Parasitology Research Monographs 17

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Infectious Diseases along the Silk Roads

The Spread of Parasitoses and Culture Past and Today

Springer

Parasitology Research Monographs

Volume 17

Series Editor

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This book series “Parasitology Research Monographs” presents carefully refereed volumes on selected parasitological topics. Parasites have an increasing impact on animal and human health in the present times of globalization and global warming. Parasites may be agents of diseases and- often at the same time- vectors of other agents of disease such as viruses, bacteria, fungi, protozoa and/or worms. The growth in knowledge of parasitic physiology, cell structure, biotechnological and genetic approaches, ecology, therapeutic capabilities, vaccination, immunology, diagnosis, transmission pathways and many other aspects of parasitology is increasing dramatically, even in the face of the breakthroughs that have already been made. Reflecting these most recent achievements and the importance of parasites as a threat to human and animal health, the series’ broad scope concentrates on particularly hot topics emerging from the scientific community. Chapters offer compact but intense insights into the ongoing research and into the methods and technologies used to control parasites. The volumes in the series build on these topics, and the volume editors are well-known experts in their respective fields. Each volume offers 10 to 20 comprehensive reviews covering all relevant aspects of the topic in focus.

Heinz Mehlhorn • Xiaoying Wu •
Zhongdao Wu
Editors

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ISSN 2192-3671 ISSN 2192-368X (electronic)
Parasitology Research Monographs
ISBN 978-3-031-35274-4 ISBN 978-3-031-35275-1 (eBook)
https://doi.org/10.1007/978-3-031-35275-1

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The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Contents

Part I

The Silk Roads: Past and Future

1

Network Expansion and Disease Spread along the Former and Present Straits of the Silk Road(S) and Other International Straits

Heinz Mehlhorn

Abstract

The term Silk Road was created in the Middle Ages for a rather low spectrum of streets (roads) being used to transport goods from China to Europe and back, passing different cultures. However, not only goods had been and are still today (intensively) spread along this pathway, but also agents of (often) severe diseases. Thus, constant control systems have to be established and permanently controlled with respect to their efficacy. Today, it takes only a few days (if not hours) until persons, goods, and agents of diseases are transported from one continent to the other. The old and the present pathways are enlarged daily, thus increasing the worldwide network.

Keywords

Cultural and economic spread · Pathways of wandering diseases as severe epidemics · Control measurements · Worldwide transportation of agents of diseases by cars · Ships · Planes

The precursors of the recent mankind on earth apparently started their successful leadership in rather small groups, which had been able to adapt themselves to the changing of living conditions in special regions, which forced them to develop capacities to get sufficient food for the slowly but continuously growing mankind. This afforded that mankind had to organize a constant spreading of groups, which finally settled on all continents. Wandering human groups and their contacts with animals, which mostly had been ingested in a raw or poorly cooked status, helped to spread permanently a broad spectrum of agents of diseases among groups of many

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_1

persons and animals. Since the temperatures varied on the different continents, humans started very early contacts with other humans in other regions of their own continent and in other ones. This led to the fact that in former centuries agents of diseases were easily spread potentially in a few months and today even within a few days. Since at the beginning the symptoms of infections are mostly rather low-graded and thus mostly not noted immediately, agents of diseases had and have significant changes to become easily spread—especially in countries where many people live close together.

1.1 Examples of Agents of Selected Diseases along the Silk Roads and further Related Sites

Thus, the spreading of humans (sensu stricto "homo sapiens") around the globe led to the fact that also agents of diseases are spread, often leading to high death rates among people in regions where people had not been infected before. The increasing business contacts between people in Eastern, Western, Northern, and Southern regions on earth induced the spreading of severe, often fatal diseases. Thus, it was not astonishing that different and often severe diseases become spread via business activities from continent to continent. Some of them had been spread in special periods as shown below:

- Cholera: ~1500 BC in China.
- Tuberculosis: ~730 BC in Palestine.
- Plague of Justinian: ~600–750 AD in Palestine.
- Plague in Europe (1347–1353) killing about one-third of the population.
- Repeated plague epidemics: e.g., fifteenth century in Germany, sixteenth century in Southern Europe, seventeenth century in Italy and England, fifteenth century in France, nineteenth century in India and surrounding regions, 1910–1911 in Manduria, 1946–1947 in Algeria and later single case imported, but individually treated in Europe.
- So-called "large plague" (1615) starting in London and spreading from there to Europe.
- Plague also occurred in countries in East and North Europe in 1707–1713.
- So-called Indian Ganges-Brahmaputra pandemic spreading in whole Asia (1817–1823).
- Second large cholera pandemic (1826–1837) in various countries in America, Europe, North Africa, and Asia.
- Plague epidemic in China (1855) growing up to a worldwide pandemic.
- Repeated plague epidemics starting in 1885 and spreading into Europe and America.
- 1865–1896: fourth and fifth cholera pandemic
- 1892: Cholera epidemic in Hamburg, Germany
- 1894–1912: Worldwide plague pandemic in countries in Asia, Europe, and North and South America

- 1918–1920: Influenza pandemic (Spanish flu): about 30 million death cases in Europe
- 1918: Spotted fever in Russia
- 1957–1958: Asian flu (A-H2N2)
- 1961: Start of the seventh cholera pandemic, which is still ongoing today
- 1976: First Ebola epidemic in Zaire
- 1980: Starting of the HIV epidemic in the USA
- 1991: Cholera epidemic in the whole of South America
- 2002–2003: Starting of the SARS pandemic
- 2008: Broad dengue fever in Brazil (~300,000 cases per year)
- 2009: So-called Pig flu, still spreading in recent times
- 2015: Zika virus epidemic started in its homelands, spread from there to Brazil, and endangered in the year 2016 also the visitors of the Olympic Games.

