiency virus-1 (HIV-1) and helminth infections largely overlap in many regions of the world, including the East Asian region, HIV-1/helminth coinfection is a common finding. Both HIV-1 and helminth infections mutually interact on several levels, especially on the level of immunomodulation, which has potential effects on the risk of acquisition and the clinical course of the involved pathogens. In this chapter, we present the epidemiology of HIV-1/helminth coinfection in East Asia and summarize the current knowledge on mutual interaction and its effect on epidemiology, clinical course, and treatment of the respective pathogen.

Keywords HIV-1 · Helminth infection · Coinfection · East Asia

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1 Introduction

The term coinfection refers to a concomitant infection with two or more pathogens in the same host. Different pathogens in the same host may interact in multifaceted ways, which may affect the epidemiology, course, and treatment of the associated diseases. In contrast, opportunistic infections are caused by pathogens that may produce invasive infections only under the precondition of a weakened immune system, e.g. acquired immune deficiency syndrome (AIDS) as a result of an advanced human immunodeficiency virus-1 (HIV-1) infection. Most AIDS patients die from a variety of opportunistic coinfections, including viruses (herpes viruses, JC virus, etc.), bacteria (*Mycobacteria*, *Bartonella*, etc.), fungi (*Cryptococcus* spp., *Histoplasma capsulatum*, *Penicillium marneffei*, *Pneumocystis jirovecii*, etc.), and parasites (*Toxoplasma gondii*, etc.) (Domingues and Waldman 2014).

HIV-1 coinfections with the hepatitis B and C viruses, *Mycobacterium tuberculosis*, and other opportunistic pathogens have been and continue to be the focus of international research efforts, whereas HIV-1/parasite coinfection received less attention. Reports originate mostly from Asia and Africa and mainly concern coinfections with *Plasmodium falciparum*, *Leishmania* spp., and intestinal parasites (*Cryptosporidium*, *Microsporidia*, *Cyclospora*, Entamoeba histolytica and Giardia intestinalis) (Tian et al. 2009). Even though there has been increasing interest in coinfection with HIV-1 and helminths during the past years, this research domain remains neglected.

Helminth infections affect more than a billion individuals, and more than 35 million persons are infected with HIV-1 globally. Both infections disproportionally concern people in low- and middle-income countries (LMICs), also in the Eastern Asian region, where especially in the Chinese provinces of Yunnan and Sichuan and in Southeast Asia, the burden of both diseases is high (Hotez and Ehrenberg 2010). Here, concomitant infections are common, and prevalence of helminth infection may reach above 20% in HIV-1-infected individuals.

Both HIV-1 and helminth infection have significant effects on multiple aspects of the host's immune system and may induce an inadequate immunological reaction to concomitant infections. Therefore, concerns have been raised that HIV-1 infection may increase the susceptibility to helminth infections and vice versa, negatively influencing their natural course and response to treatment.

In the following, we will cover the epidemiology of helminth/HIV-1 coinfections in East Asia and give an overview of HIV-1/helminth interaction on immunological and clinical level.

2 Epidemiology of Helminthiases in East Asia

Helminths are the most common infectious agents of humans in LMICs with over one billion people infected with one or more helminth species. Usually helminth infections are of chronic nature due to persistence of the parasite over years and frequent reinfections in endemic areas (Hotez et al. 2008). All helminth infections have in common that their prevalence is closely linked to poor sanitation and hygiene and therefore to poverty and a lack of education (Hotez and Ehrenberg 2010). National control programmes for different helminth infections have been implemented in many countries with variable success. In the People's Democratic Republic of China, for example, overall helminth infection rates have dropped from 55% to 21% from 1990 to 2006. However, infection rates remain at high levels in the western part of the People's Republic of China, especially in rural areas (Coordinating Office of the National Survey on the Important Human Parasitic Diseases 2005). This region remains the hot spot for helminth infections in the East Asian region, as helminth infection rates in other East Asian countries, such as Japan, South Korea, and Taiwan, have remained at relatively lower levels (Kim et al. 2009; Brooker et al. 2006).

2.1 Important Helminth Infections in East Asia

Soil-transmitted helminths (STHs: *Ascaris lumbricoides, Trichuris trichiura, and hookworm*) are the most common human pathogenic helminths worldwide (Lustigman et al. 2012). They are widely endemic in Southeast Asia and the People's Republic of China, especially in the southwestern provinces (Hotez and Ehrenberg 2010). In the People's Republic of China, it was estimated that around 129 million people were infected with STHs in 2005 (Coordinating Office of the National Survey on the Important Human Parasitic Diseases 2005).

Strongyloides stercoralis is endemic in several countries of East Asia (Schär et al. 2013). It has been estimated that worldwide, 30–100 million people are infected (Olsen et al. 2009). However, this number might be much higher as the infection is difficult to diagnose with current standard diagnostic methods (Steinmann et al. 2007). Exact prevalence data from eastern Asia is scarce, but a country-wide prevalence of as high as 14% for the People's Republic of China and 18.7% for Japan has been suggested (Schär et al. 2013).

Schistosoma japonicum, causing intestinal schistosomiasis, represents *Schistosoma* spp. in East Asia, where it is present in the People's Republic of China along the Yangtze River (Zhou et al. 2010). Its distribution is closely linked to water sites, which are habitat to the intermediate host snails. Due to successful control programmes, the number of people infected with *S. japonicum* in the People's Republic of China decreased dramatically in the last decades from 11.6 million in the mid-1950s to below 300,000 in 2011 (Yang et al. 2014).

Most cases of food-borne trematodiasis worldwide are found in the Southeastern and Eastern Asian region. The most important food-borne trematodes in this area are the liver flukes (*Clonorchis sinensis* and *Opisthorchis viverrini*) and lung flukes (*Paragonimus* spp.). These helminths are all transmitted via raw or undercooked freshwater fish, other aquatic products or water plants and lead to chronic inflammation of the liver, biliary tract, or lung tissue (Keiser and Utzinger 2009).

The global distribution of *C. sinensis* is restricted to this region, with an estimated 35 million people infected. The majority of cases (15 million) are found in the People's Republic of China, but the infection is also endemic in the Republic of Korea, Taiwan, and Vietnam (Lun et al. 2005). Global distribution of *O. viverrini* is limited to Southeast Asia, with an estimated ten million people infected, of which eight million are found in Thailand and two million in the Lao People's Democratic Republic (Keiser and Utzinger 2009). Fascioliasis and paragonimiasis are found both in Asia and on other continents. Global burden estimates for *Paragonimus* are 20 million and for fascioliasis 4–17 million infected individuals worldwide (Keiser and Utzinger 2009).

Lymphatic filariasis, leading to the clinical picture of elephantiasis, is no longer endemic in East Asia, especially due to successful control programmes, such as in Japan and the People's Republic of China (Yang et al. 2014). However, in several countries of Southeast Asia, the disease is still widely endemic with approximately 15 million people infected, representing a quarter of the global burden of lymphatic filariasis (Sudomo et al. 2010).

Echinococcosis is present in most countries of Eastern Asia. The vast majority of cases are caused by *Echinococcus granulosus*. However, it is estimated that the People's Republic of China contributes to 90% of the global burden of alveolar echinococcosis due to infections with *E. multilocularis* (World Health Organization et al. 2013; Torgerson et al. 2010). In the People's Republic of China, new cases of echinococcosis have been increasing continuously since 2004 (Zheng et al. 2013). During the 2006 national survey, 380,000 people in the People's Republic of China where infected with *Echinococcus* (Coordinating Office of the National Survey on the Important Human Parasitic Diseases 2005) with 90% of infections caused by *E. granulosus* and 10% by *E. multilocularis* (Yang et al. 2014).

Cysticercosis, caused by the pork tapeworm *Taenia solium*, occurs in areas with inadequate sanitation and pork meat management. The exact prevalence in East Asia is unknown. In the People's Republic of China, the estimated number of cases of cysticercosis is currently three to six million (World Health Organization et al. 2013).

3 Epidemiology of HIV-1/AIDS in East Asia

Since the first HIV-1/AIDS patients were reported in the USA in 1981, the virus rapidly spread all over the world. Currently, HIV-1 is present in 210 countries, and around 75 million people have become infected with HIV-1, and about 35 million have died of AIDS worldwide. Thus HIV-1/AIDS has become one of the greatest pandemics in modern times with devastating socio-economic and demographic consequences (UNAIDS 2013; Piot and Quinn 2013). According to UNAIDS estimates, there were 35.3 million people worldwide living with HIV-1 infection in 2012, of whom 880,000 resided in East Asia (the People's Republic of China, Taiwan, North Korea, South Korea, and Japan). All countries, except for North

Korea, had reported HIV-1 and AIDS cases, with the People's Republic of China being the major contributor (Suguimoto et al. 2014).

Though the national estimated prevalence of HIV-1 infection remains low at 0.037% (501,000/1367.82 million), the People's Republic of China is the most affected country in East Asia in terms of absolute numbers due to its big population (UNAIDS 2015a). After the detection of the first case of HIV-1/AIDS in 1985, the epidemic rapidly spread among injection drug users (IDUs) and female sex workers from rural regions in Yunnan province, an opium producing area, along major drug trafficking routes throughout the country (Suguimoto et al. 2014). In the twenty-first century, the pattern of the endemic is changing, and especially homosexual HIV-1 transmission in urban areas is becoming increasingly important; thus, HIV-1 prevalence among men

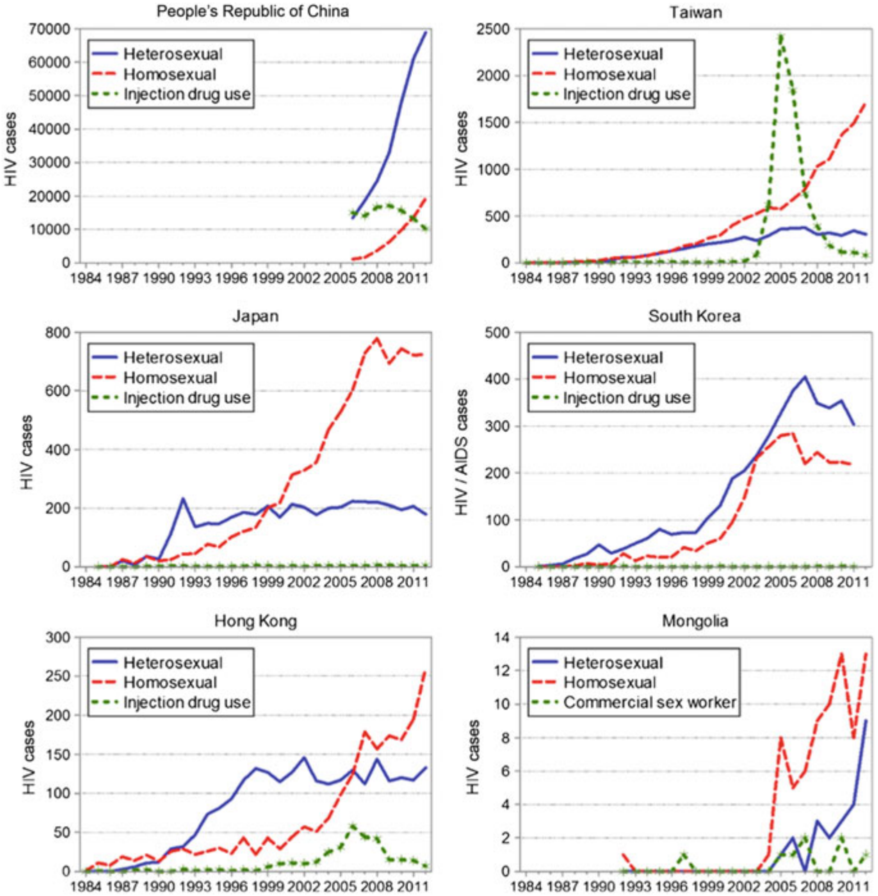

Fig. 1 Change in the trend of the annual number of HIV cases by main routes of transmission in the People's Republic of China, Taiwan, Japan, South Korea, Hong Kong, and Mongolia (1984–2012; People's Republic of China 2006–2012) (Reprinted by permission from Springer Nature: Springer, Current HIV/AIDS Reports, Changing patterns of HIV epidemic in 30 years in East Asia, Suguimoto et al. 2014)

having sex with men (MSM) is already higher than in IDUs and female sex workers in most of the provinces and reaches up to 10% in the southwestern part of the People's Republic of China, which remains the epicenter of the Chinese HIV-1/AIDS epidemic (Zhang et al. 2013).

Figure 1 shows temporal trends in the annual number of HIV cases. In Japan, South Korea, Taiwan, and Hong Kong, the prevalence of HIV-1 in the general population remains very low (e.g. in Japan 0.018% and in South Korea 0.014%) (Report to UNAIDS—HIV/AIDS Trends in Japan 2015; UNAIDS 2015b). In these countries, the HIV-1/AIDS epidemic is largely driven by MSM. In Japan the male-to-female ratio ranges between 16:1 and 12:1, and in Taiwan it is 30:1. In Japan and Taiwan, 74% and 84% of HIV-1-infections are attributed to homosexual transmission (Suguimoto et al. 2014; Centers of Disease Control, R.O.C. (Taiwan), Statistics of HIV 2015; Centers for Disease Control, R.O.C. (Taiwan)—Annual Report 2015). In South Korea, 92% of HIV-1 infections were diagnosed in men in the period between 1985 and 2011 (UNAIDS 2015b). In all these countries, the incidence of new HIV-1 infections is increasing. For example, in Japan, the number of newly reported HIV-1 infection in MSM increased steeply from 314 to 724 per year from 2001 to 2012, resulting in a prevalence of up to 6% among MSM in the large cities of the country (Report to UNAIDS—HIV/AIDS Trends in Japan 2015), and in Hong Kong, the number of cases is steadily increasing from about 400 in 2009 to 651 mainly male (84%) cases in 2014 (Prepared by Special Preventive Programme: FACTSHEET on HIV/AIDS Situation in Hong Kong 2014).

4 Epidemiology of HIV-1/Helminth Coinfection in East Asia

The geographic distributions of HIV-1/AIDS and helminth infections considerably overlap in sub-Saharan Africa, South America, and Asia. In East Asia, the Chinese provinces of Guizhou, Guanxi, Sichuan, and Yunnan are of special concern, as they represent the regions with the highest burden of both HIV-1 and helminth infections in East Asia. This corresponds to the mostly rural and less developed areas in the People's Republic of China (Tian et al. 2012). In Yunnan province, which in 2014 was the province with the highest HIV-1 prevalence in the People's Republic of China, the helminth overall infection rate was as high as 22% in the last national survey (Coordinating Office of the National Survey on the Important Human Parasitic Diseases 2005). However, exact numbers of HIV-1/helminth coinfections in Asia are not available. Few studies have investigated the prevalence of helminth infection among HIV-1 patients and showed corresponding prevalence rates compared with non-HIV-1-patients (with the exception of lymphatic filariasis and *S. stercoralis*, which have been reported more frequently in HIV-1 infected patients) (Tian et al. 2012; Wiwanitkit 2001; Paboriboune et al. 2014).

5 Interaction of HIV-1 and Helminths in Coinfected Patients

Because of the largely overlapping geographic distribution of the HIV-1/AIDS epidemic and helminth infections, elevated HIV-1 transmission rates in sub-Saharan Africa compared with more industrialized countries, and a supposed harmful mutual interference on an immunological level, helminth infections have been postulated since the 1990s to affect the risk of acquiring and the course of HIV-1 infection (Lawn 2004; Borkow and Bentwich 2004; Bentwich et al. 1995).

5.1 Evidence for Interaction of HIV-1 and Helminths in Coinfected Patients Based on Immunological Findings

This chapter summarizes how helminth-induced immunological changes, including strong T-helper 2 (Th2) bias, chronic immune activation, and immune suppression, may affect the viral capacity of transmission and replication and lead to a faster disease progression of HIV-1 infection.

A pronounced type 2 immune response is the hallmark of a helminth infection and other large eukaryotic pathogens. A Th2 immune response is mediated by Th2 cells, secreting corresponding interleukins (IL-4, IL-5, IL-10, and IL-13), and characterized by the proliferation of B cells and immunoglobulin E (IgE) as well as eosinophil production (Brown et al. 2004). A Th1 immune response, in contrast, includes the secretion of interferon-γ (IFN-y) and interleukin (IL)–2 by Th1 lymphocytes, promoting the activation of macrophages and dendritic cells and thereby enhancing the ability to kill intracellular pathogens, which is essential for the control of viral infections (Brown et al. 2004). These two immune responses cross-regulate each other: cytokines produced by the Th1 subset suppress the secretion and/or the activity of cytokines of the Th2 subset and vice versa (Borkow and Bentwich 2004). Helminth-induced pressure towards a Th2-type immune response is so potent that bystander antigens become a target (Kullberg et al. 1992). It has been shown in humans and in animal models that an aberrant Th2 cell response to pathogens that are controlled by IFN-y and a Th1 cell response can result in progressive infection (Bretscher 2014). In HIV-1 infection, the Th1 cell response is associated with low viremia, slow disease progression, and better survival (Bretscher 2014; Clerici and Shearer 1993; Li et al. 2012). On the other hand, a switch to a Th2-induced cytokine profile may be related to progression to AIDS (Bretscher 2014; Clerici and Shearer 1993; Li et al. 2012). However, this point is still being debated (Zanussi et al. 1996). On the basis of this mechanism, helminth-induced Th2 immune response may affect the course of HIV-1 infection.

Chronic immune activation characterizes both helminth and HIV-1 infection, and levels of immune activation are higher in individuals coinfected with HIV-1 and helminths than in those with HIV-1 mono-infection (Mkhize-Kwitshana et al. 2011).

In HIV-1 infection, progression is marked by a continuous rise of the viral load accompanied by a progressive depletion of the total helper CD4$^+$ T-lymphocytes with a subsequent fatal immunodeficiency. It is widely accepted that during the acute phase of HIV-1 infection, the massive loss of CCR5$^+$ CD4$^+$ memory T cells located predominately in the mucosal surfaces of the intestinal, respiratory, and reproductive tract occurs in the first few weeks of infection due to the direct cytolytic effect of HIV-1. On the other hand, systemic chronic immune activation, which is considered a hallmark of the asymptomatic phase of infection, is the driving force of the progressive CD4$^+$ T-cell depletion over the years following initial infection (Borkow and Bentwich 2004; Douek et al. 2003; Sauce et al. 2011). High levels of immune activation in HIV-1-infected individuals without antiretroviral therapy (ART) are associated with increased levels of plasma viral load and accelerated disease progression (Lawn et al. 2001). High viral load is a major risk factor for sexual transmission and mother-to-child transmission of HIV-1. It is therefore conceivable that helminth-induced excess immune activation results in an increased risk of sexual and vertical HIV-1 transmission as well as in an accelerated disease progression (Lawn et al. 2001; Fang et al. 1995; Quinn et al. 2000).

Additionally, helminths and their excretory-secretory molecules manipulate the regulatory network of the innate and the adaptive immune system and reduce the ability of the host to generate a potent and protective immune response (Borkow and Bentwich 2004; Shapira-Nahor et al. 1998; Wammes et al. 2014; Schmiedel et al. 2015). In particular FOXP3$^+$ regulatory T (Treg) cells, which exert their function among others by the secretion of IL-10 and TGF-β, may be involved in the downregulation of both Th1 and Th2 cell responses (Schmiedel et al. 2015). The responsiveness is diminished to antigens from the infecting parasite but also to bystander antigen, to routine vaccinations, and even to allogenic tissue transplants (Maizels and Yazdanbakhsh 2003; Greene et al. 1983). While in helminth infection the modulation of the immune system serves to enhance the survival of the parasite and to reduce acute morbidity of the host due to immunopathologic complications, a downregulation of the Th1 immune response may be associated with an increased susceptibility to HIV-1 infection and diminished ability to control HIV-1 infection. However, Tregs interact with the immune system on several levels, which makes the impact of helminth-induced Treg expansion on HIV-1-related outcomes unpredictable (Chevalier and Weiss 2013). A study on HIV-1-exposed seronegative individuals in Kenya suggests that high Treg cell frequencies may protect from HIV-1 infection by reducing levels of immune activation and rendering CD4$^+$ T cells less susceptible to HIV-1 infection (Card et al. 2009).

It has been shown that deworming of helminth-infected patients results in a normalization of immunological parameters related to immune activation, Th2 immune response, and Treg-induced T-cell hypo-responsiveness (Borkow and Bentwich 2004; Schmiedel et al. 2015).

5.2 Evidence for Interaction of HIV-1 and Helminths in Coinfected Patients Based on Epidemiological Findings

With regard to the effect of helminthiases on the risk for HIV-1 transmission, the most consistent epidemiological evidence is available for female urogenital schistosomiasis (FUS) in sub-Saharan Africa (Downs et al. 2011, 2012). FUS results from the disposition of eggs of *S. haematobium* in the interconnected vascular network of the pelvic region and is characterized by a number of genital disorders, including pain, spontaneous and contact bleeding, vesicovaginal fistula, and infertility. FUS develops in 33–75% of women infected with *S. haematobium* and is associated with a three- to fourfold increased risk of HIV-1 infection (Downs et al. 2011; Kjetland et al. 2006; WHO 2009), which has been attributed not only to damage of the mucosal epithelial barrier but also to an increase of mucosal HIV-1 target cell populations (Kleppa et al. 2014). Gastrointestinal schistosomiasis, which is mostly prevalent in Asia, targets primarily the rectum and the distal colon, where migrating eggs harm the integrity of the mucosa. Therefore gastrointestinal schistosomiasis may represent a risk factor for HIV-1 transmission especially in individuals practicing active and passive anal sexual intercourse in analogy to other sexual-transmitted diseases and FUS. So far, no study analyzed the impact of gastrointestinal schistosomiasis on the risk of HIV-1 transmission in exposed target groups as MSM (Downs et al. 2011; Kjetland et al. 2006; WHO 2009; Craib et al. 1995). However, data from Tanzania suggest an association between gastrointestinal schistosomiasis and HIV infection even in women (Downs et al. 2012).

In primates, infection with *S. mansoni* leads to increased susceptibility for simian HIV (SHIV) virus without increasing parenteral susceptibility, which suggests higher mucosal susceptibility to HIV-1 also in gastrointestinal schistosomiasis (Chenine et al. 2008; Siddappa et al. 2011). However, other studies did not show an association of schistosomiasis or other helminths and HIV prevalence in epidemiological surveys (Nielsen et al. 2006; Sanya et al. 2015).

5.2.1 Impact of Helminth Infection on the Risk of HIV-1 Infection

Remarkable results have been reported from studies investigating the risk for HIV-1 infection in patients with lymphatic filariasis. An increased susceptibility to HIV-1 infection of peripheral blood mononuclear cells in vitro has been described in patients with filarial infections in the past (Gopinath et al. 2000). A recently published report raised the additional concern on the risk of HIV-1 transmission in the context of lymphatic filariasis. This prospective cohort study from Tanzania showed a significantly increased risk for HIV infection in patients with lymphatic filariasis (Kroidl et al. 2016). Even though lymphatic filariasis is no longer endemic in East Asia, these results have important implications for further research, also regarding other helminth infections.

Besides horizontal HIV-1 transmission, concerns have been raised regarding an increased risk of vertical HIV-1 transmission in coinfected mothers. Helminths' intravascularly secreted molecules can cross the placenta and induce immunological changes in the fetus similar to those observed in adults (Malhotra et al. 1997). By such an alteration of the fetal defense, the parental helminth infection may increase the risk for mother-to-child transmission (PMTCT) of HIV-1, which may occur in utero, peri-, and post-partum (by breast feeding). A retrospective study suggests an elevated risk for PMTCT by showing a positive association between an active helminth infection of the mother with high Th2-type cytokine response in the cord blood cells and the risk of HIV-1 infection of the fetus (Gallagher et al. 2005), whereas a randomized controlled trial did not find a benefit of deworming during pregnancy for vertical transmission of HIV-1 (Webb et al. 2011).

5.2.2 Impact of Helminth Infection on the Course of HIV-1 Infection

On the basis of the aforementioned alterations of the immune system, helminths may theoretically promote HIV-1 disease progression. Early, smaller studies suggested a faster disease progression in HIV-1-infected individuals living in sub-Saharan Africa and other developing countries compared with populations in the western hemisphere (Morgan et al. 1997; Deschamps et al. 2000; Hira et al. 2003). These discrepancies were attributed to differences in the virulence of the pathogen and disparities in access to healthcare but also to higher levels of immune activation generally seen in African subjects due to high prevalence of chronic coinfections (Bentwich et al. 1995; Lawn 2004), though a more recent study of nearly 2000 men working in South African gold mines with known date of seroconversion did find similar survival patterns compared with western populations (Glynn et al. 2007).

A large cross-sectional study enrolling more than 1500 HIV-1-seropositive individuals in Kenya found significantly higher $CD4^+$ T-cell counts in HIV-1 patients with helminth coinfection compared with HIV-1 mono-infected patients (Walson et al. 2010), which was confirmed by another trial in Uganda (Brown et al. 2004; Elliott et al. 2003). One of these trials additionally found similar viral loads and a similar CD4 cell decline over 12 months in co- and mono-infected individuals (Brown et al. 2004). A more recent study in a South African helminth-HIV-1 coinfected population classified the participants into four helminth infection phenotypes, according to the presence of eggs in the stool and to IgE concentration in the serum. High levels of immune activation and viral load and low CD4 cell counts could be demonstrated in individuals with Th2 bias as indicated by high egg count and IgE response, whereas patients with high egg counts and low IgE responses displayed low viral loads and higher CD4 cell counts (Mkhize-Kwitshana et al. 2011). This study demonstrates that individuals do not react in a uniform manner to parasite infections. Indeed only 38% of HIV-1-infected patients with a proven *A. lumbricoides* infection had elevated levels of *Ascaris*-specific IgE as a surrogate marker for Th2 immune response.

Several studies have explored the effect of anthelminthic treatment on the natural course of HIV-1 infection in helminth coinfected individuals and are summarized in two recent systematic reviews. The first review concluded that five of six included studies showed a statistically significant decrease in viral load after anthelminthic treatment (Modjarrad and Vermund 2010). The second systematic review presented meta-analyses separately by helminth species: a nonsignificant trend towards lower plasma viral load after treatment of *S. mansoni* coinfections was reported, but no effects in the case of other worm species (Sangaré et al. 2011). A recently published Cochrane review including 8 trials that enrolled 1612 participants concluded that on the basis of low-quality evidence, treating confirmed helminth coinfections may have small, short-term favourable effects on markers of HIV-1 disease progression (Means et al. 2016).

Nearly all studies addressing the issue of the effect of helminthiasis on HIV infection were limited to antiretroviral therapy (ART)-naïve patients. Only few studies so far have investigated the response to ART in individuals coinfected with HIV-1. Efraim et al. (2013) showed that in coinfected patients, the odds for immunologic treatment failure was four times higher and that CD4$^+$ T-cell count increases were significantly lower compared to HIV-seropositive patients without schistosomiasis (Efraim et al. 2013). Interestingly, Muok et al. (2013) observed that increase of CD4 counts 1 month after initiation of ART was significantly higher in HIV-1-infected patients with intestinal schistosomiasis than in non-coinfected patients (Muok et al. 2013). In the era of massive roll out of ART in resource-limited settings with high rates of helminth-HIV-1 coinfection, research on the effect of helminth coinfection on response to ART should get more attention by the scientific community and funding institutions.

5.2.3 Impact of HIV-1 Infection on the Risk for Helminth Infections

The impaired cellular immunity in HIV-1-infected patients makes them more susceptible for several intestinal parasitic infections, including *Cryptosporidium*, *Isospora belli*, and *Microsporidia* (Wiwanitkit 2001). This raises the question whether the risk of acquiring intestinal and extraintestinal helminth infections might be higher in HIV-1-infected individuals living in endemic regions.

Few studies have compared the prevalence of helminth infections between HIV-1-infected and HIV-1-uninfected individuals. During a large survey in the People's Republic of China, no difference in prevalence of helminth infections between these two groups was found (Tian et al. 2012). Equally, a large study in Tanzania did not find a significant difference in *S. mansoni* infection prevalence and infection intensity between HIV-1-infected and HIV-1-uninfected individuals (Mazigo et al. 2014). Another survey in Brazil did not find a difference in the prevalence for STH or schistosomiasis, while reporting on a higher prevalence for *S. stercoralis* in HIV-1-infected patients (Feitosa et al. 2001). A recent meta-analysis identified 16 case-control studies comparing HIV-1-seropositive individuals with seronegative controls of which 12 showed a higher and 3 studies a statistically significant higher

S. stercoralis infection risk for HIV-1-infected individuals and resulted in a pooled odds ratio (OR) of 2.17 [95% Bayesian confidence interval (BCI): 1.18–4.01] for HIV-1-infected individuals compared to the HIV-1-seronegative controls. This suggests an opportunistic component in infection with *S. stercoralis* (Schär et al. 2013).

Data on coinfection with food-borne trematodiasis and HIV-1 is mainly limited to the observation that coinfections exist (Tian et al. 2012; Paboriboune et al. 2014). A study from Lao People's Democratic Republic showed a significant association between low CD4 counts and infection with *O. viverrini* (Paboriboune et al. 2014), whereas in another survey in the People's Republic of China, no difference was found in prevalence of *C. sinensis* between HIV-1-infected and HIV-1-uninfected individuals (Tian et al. 2012).

An association between lymphatic filariasis and HIV-1 infection has been found in different studies. It has been debated whether this is due to the suspected increased susceptibility for HIV-1 infection in people with lymphatic filariasis or vice versa (Nielsen et al. 2006; Gopinath et al. 2000; Kroidl et al. 2016; Gallagher et al. 2005). For another filarial infection, onchocerciasis, which is not present in East Asia, an impaired antibody response to filarial antigens has been described in HIV-1-positive patients (Tawill et al. 1996). However, as no epidemiological associations between HIV-1 and filarial infections have been found in other surveys, this topic is still debated (Fischer et al. 1995; Nielsen et al. 2007; Tafatatha et al. 2015).

Overall, data on risk of helminth infection in HIV-1-infected patients are scarce, and further research is needed to address this subject.

5.2.4 Impact of HIV-1 Infection on the Course of Helminth Infections and the Efficacy of Anthelminthic Treatment in Coinfected Patients

It has been suspected that the course of a helminth infection might be negatively influenced by HIV-1 infection in the coinfected host. However, data on this subject are scarce, and there is no clear evidence that HIV-1 infection has a significant impact on the course of disease for most of STHs and food-borne trematodes (Karp and Auwaerter 2007).

In schistosomiasis, epidemiological surveys and experimental studies in mice suggested that egg excretion and maturation of parasites may depend on the host's immune response and that CD4$^+$ T-cell depletion in HIV-1-infected individuals may be linked to a decreased luminal migration of schistosome eggs and an arrest of worm development (Karanja et al. 1997; Fontanet et al. 2000; Mwanakasale et al. 2003; Doenhoff et al. 1981; Davies et al. 2001; Kallestrup et al. 2005; Dunne et al. 1983). An impaired excretion of schistosome eggs in HIV-1-coinfected individuals would reduce the sensitivity of *Schistosoma* diagnostics in endemic countries and preclude schistosome treatment which may be beneficial for the course of HIV-1 infection. However, as no difference in infection intensities and egg output was found in two large survey in Zimbabwe and South Africa, the effect of HIV-1 infection on egg output in schistosomiasis remains unclear (Kallestrup et al. 2005; Kleppa et al. 2015).

Praziquantel is a safe, cost-effective, and easily applicable treatment of all species of schistosomes (Panic et al. 2014). The effect of praziquantel is immune dependent and leads to exposure of antigens of the worm to its surface, making it more susceptible to antibody-induced immune response. In mouse models, praziquantel was found to kill fewer schistosomes in both T-cell- and B-cell-deprived mice. Concerns have been raised whether praziquantel is an efficacious drug for treatment of immunocompromised patients, in particular people living with HIV/AIDS (Sabah et al. 1985; Doenhoff et al. 2008; Brindley and Sher 1987).

Few studies have assessed the efficacy of praziquantel in HIV-1-schistosome coinfected patients demonstrating equal cure rates based on egg output for HIV-1-infected and HIV-1-uninfected patients, both for infections with *S. haematobium* and *S. mansoni* (Mwanakasale et al. 2003; Kallestrup et al. 2005; Karanja et al. 1998). However, in one study, antigen levels of *Schistosoma* spp. after praziquantel treatment were found to be significantly higher in HIV-1-infected versus HIV-1-uninfected individuals, even though cure rates based on egg output were not significantly different. This has led to the conclusion that the effect of praziquantel is limited to affecting the fecundity of adult schistosomes in the immunocompromised host, thus reducing egg excretion while leaving schistosomes metabolically active (Kallestrup et al. 2005).

This finding raises the concern that anthelminthic treatment regimens for HIV-1-infected patients might have to be adapted in order to achieve worm clearance and suggest that treatment control in immunocompromised patients might need to be based on antigen detection, since microscopic methods might give false negative results.

S. stercoralis is known to cause severe hyperinfection syndrome under different forms of immunosuppression, i.e. corticosteroid therapy or HTLV-1 virus infections. However, HIV-1 infection is not considered as a risk factor for hyperinfection syndrome as compared with the expected high numbers of HIV-1-*S. stercoralis* coinfections worldwide, only few reports of hyperinfection syndrome in HIV-1 patients are available, and most of them received concomitant corticosteroid therapy (Karp and Auwaerter 2007). The virtual absence of hyperinfection syndrome in HIV-1 infection may be explained by the finding that lower CD4 T-cell counts impede the development of infectious larvae which are necessary for autoinfection and therefore might protect from disseminated disease (Viney et al. 2004). Under this aspect, anecdotal reports of dissemination of *S. stercoralis* after initiation of ART might be considered as an immune reconstitution inflammatory syndrome (IRIS) in strongyloidiasis (Lanzafame et al. 2005; Brown et al. 2006).

Data on the course of cestode infections in HIV-1 patients is limited to single case reports. For echinococcosis, a case series from the People's Republic of China reports unusual growth rates and sizes of cysts in hepatic cystic echinococcosis among HIV-1-seropositive patients (Ran et al. 2015). A case of rapid progressive hepatic alveolar echinococcosis has been described in a patients infected with HIV-1 (Sailer et al. 1997).

Several cases on unusual manifestations of infections with *Taenia crassiceps* have been reported. This cestode is prevalent in the northern hemisphere with dogs and foxes as definite host. Unusual skin manifestations have been reported in HIV-1 patients. *T. crassiceps* is therefore discussed as an opportunistic infection (Klinker et al. 1992; Flammer Anikpeh et al. 2014; François et al. 1998; Chermette et al. 1995). Data on the cause of neurocysticercosis caused by *T. solium* in HIV-1-seropositive patients are scarce. It has been suggested that the frequency of giant cysts and racemose forms is higher in patients with HIV-1 (Delobel et al. 2004). Furthermore an IRIS in neurocysticercosis after starting ART has been suspected (Serpa et al. 2007).

6 Implications for Public Health

Coinfections of HIV-1 and helminths appear to be highly prevalent globally. Even though interaction of these infections is of growing interest in public health research, there is still a lack of data regarding this issue, the majority of studies originating from sub-Saharan Africa. However, more data from the Asian continent on this issue are needed, especially on helminth species that are specific to this region, such as *S. japonicum* or *C. sinensis*.

Several studies have suggested a negative impact of helminth infection on the risk of acquisition and the course of HIV-1 infection. Most helminth infections can be treated with a single and cost-effective treatment. Helminth control might therefore be an easy and efficient tool for HIV-1 management strategies.

Rural regions in the southwestern part of the People's Republic of China are the hot spots of HIV-1/AIDS endemic and helminth infections in East Asia. Therefore, the issue of HIV-1-helminth coinfection could be of particular relevance in these areas. Local control programmes for helminth infections may consider developing a special focus on HIV-exposed and HIV-infected populations as anthelmintic treatment may potentially reduce the risk for HIV-1 infection and slow down disease progression.

With regard to helminth infections in HIV-infected individuals, it needs to be noted that of selected helminth infections, the frequency (e.g. *T. crassiceps* and *S. stercoralis*) and the natural course of disease (e.g. *Echinococcus*, *T. crassiceps, and S. stercoralis*) might be altered by HIV-1 infection and associated therapies. Therefore campaigns and trainings to raise awareness and form local physicians in the field of HIV care may be discussed.

Additionally, HIV infections may complicate routine diagnostics of helminths infections, such as microscopy for the diagnosis of schistosome infection in HIV-1-seropositive individuals. Thus an alternative diagnostic work up, e.g. by measuring schistosome antigen in urine and/or serum, could be considered.

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Links Between the Epidemiology and Control of Noncommunicable Diseases and Neglected Tropical Diseases in Asia

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Contents

Abstract The Southeast Asian region is undergoing an epidemiological transition with a double burden of communicable and noncommunicable diseases (NCDs). The region accounts for a high share of both neglected tropical diseases (NTDs) and NCDs at the global level. Chronicity of both diseases, high prevalence of risk behaviours, and parallel health system issues along with similar affected populations provide a unique setting for rationalization of health interventions for the control of NTDs in the region.

Keywords Asia · Burden · Community-based · Determinants · Health services · Noncommunicable diseases · Neglected tropical diseases

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1 Background

Southeast Asia is home to more than half of the world's population (Nations Online Project 2014). Nearly 45% of the world's poor also live in the Southeast Asia region (Dhillon et al. 2012). Southeast Asia accounts for nearly one fourth of the global soil-transmitted helminth infections, one third of all rabies deaths, and more than half of the global burden of lymphatic filariasis, visceral leishmaniasis, and leprosy. Other Neglected Tropical Diseases (NTDs), such as dengue fever, are emerging (Lobo et al. 2011). In addition, the region is going through an epidemiological transition reflected by a double burden of communicable and noncommunicable diseases (NCDs). Low- and middle-income countries (LMICs) already account for more than 80% of the global NCD deaths. Countries in the World Health Organization (WHO) Southeast Asia region (SEAR) account for more than one fifth of the global NCD burden. The highest increase (21%) of deaths from NCDs in the next 10 years is predcited to occur (Narain et al. 2011).

Infections have an aetiological role in the development of many NCDs, as demonstrated in studies conducted in various African countries. They thus contribute to substantial chronic disability, lifelong impairments, and economic loss at personal and national levels. In addition to the classical risk factors, it has been suggested to prioritize infections as one of the major risk factors for NCDs in Africa (Mensah and Mayosi 2013). There is scarce documentation of a similar association between infections and NCDs in Asia, even though several Asian countries, such as the people's Republic of China, India, and Indonesia, have a high burden of both NTDs and NCDs (Institute of Health Metrics and Evaluation 2016). NTDs and NCDs share similar characteristics due to their chronic and debilitating nature. They also share several social determinants that influence the exposure, health-seeking behaviours, and health outcomes. The high prevalence of risk behaviours combined with poor health-seeking behaviour may lead to poor health outcomes for both NTDs and NCDs. Furthermore, overlapping determinants, similar target populations, and similar health system challenges for both the NCD and NTD control provide opportunities for cross-learning and streamlining of health interventions at the grassroot level. The available evidence regarding effectiveness of community-based and primary care interventions for NCDs and challenges can be used for planning NTD interventions and vice versa.

1.1 Disease Burden of NTDs and NCDs

Asia has a high disease burden of both NTDs and NCDs according to the recent global burden estimates (GBD 2016 DALYs and HALE Collaborators 2017). Globally, around a billion people, mostly poor, are affected by NTDs and as a consequence suffer from disability and poor quality of life (World Health Organization 2013). According to the estimates of the Global Burden of Disease study 2010, the 17 NTDs together accounted for about 26.05 million disability-adjusted life years (DALYs), 1% of the global burden of disease and injuries, and an estimated 152,000 deaths. The most prevalent NTDs, worldwide, include leishmaniasis, schistosomiasis, soil-transmitted helminthiasis, and lymphatic filariasis. Asia contributes the largest number of DALYs from NTDs. The largest number of DALYs for leishmaniasis, hookworm disease, lymphatic filariasis, food-borne trematodiases, rabies, ascariasis, and dengue occur in South, East, and Southeast Asian countries. In Asia, the leading NTDs are leishmaniasis in India; food-borne trematodiases in the People's Republic of China, North Korea, the Mekong region, and Japan; and intestinal nematode infections in Southeast Asian countries as a whole (Hotez et al. 2014). NCDs were the leading cause of death with 56 million deaths globally in 2010. LMICs account for nearly 75% of these deaths. NCD deaths increased from 6.7 million to 8.5 million in the WHO Southeast Asia region from 2000 to 2012. Nearly half (48%) of the NCD mortality in LMIC was among people below 70 years as compared to 28% in high-income countries (World Health Organization 2014).

In Asia, the mortality due to NTDs is highest in the South Asian countries, particularly in India. Among the various NTDs, the mortality rate is highest for dengue in South and Southeast Asia (Institute of Health Metrics and Evaluation 2016). Years lived with disability (YLD) for NTDs range from 168 in India to 140 per 100,000 population in the People's Republic of China. India accounts for the most YLD per 100,000 for dengue. The Southeast Asian countries and the People's Republic of China contribute the most YLD due to intestinal nematodes and trematodes, respectively. India also contributes the most DALYs per 100,000 population attributable to NTDs, followed by the Southeast Asian countries as a group. The countries in Southeast Asia contribute the most DALYs per 100,000 population due to dengue and intestinal nematodes, while the People's Republic of China leads in food-borne trematodiases (Table 1; Fig. 1).

Table 1 Burden of neglected tropical diseases in Asia according to the Global Burden of Diseases Study 2016

NTD	Southeast Asia	People's Republic of China	India	South Asia
Deaths (per 100,000)	1.7	0.15	2.6	2.3
Dengue	1.5		1.7	1.5
Rabies	0.1	0.07	0.3	0.3
Leishmaniasis			0.5	0.4
YLD (per 100,000)	184	140	168	168
Intestinal nematodes	75.4	18.5	48.9	60.2
Dengue	28.9	1.9	39.1	34.1
Lymphatic filariasis	33.8		16.1	13.8
Food-borne trematodiasis	20.4	113.6		
DALY (per 100,000)	300	150	300	275
Dengue	130.9	1.9	118.3	103.1
Intestinal nematodes	78.8	18.6	50.8	62.3
Leishmaniasis			27.4	24.1
Lymphatic filariasis	33.8		16.1	13.8
Food-borne trematodiasis	20.4	113.6		
Rabies	4.8	2.9	16.2	17.1

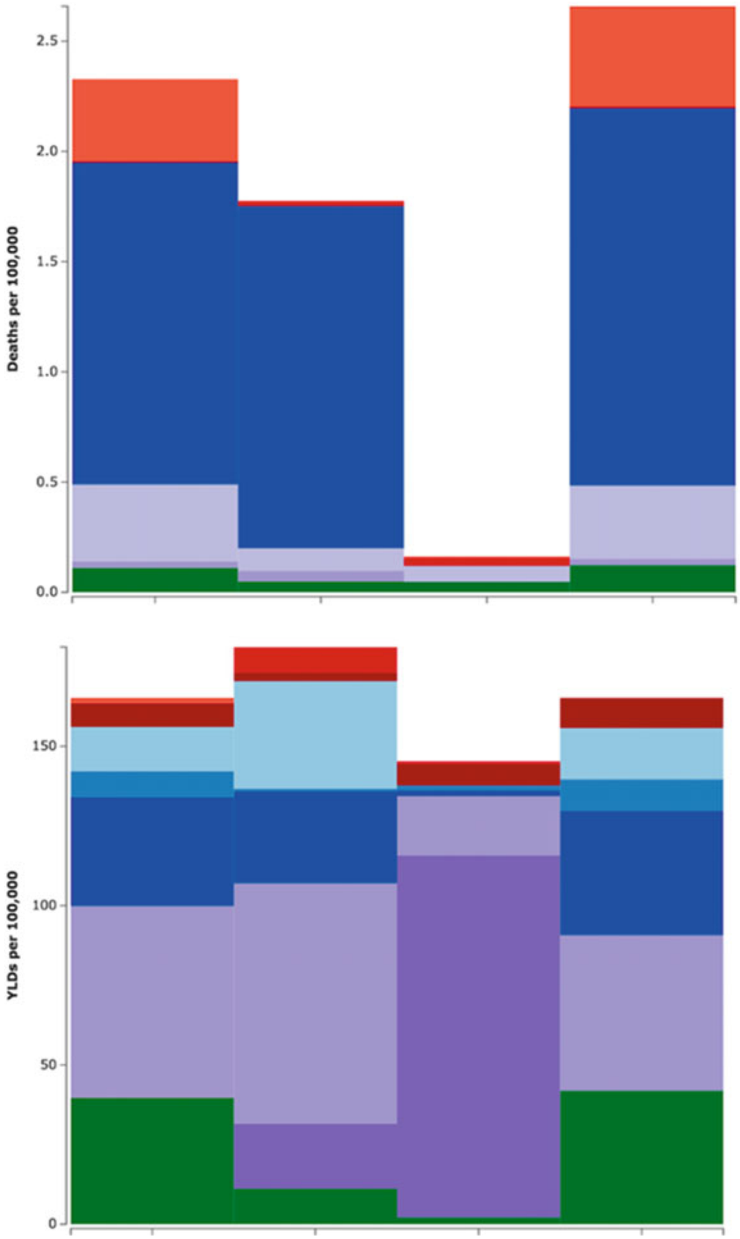

Fig. 1 Burden of neglected tropical diseases in Asia according to the Global Burden of Disease Study 2016

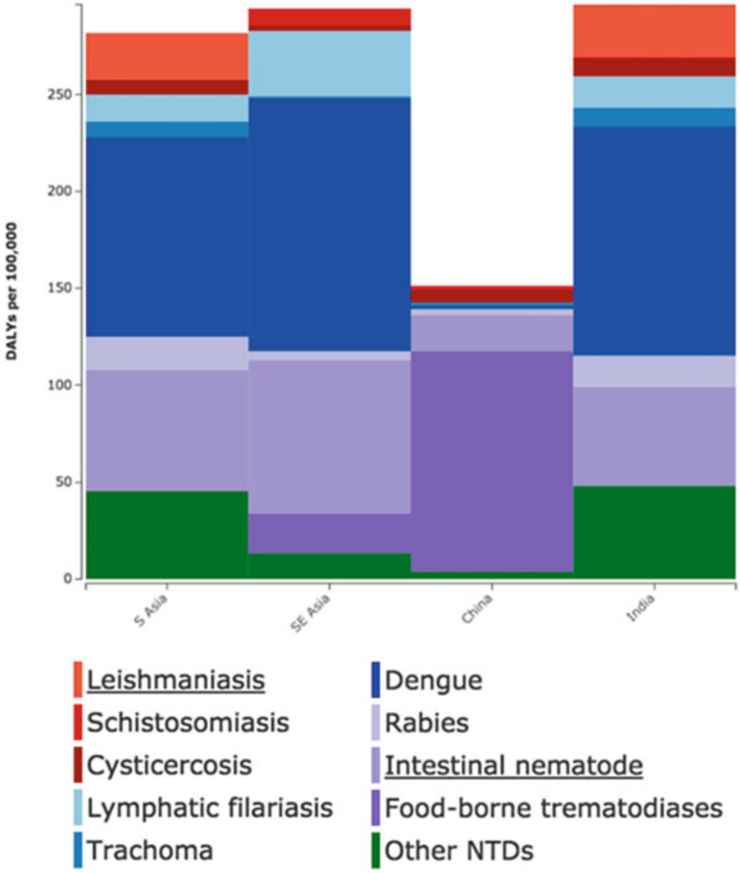

Fig. 1 (continued)

South Asia and Southeast Asia have a high burden of NCDs that account for 62% and 75% of the deaths in these regions, respectively. NCDs account for 60% and more than 80% of the deaths in two major countries in the region, India and the People's Republic of China, respectively. Among the NCDs, cardiovascular diseases (29–32%), cancers (9–14%), and chronic respiratory diseases (6–10%) were the leading causes of death in South Asia (including India) and Southeast Asia. In 2016, NCDs accounted for 75—82% of the collective YLD in Asian countries. Mental disorders and substance use (16–20%) and musculoskeletal disorders (14–19%) were the major contributors to YLD in these countries. NCDs accounted for 58%, 68%, and more than 80% of the DALYs in South Asia (including India), Southeast Asia, and the People's Republic of China, respectively, in 2016 (Institute of Health Metrics and Evaluation 2016) (Table 2; Fig. 2).

Table 2 Burden of noncommunicable diseases in Asia according to the Global Burden of Disease Study 2016

NCD	Southeast Asia	People's Republic of China	India	South Asia
Deaths (%)				
CVD	32	41	28	28.9
Neoplasm	14	24	8.3	8.7
CRD	5.8	9.5	10.9	10.3
Diabetes and endocrine	9	3.6	6.5	6.6
YLD (%)				
Mental and substance use	17.2	20.3	16.1	16.7
Neurological disorders	8.8	7.1	8.5	8.8
Musculoskeletal	17.7	18.9	14	14.3
Diabetes and endocrine	7.4	9.1	7.1	7.2
DALY (%)				
CVD	16.6	22.5	14	14.1
Neoplasm	8.5	16.9	5	5.2
Diabetes and endocrine	7.5	5.8	5.6	5.6
Mental and substance use	6.2	8.6	5.6	5.7
CRD	4.5	5.1	6.4	5.8

2 Economic Burden of NTDs and NCDs

A dual burden of NTDs and NCDs can inflict a high economic burden on the affected population due to high treatment costs and consequently low affordability. Most health expenditure in poor countries is out of pocket, and the cost of treatment for these diseases therefore puts a direct burden on low-income families. The huge macroeconomic impact of these diseases is due to a combination of costs to individuals, families, governments, and health systems.

Direct and indirect costs incurred for the treatment of NTDs can lead to "catastrophic health expenditures" (Damme et al. 2004). Inability to pay has been associated with all NTDs (Aagaard-Hansen and Chaignat 2010). There is documented evidence for the high cost of dengue fever in Thailand and high out-of-pocket expenditure (OOPE) leading to debt during dengue epidemics in Cambodia (Damme et al. 2004; Anderson et al. 2007). Poverty has been described as "a potentiator of leishmaniasis morbidity and mortality" (Alvar et al. 2006). Treatment for leishmaniasis in the private sector health facilities had led to the sale of assets and heavy borrowing in Nepal (Uranw et al. 2013). A study from Bangladesh demonstrated the negative financial impact of visceral leishmaniasis (Anoopa Sharma et al. 2006). Loss of productivity due to acute and chronic lymphatic filariasis has been demonstrated by studies from India's Odisha state and South India (Ramaiah et al. 2000; Babu and Babu 2014). The economic impact of the NTDs also results from its adverse effects on school attendance and child development, agriculture (especially from zoonotic NTDs), and overall economic productivity, including loss of tourism (Miguel and Kremer 2004; Mavalankar et al. 2009).

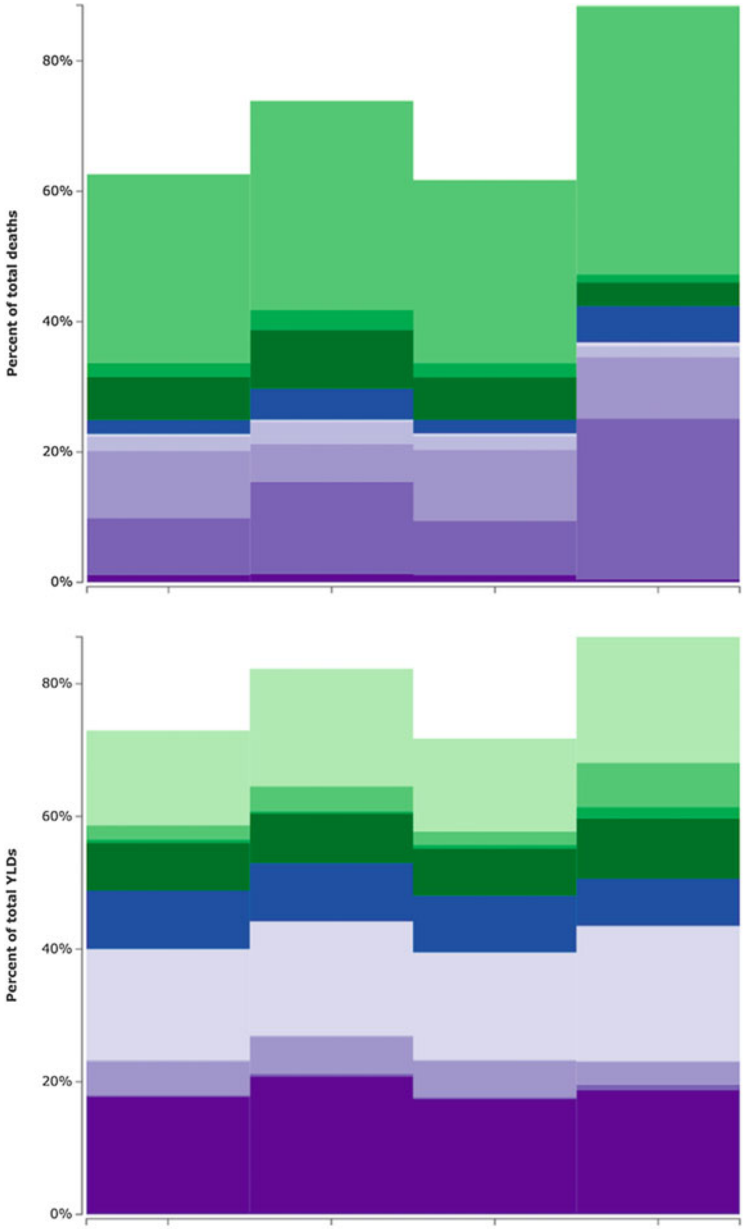

Fig. 2 Burden of noncommunicable diseases in Asia according to the Global Burden of Disease Study 2016

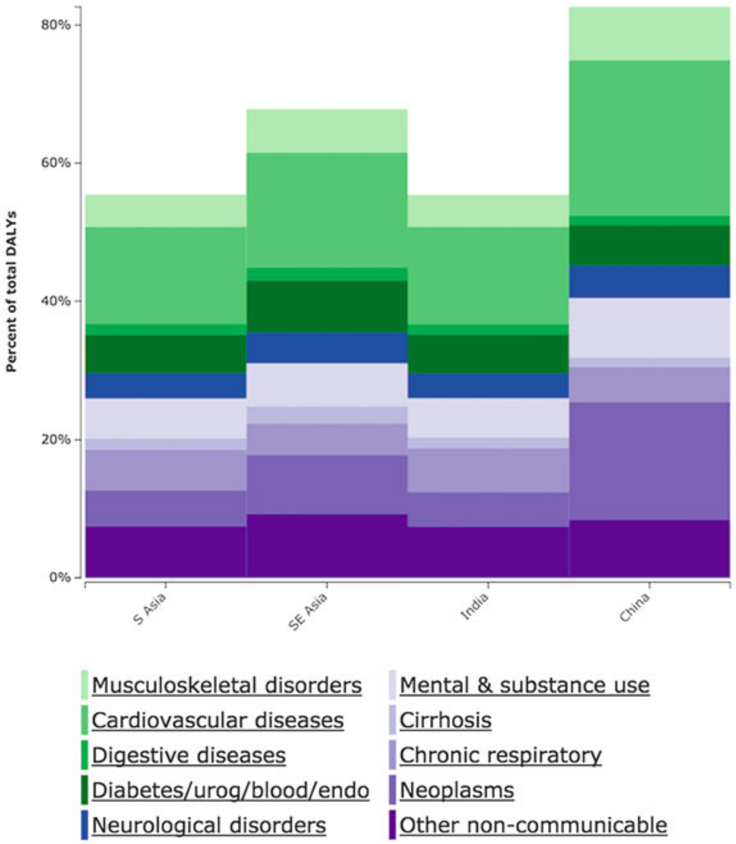

Fig. 2 (continued)

The economic burden of NCDs occurs at both macroeconomic and household levels. It is estimated that there is 0.5% reduced annual economic growth for every 10% rise in NCDs (World Health Organization 2011). The gross domestic product (GDP) loss at the country level will be very high if nothing is done to reduce the risk of NCDs in the region. The GDP loss was estimated to be US$16.68 billion, US $4.18 billion, US$1.49 billion, and US$1.14 billion in India, Indonesia, Thailand, and Bangladesh, respectively, during the 2006–2015 period (Abegunde et al. 2007a). The rising burden of NCDs in the SEAR has led to the loss of household income due to the loss of productivity and high OOPE for the treatment. The share of chronic diseases among the household OOPE increased from 31.6% to 47.3% from 1995–1996 to 2004 in India. Medicines, diagnostic tests, and medical appliances contributed to nearly half of the OOPE on chronic diseases in India (Engelgau et al. 2011). OOPE for hospital treatment accounted for a large proportion of household expenditures, i.e. 30% for CVD and 17% for diabetes as per a national survey in India in 2004 (Rao et al. 2011). The People's Republic of China also has huge healthcare expenditure for NCD with 31.9 billion and 10.7 billion Chinese yuan spent on hypertension and diabetes treatment, respectively, which accounted for 5.6% and 1.9%, respectively, of the total national health expenditure (Xiao et al. 2014).

3 NTDs as Risk Factor for NCDs

Most NTDs have a chronic course of disease resulting in long-term disability. Similar to NCDs that require lifelong treatment, many NTDs may persist for decades or longer. There is limited but growing evidence for the contribution of NTDs to the NCD burden, especially in the context of the poor populations in LMICs.

Many of the NTDs prevalent in Africa were associated with an increased risk of NCDs. This association is also documented for specific NTDs prevalent in Asia. Among the cancers, opisthorchiasis and clonorchiasis have been shown to cause bile duct carcinoma in Southeast Asia and The People's Republic of China. Schistosomiasis has been linked to intestinal and liver fibrosis in East Asia and amebiasis to liver cysts in India. Hookworm infection and schistosomiasis significantly contribute to anaemia, particularly in children and pregnant women in LMICs. Paragonimiasis and ascariasis lead to chronic respiratory conditions such as hemoptysis in East Asia and asthma, respectively (Hotez and Daar 2008). Congestive heart failure is one of the complications of hookworm infection. Myocardial dysfunction was found in 6.7% of all cases with dengue fever, 13.8% with dengue haemorrhagic fever, and 36% with dengue shock syndrome (Moolani et al. 2012).

3.1 Social Determinants and Consequences of NCDs and NTDs

3.1.1 Poverty and Socio-economic Status

The high burden of NTDs and NCDs among the poor can be partly attributed to their high exposure to risk factors and behaviours. Poverty has been documented as determinant for all major NTDs and is closely linked to intermediate determinants such as education, occupation, water, sanitation, and housing (Aagaard-Hansen and Chaignat 2010; Conteh et al. 2010). NCDs such as cardiovascular diseases were initially considered diseases of the affluent class; however, lower socio-economic groups are also affected by these diseases, particularly if they adopt some modern lifestyles and foods (Jeemon and Reddy 2010).

Tobacco use, a major risk factor for NCD, is highly prevalent in the Southeast Asia region with very high per head annual cigarette consumption in Indonesia (974 cigarettes) and the Philippines (1073 cigarettes). Prevalence of tobacco consumption was two times higher among least wealthy population, as compared to the highly affluent in Myanmar, Malaysia, the Philippines, Lao People's Democratic

Republic, and Vietnam (Dans et al. 2011). Similarly, smoking prevalence was higher among males with no formal schooling (39 vs. 14%) as compared to those with secondary or above education in a national survey in India (Indian Institute of Population Sciences and Ministry of Health and Family Welfare 2010). There was also an increase in smoking, diabetes, and dyslipidemias in the lower socioeconomic groups in serial epidemiological surveys in an urban population in western India (Gupta et al. 2003). A multicentric study of 19,969 individuals in the urban industrial populations across India showed an inverse gradient between education and risk factors such as tobacco usage and hypertension. In addition, there was also an inverse gradient for diabetes and overweight in the industrial populations in highly urbanized settings (Reddy et al. 2007).

Poverty is also one of the consequences of NTDs and NCDs that may further lead to higher vulnerability and poor health outcomes. It can be an outcome of NTDs due to the high cost of treatment or loss of wages associated with diseases such as leishmaniasis and lymphatic filariasis (Aagaard-Hansen and Chaignat 2010). Several NTDs are characterized by a cycle of poverty and disease (Hotez et al. 2009). Similarly, high costs of treatment for NCDs can push people into poverty. The odds of catastrophic spending and impoverishment were higher for those hospitalized with chronic diseases than for those hospitalized with communicable diseases, the highest being for CVD and cancers in India (Mahal et al. 2010).

3.1.2 Urbanization and Migration

Migration is linked to socioeconomic factors and leads to change in behaviours, vulnerability, access to health services, and healthcare outcomes for NTD and NCDs. NCD risk factors were highly prevalent in the suburban slums in metropolitan cities such as Delhi and Kolkata in India that have predominantly migrant populations (Anand et al. 2007; Acharyya et al. 2014). The industrial workers who migrated from rural areas to urban areas in India had higher rates of obesity and diabetes as compared to their siblings who continued to stay in rural areas (Ebrahim et al. 2010). Studies among migrating communities have documented the inadequacy of health services and control programmes for Guinea-worm disease in India and Pakistan and parasitic diseases in Thailand (Watts 1987; Petney 2001). Increasingly mobile populations and livestock migrations into mountainous regions have been shown to be a challenge for schistosomiasis control in the People's Republic of China (Xianyi 2002).

3.2 Psychosocial Determinants and Consequences of NCDs and NTDs

Patients with NCDs and NTDs have an increased psychosocial burden due to the need for prolonged treatment, which naturally results in additional costs of care. In addition, stigma adds to the psychosocial burden specifically for NTDs and influences health-seeking behaviour and treatment adherence (Reithinger et al. 2005). Depression is one of the comorbidities observed in NCDs and NTDs. Depression is highly prevalent among patients with myocardial infarction, cancers, chronic respiratory disease, and neurological disorders in Southeast Asian countries (Hengrasmee et al. 2004; Lueboonthavatchai 2007; Nidhinandana et al. 2007; Agarwal et al. 2011; De 2011). Social stigma is also associated with many of the NTDs, at the individual, family, and community level. Stigma and psychiatric morbidity has been associated with NTDs prevalent in Asia, including lymphatic filariasis, trachoma, and leprosy (Perera et al. 2007; Weiss 2008). Stigma is one of the contributors to poor mental health in addition to limited access to health services, the negative economic impact, and the violation of socio-political rights among patients with NTDs (Litt et al. 2012; Molyneux 2012). Various psychological consequences of stigma derived from NTDs, including depression, have been linked to lymphatic filariasis, onchocerciasis, and leishmaniasis (Hofstraat and van Brakel 2016). Stigma not only influences disease outcomes but also has a negative economic impact. Disfigurement caused by lymphatic filariasis stigmatizes communities where cases cluster and has been shown to impair earning capacities in India (Bandyopadhyay 1996).

In addition to stigma, gender issues might further contribute to differentials in morbidity, mortality, societal function, and health-seeking behaviour for many of the NTDs, depending on the country-specific cultural context (Vlassoff and Manderson 1998). Women were documented to underreport leishmaniasis, which delayed their access to diagnosis and treatment (Ahluwalia et al. 2003). One explanation for this behaviour might be that women are disproportionately stigmatized by the scarring sequelae of cutaneous leishmaniasis that can impair social life in Pakistan and Afghanistan (Reithinger et al. 2005; Kassi et al. 2008). Female leprosy patients in India reported delayed initiation of treatment, coupled with more adverse community response and more disruption of their routine activities (Rao et al. 1996; Zodpey et al. 2000).

3.3 Interventions for NTD and NCD Control: Learning from Experiences in the Region

3.3.1 Prioritizing NTD and NCD Control in Global and Regional Health Agendas

There have been efforts at the global and regional level to put NTDs and NCDs on the priority agenda. The World Health Assembly (WHA) passed resolutions calling for the global elimination of leprosy and lymphatic filariasis in 1991 and 1997, respectively (World Health Assembly 1991, 1997). There have been many efforts to address NCD control in the past decade. The WHO FCTC was adopted by the WHA in 2003 and ratified by many countries in the Asia region. The Global Strategy on Diet, Physical Activity and Health was endorsed by the WHA in 2004. Another major milestone was the development of the 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of NCDs. The high-level meeting of the general assembly in September 2011 with participation of heads of states brought NCDs on the priority agenda of most countries in the Asian region (World Health Organization 2011).

The countries of the Southeast Asia region are making progress towards eliminating leprosy, lymphatic filariasis, visceral leishmaniasis, and yaws as public health problems (i.e. reducing annual incidence to less than 1 per 10,000 population at the district or subdistrict level, depending on the country). India, Bangladesh, and Nepal have scaled up treatment and control strategies towards elimination of visceral leishmaniasis. Indeed, a memorandum of understanding was signed by India, Nepal, and Bangladesh for joint efforts to eliminate visceral leishmaniasis by the year 2015, and a resolution was passed by the WHO Southeast Asia Regional Committee in 2006, to intensify efforts towards achieving the goals of eliminating selected NTDs (World Health Organization Regional Office for South-East Asia 2006). A Regional Programme Review Group in the Southeast Asia region monitors the goal of eliminating lymphatic filariasis by 2020. The main strategy for the elimination of lymphatic filariasis is mass administration of diethylcarbamazine (DEC) and albendazole. Areas endemic for lymphatic filariasis have been fully mapped in all endemic countries of the region except Indonesia. High coverage of mass drug administration (MDA) for treatment of lymphatic filariasis has been shown in Bangladesh and India, while Maldives, Sri Lanka, and Thailand have already achieved elimination. India declared elimination of yaws in 2006 (Narain et al. 2010). In Indonesia, a yaws elimination programme was initiated in four hyperendemic provinces, while in Timor-Leste, yaws control is part of an integrated campaign that includes other skin diseases, such as leprosy (Narain et al. 2010). All countries of the region except Timor-Leste have attained leprosy elimination.

Several international initiatives further support national NTD control and elimination programmes in terms of advocacy, technical assistance, and/or financing. These include the Global Alliance for the Elimination of Lymphatic Filariasis (GAELF) and the International Trachoma Initiative in Nepal and Vietnam as external partners of WHO and the International Federation of Anti-Leprosy Associations

(ILEP), an umbrella organization of non-governmental organizations (NGOs) (Liese et al. 2010).

In contrast, there is limited progress made in NCD control. For example, there is varying level of implementation of tobacco control interventions such as taxation measures, legislation to prevent exposure to tobacco smoke, enhancing public awareness, bans on tobacco advertising, promotion and sponsorship, and reducing tobacco dependence (Narain et al. 2011).

3.4 *Strategies, Policies, and Programmes for NCD and NTD Control*

The interventions to address NCDs and NTDs share certain common strategies that can be implemented synergistically considering limited resources available to address these diseases. The WHO promotes the use of five public health strategies to control, eliminate, and eradicate NTDs. These include (1) preventive chemotherapy; (2) innovative and intensified disease management; (3) vector control and pesticide management; (4) provision of safe drinking water, basic sanitation and hygiene, and education; and (5) veterinary public health services (World Health Organization 2013). The strategies recommended for NCD control include reducing risk factors through primary prevention and health promotion, early detection and management of NCDs, surveillance, and delivering interventions through primary care (Narain et al. 2011). Strategies for NTD and NCD control thus have common focus on determinants for primary prevention and a primary care approach to early detection and treatment.

The countries in Southeast Asia and East Asia require a national policy and organizational structures to support interventions for NCDs and NTDs. There has been encouraging progress in the response from governments for NCD and NTD control. There has also been a change in the organizational structure of NTD and NCD programmes with a growing trend towards horizontal integration of multiple NTDs or multiple NCDs under one programme.

There has been major progress in the governance of NCD programmes over the past decade. A review of governance structures in 18 LMICs in East Asia and the Pacific reported separate governance structures for different chronic diseases in 2010. Many countries initially started multiple vertical programmes, but in recent years, there was a trend towards merging the programmes, e.g. the Philippines merged three vertical programmes in 2000, and similar trends were observed in Mongolia and Malaysia. National health plans of the majority of the LMICs mentioned chronic diseases in the sector-wide plans (Rani et al. 2012).

India had several programmes addressing various NCDs and NTDs. The National Rural Health Mission was launched in 2004 by the government of India. It provided a platform for integrating various vertical disease control programmes. Historically, the government of India had several vertical programmes for NCDs. The National

Health Programmes for cancer, blindness, and mental health were started in 1975, 1976, and 1982, respectively. A national programme for prevention and control of cancer, diabetes, CVD, and stroke was launched in 2010–2011. Cancer is integrated in this programme under the broad structure of National Health Mission (Srivastava and Bachani 2011). The National Vector Borne Disease Control Programme (NVBDCP) includes the control of all major NTDs in the country, including visceral leishmaniasis, lymphatic filariasis, and chikungunya. The visceral leishmaniasis control programme, originally a vertical programme, was merged with the NVBDCP under the "National Rural Health Mission" in the year 2005 with the strategy of oral administration of miltefosine and indoor residual spraying (Muniaraj 2014). In addition to various programme-based initiatives, the government of India has also worked to catalyze research and development (R&D) for NTDs. One such initiative in the Indian biotech sector is the launching of a public-private partnership, Biotechnology Industry Research Assistance Council (BIRAC). Furthermore, the Open Source Drug Discovery (OSDD) platform of the Council of Scientific and Industrial Research (CSIR) of India is part of a global network of OSDD groups and includes R&D projects for NTDs (Global Health Progress 2013).

Bangladesh started its visceral leishmaniasis elimination programme in 2007 and is now considered to be on track for elimination by the end of 2017. In 2011, a visceral leishmaniasis research centre was established in Northern Bangladesh in collaboration with the Directorate General of Health Services (Ministry of Health and Family Welfare, Bangladesh), Drugs for Neglected Diseases initiative (DNDi), Japan International Cooperation Agency (JICA), and Japan Science and Technology Agency (JST), Institute of One World Health (now merged with PATH), and the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) (Nawaz 2014).

The Second Long-Term Health Plan (1997–2017) of Nepal has also included visceral leishmaniasis in the "Essential Health Care Services" (EHCS) with provision of free treatment and indoor residual spraying. However, concerns have been raised over the ineffective implementation of the control strategies, including poor surveillance, inaccessibility to treatment, low quality of spraying, ineffective public awareness measures, and availability of treatment only in public sector hospitals (Adhikari 2013).

As part of its NTD National Action Plan (2011–2015), the Indonesian Ministry of Health conducts MDA for soil-transmitted helminth infections in collaboration with the Directorates of Maternal-Child Health (MCH) and Nutrition, local NGOs ("Kusuma Buana"), and with technical and financial assistance from RTI International and the US Agency for International Development (USAID) (World Health Organization and Husada 2011). In addition, the IMOH's Centre for Health Promotion has implemented a programme for hygiene education and outreach. The control programmes for NTDs in Indonesia are implemented by the Ministry of Health with additional financial support from UNAIDS, the Australian Department of Foreign Affairs and Trade, and UNICEF (Tan et al. 2014). Working towards the goal of global elimination of lymphatic filariasis by 2020, different parts of the country are in various stages of the lymphatic filariasis elimination programme, including mapping of endemic areas, MDA implementation, and post-transmission assessment surveillance (TAS) (Krentel et al. 2016). Currently, albendazole is provided free of cost by GlaxoSmithKline through WHO, while DEC is procured with the national budget (World Health Organization and Husada 2011).

3.5 Service Delivery Using Primary Care Approach

The health systems in most East Asian countries are oriented to maternal and child health and communicable diseases. Most of the NTDs and all NCDs require long-term care, prolonged drug treatment, and disability prevention and management. Health systems need to be restructured for efficient use of limited resources. Current health services require the visit of multiple facilities by patients that are not appropriate for efficient and effective chronic disease management (Allotey et al. 2011). Available models and ongoing programmes that focus on primary care in either NCDs or NTDs provide an opportunity to identify the elements that can be scaled up in low-resource settings.

Several countries in Asia are developing strategies for integrating NCD interventions in primary healthcare systems. NTD interventions can be integrated and implemented along with ongoing primary healthcare activities, including immunization campaigns, antenatal care, maternal and child health services, and school health programmes (Bhutta et al. 2014). Malaysia has developed NCD screening and management interventions in the primary healthcare system with key roles played by nurses and medical assistants. These healthcare providers were trained to provide services related to chronic conditions, such as self-management and clinical care for chronic diseases (Mustapha et al. 2014). The People's Republic of China has also developed a primary healthcare-based NCD program that involves establishing personal health record of each individual, identification of individuals with risk factors and treatment, and follow-up of patients with hypertension and diabetes (Xiao et al. 2014).

Patients with NTDs and NCDs require counseling in addition to medical management for modifying risk behaviours, self-management, and associated psychosocial comorbidities. A clinical trial on smoking cessation intervention among diabetics in a primary care setting in Kerala, India, demonstrated higher odds for quitting smoking [8.4, 95% confidence interval (CI): 4.1–17.1] in the intervention group at 6 months (Thankappan et al. 2013). Psychosocial issues related to stigma from NTDs and comorbidities such as depression that occur in both NCD and NTD patients can also be addressed in primary care. A combination of drugs and psychosocial interventions involving lay health workers trained as counselors and primary care physicians was effective in primary healthcare settings in Goa, India. Six-month recovery from depression was higher in the intervention as compared to the control arm (65 vs. 53%, risk ratio (RR) 1.22, 95% CI 1.00–1.47) (Patel et al. 2010).

3.6 Human Resources for Service Delivery

One of the challenges in managing NTDs and NCDs is the lack of adequate human resources. Programmes require active involvement of community healthcare workers and other non-physician health workers to sustain the programme activities. Health workers need to be properly incentivized to ensure their retention and programme sustainability (Bhutta et al. 2014). There has been a trend towards developing capacity at all levels and involving all cadres of health workers to implement programmes in low-resource settings. WHO supports capacity building of endemic countries by strengthening the training and implementation capacity for NTD control (World Health Organization 2013). WHO has also developed a CVD risk management package for use by health workers in low-resource settings (Abegunde et al. 2007b).

Nurses are one category of paramedical workers that can be trained to deliver interventions in primary care settings. They can play a key role in providing services in low-resource settings. Tamil Nadu, India, has a nurse-based model for screening and management of NCDs in primary health centres (PHC) and secondary care hospitals. The programme has placed a nurse in every PHC that conducts screening for cervix (VIA/VILI) and breast (clinical breast examination) cancers, hypertension, and diabetes as per protocol. The nurse does counseling, monitors the blood pressure and other parameters for patients on follow-up for hypertension/diabetes, maintains records, and prepares monthly reports. This model is feasible and has led to the implementation of NCD interventions in a systematic manner (Tamil Nadu Health Systems Project 2012).

Community volunteers and lay health workers can also play key roles in delivering various interventions at the community level for NTDs and NCDs. MDA programmes for filariasis involve various human resources such as community volunteers, auxiliary nurse midwives, Accredited Social Health Activists (ASHAs), school teachers, and local administrative bodies to achieve their goals (Srivastava et al. 2014). Non-physician health workers played a key role in identifying high-risk groups in various NCD interventions. A study from India and Pakistan demonstrated 80% agreement between doctor and non-physician health worker in implementing the CVD risk management package developed by WHO for cardiovascular risk assessment in low-resource settings (Abegunde et al. 2007b). Lay health workers from the community have been successfully employed to conduct screening, follow-up, and behavioural interventions for diabetes and mental disorders. A systematic review to improve diabetes care among the socially disadvantaged populations identified lay people as best suited to leading the intervention due to their frequent contact with the patient. Tailoring the interventions within the context of local communities and focusing on behaviour-related tasks have been proven to improve diabetes management (Glazier et al. 2006). Community-based mental health programmes that involve community volunteers in Tamil Nadu, India, were well accepted by the community and feasible with limited resources (Padmavati 2005).

4 Drugs for the Management of NTDs and NCDs

Availability and access to drugs is a challenge for both NCDs and NTDs. There have been efforts to enhancing the availability of drugs for NTD, but a substantial gap of US$300 million per year for the procurement and delivery of quality essential drugs remains (Molyneux 2014). The access to essential medicines for the management of NCDs is also not adequately addressed in most South and Southeast Asian countries (Mendis et al. 2007b).

NTD control measures can be integrated by combining vertical MDA efforts and creating a "rapid impact" package of donated or low-cost generic drugs that is implemented using WHO guidelines. In Asia, such drugs include albendazole or mebendazole, DEC, praziquantel, ivermectin, and azithromycin (Hotez et al. 2009). A combination of albendazole, praziquantel, and ivermectin was reported to be well tolerated, with negligible adverse events among healthy volunteers in Thailand (Na-Bangchang et al. 2006). NTD programmes in endemic countries are often beneficiaries of public-private partnerships in terms of the drug donations by 10 pharmaceutical companies that reach an estimated annual value of US$2 billion (Bush and Hopkins 2011). In Asian countries, free supply of multidrug therapy for leprosy is provided by Novartis since 2000, while albendazole, required for MDA to eliminate lymphatic filariasis, is provided by GlaxoSmithKline (1998–2020) through WHO. Pfizer and Johnson & Johnson have an open-ended programme for supply of azithromycin for trachoma and mebendazole for soil-transmitted helminthiasis, respectively (Liese et al. 2010).

Drug availability for NCDs is poor in the public sector in most countries. A study of 32 essential medicines in 6 LMICs including Bangladesh, Nepal, and Sri Lanka from Southeast Asia found that only 7.5% of 32 medicines were available in the public sector except in Sri Lanka, where 28% were available. There was a large variation in the cost of 1 month worth of combination treatment for coronary heart disease. The cost ranged from 6.1 daily wages in Nepal to 1.6 daily wages in Bangladesh (Mendis et al. 2007a). High costs and a lack of availability of essential medicines for chronic respiratory disease were reported in a study from five Indian states. Beclomethasone and salbutamol inhalers for chronic respiratory diseases were available in only 25% and 30% of public facilities in Rajasthan state. The cost of one inhaler ranged from 1.5 to 2.5 days wages for the lowest-paid government worker (Kotwani 2009). Poor access to low-cost drugs such as aspirin, beta-blockers, and statins was reported in a multicountry survey of 10,000 cardiovascular disease patients in 10 countries including India, Indonesia, and Sri Lanka. Lessons learnt from NTD programmes in improving the access to drugs can be used to design strategies and programmes for NCDs (Yusuf et al. 2011).

4.1 Community Involvement and Community-Based Interventions

Community mobilization is one of the interventions common to NTD and NCD. Community involvement can be useful to address risk behaviours, conduct screening and long-term follow-up for NCD and NTD, and increase acceptance of MDA. Community-based interventions for dengue, trachoma, leishmaniasis, and leprosy have been shown to be effective in several Asian countries, especially in combination with vertical vector control programmes which resulted in wide community coverage and acceptance (Bhutta et al. 2014; Das et al. 2014).

Community-based strategies and structures can provide platforms for delivering various NCD and NTD interventions. Malaysia developed a community-based NCD intervention programme that utilized strategies developed for communicable disease programmes. One of the strategies was the involvement of healthcare volunteers who were not paid for the services but were given other incentives, such as certificates from ministry and travel support to participate in the national meetings. An annual conference was organized for volunteers which provided a platform for presenting the projects and experience sharing. Health clinic advisory panels were also constituted to act as a bridge between the community and programmes. The main role of the panels was health promotion, and they also participated in developing locally appropriate training modules (Mustapha et al. 2014).

There is evidence of the effectiveness of community-based approaches for NCD and NTD control. Community-based interventions were effective in reducing the burden and intensity of soil-transmitted helminthiasis, schistosomiasis, and anaemia globally, including in Asia (Salam et al. 2014). Knowledge and education of the community, strong commitment of all stakeholders, and ensuring participation and enthusiasm of healthcare workers in the routine health services have been demonstrated to be key for the effectiveness of interventions against helminth infections in Vietnam (Phuc et al. 2009). Community-based interventions targeting NCD risk factors in large intervention programmes in Vietnam reported a reduction in blood pressure in the intervention group (Nguyen et al. 2012). Community mobilization has also been demonstrated to be an effective tool for reducing alcohol use. Community leaders can be sensitized, and locally relevant solutions can be developed involving community stakeholders (Schmidt et al. 2010).

One of the major community-based interventions against NTDs in Asian countries is community-directed MDA. The People's Republic of China was the first country to eliminate lymphatic filariasis through MDA and other tools. India's National Health Policy envisaged elimination of lymphatic filariasis in India by 2015. Subsequent to a pilot project initiated in 1996–1997 with yearly single-dose MDA of DEC in 13 identified districts of 7 states and covering about 41 million people, MDA was extended to 31 districts including 11 districts with co-administration of DEC and albendazole in 2002. It was scaled up in a phased manner, and currently, all the districts are being covered with the two drugs. The MDA is driven by the health services and implemented by health workers or community volunteers, who were selected by healthcare personnel and carry out house-to-house distribution of drugs. The population coverage during MDA has improved from 73% in 2004 to 83% in 2013, resulting in a reduction of the overall microfilaria rate from 1.2% (2004) to 0.3% (2013). In all, 203 out of 255 districts reported a microfilaria rate of less than 1%. This progress has been achieved through a coordinated implementation strategy from the central to peripheral levels, including setting up of a State Task Force and State Technical Advisory Committees; training of district level officers and nodal officers involving faculty of medical colleges, research institutions, and district coordination committees; preparation of micro action plans for rural and urban areas, plans for lymphedema management and hydrocele operations; and supply and distribution of operational guidelines and drugs (Srivastava et al. 2014). Worryingly, a recent review of India's programme for the elimination of lymphatic filariasis highlighted the gaps in the MDA infrastructure and implementation, including irregularity in monthly MDA, poor compliance to drugs, especially in urban areas, discrepancy between reported coverage and survey findings, failure by drug distributors to visit a household, absence of people from their house during MDA, lack of awareness among the at-risk population of the benefits of the MDA, misconceptions about its risks, inaccurate information about drug adverse reactions, and poor knowledge and perceptions of lymphatic filariasis in endemic communities (Babu and Babu 2014). MDA for lymphatic filariasis was seen to be poorly acceptable to people from different caste systems in Tamil Nadu, India (Ramaiah et al. 2001). There is a need to understand the social structures of endemic communities along with addressing the accessibility, acceptability, and affordability of the public health interventions (Jacobs et al. 2012).

The Indonesian Ministry of Health plans to eliminate schistosomiasis by 2020 through MDA of praziquantel to individuals over the age of 4 years, along with health education, environmental management, and agro-engineering. MDA with DEC and albendazole is the major strategy for combating lymphatic filariasis in Indonesia. However, the current drug coverage in the major endemic districts is only approximately 30% (World Health Organization and Husada 2011). Barriers to access these drugs include social stigmatization linked to lymphatic filariasis (Sudomo et al. 2010), the island geography with remote populations, compliance (Bhullar and Maikere 2010), and government budgetary constraints (Tan et al. 2014).

School-based interventions for NTDs and workplace-based interventions for NCDs have been shown to be feasible and effective in Southeast Asia. School-based delivery of preventive and promotive interventions, in collaboration with the educational authorities and the school personnel, was cost-effective in Thailand (Hathirat et al. 1992). One worksite intervention programme in India demonstrated the effectiveness of health promotion interventions for reducing the prevalence of risk factors for cardiovascular diseases (Prabhakaran et al. 2009).

4.2 Challenges and Opportunities

Although the control and management of NTDs has made significant progress in recent years, there are continuing and emerging challenges that can be stratified as biological, socio-geographical, strategic, logistic, and technical (Bockarie et al. 2013). Given that NTDs contribute to lost national income via loss in productivity in endemic countries, there is a need to fill the gap in resources and advocacy through political commitment and continued collaborations among all stakeholders (Molyneux 2014; Lenk et al. 2016). A major challenge is the coordination of governance arrangements and multiple partners—international, national governments, and local bodies for NTD programmes at the in-country implementation level. Operationally, this would require integration of the control efforts into the country's overall health system, interdepartmental collaboration, and intra-ministerial coordination (Liese et al. 2010; Molyneux 2014).

There has been progress in NCD control in the past decade with various policies and programmes being implemented. However, NCDs are not yet recognized as a national health priority in many countries in the region. LMICs in the region have the highest proportion of mortality due to NCDs, and data from countries such as India show the rising burden of NCDs among the poor, while there is a general misperception that NCDs affect the wealthy. The NCDs are predominantly linked to harmful behaviours due to individual choices, but the influence of the socio-economic status and environment is not fully acknowledged (World Health Organization 2011). Health systems in several Asian countries have competing priorities due to their high burden of infectious diseases, NTDs, and maternal and child health conditions. Health systems lack adequate resources to tackle the rising burden of NCD care.

The lessons learnt from NCD and NTD control in the countries in the South and Southeast and East Asian region provide evidence for scaling up and combining several interventions in primary care and at the community level. Community resources can be leveraged for both NCD and NTD control. The control efforts need to target the poor and focus on determinants that are influenced by socio-economic conditions. The resources in the health system should be judiciously allocated to strengthen primary care and ensure adequate availability of funds, human resources, and drugs. The interventions should not only focus on drugs but comprehensive care that also addresses psychosocial issues and behavioural change. Further research is required to understand the NCD comorbidities among patients with NTDs prevalent in the region.

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