1.2 The Shrinking of our Recent World by Enlarging the Former Straits

In the Medieval times, the human world population started increasingly to get into closer contact, whereby goods, culture, and also agents of diseases became spread over the continents. At this time, it was much easier to transport large amounts of goods back and forth on streets stretching from Europe to Asia than across the oceans. However, this type of transport took time, so people got in contact with local people and thus with local agents of diseases, leading to several epidemics (e.g., plague) spreading in both directions. Today, the longest flights may require less than 24 h. Thus, diseases (e.g., plague, coronavirus) can be spread unnoted in many countries. On the other side, helpful goods and new knowledge can be distributed in a few days.

The transportation and exchange of many products were done from Europe to China and back. Since, at this time, one of the transported goods had been silk or silk products, all relevant streets had been named *Silk Road*. This name is still used today, although many more or less parallel streets are actually available to transport goods from the East to the West and back (Fig. 1.1). Since large and economically powerful countries like China, Korea, and India detected African countries and other regions as a growing markets, especially China has developed further “Silk roads” to transport huge amounts of products to Africa and along the African coast to Europe (Fig. 1.1).

The “land-based part of the silk road” (line Shenzhen, China—Duisburg, Germany), which actually covers at least 60 trains per week passing Lanzhou, Almaty, Tashkent, Teheran, Istanbul, Moscow, and Duisburg, is expanding. From there, goods are transported to the Netherlands and Venezia, which is also reached by ships sailing via the South road along East Africa (Fig. 1.1). Thus, both “New Silk Roads” connect by their back and forth activities (via trains and ships) Africa, Asia, South East Asia, and Europe and thus increase the benefits for all countries along their routes. The inclusion of African countries into the activities of Asia and Europe

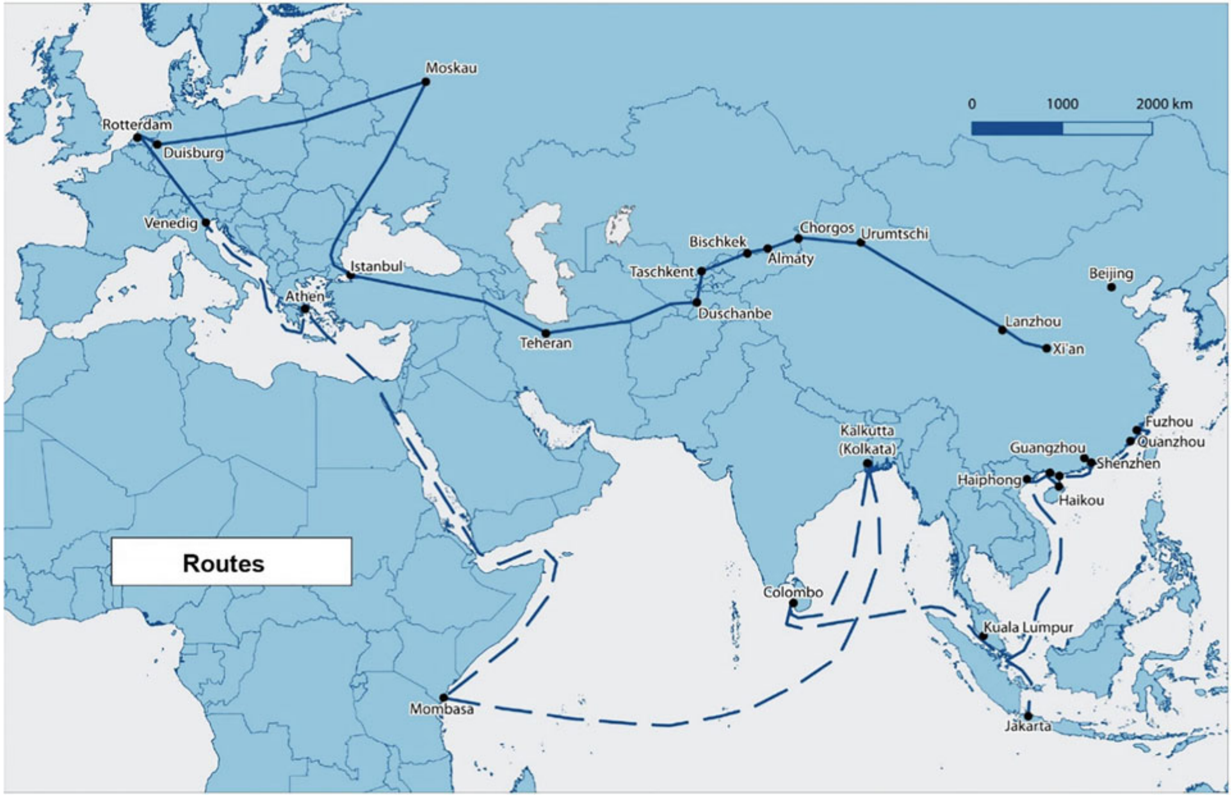

Fig. 1.1 Diagram of actual existing and planned "Silk roads" connecting Asian, African, and European countries enabling quick product exchanges in both directions (Shenzen City planning exhibition): routes by train and routes by ship. P.S.: There are also existing "roads" passing Africa from the South to the Mediterranean coast

is especially important since many of these countries suffer from the ongoing lack of connections to the rest of the world, although their economic potential is large.

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Belt and Road Initiative Revisited

2

Shengyong Qin

Abstract

The Belt and Road Initiative (BRI), as an open international cooperation and development mechanism, is adopted by the Chinese government in 2013 to build connectivity and co-operation across six main economic corridors along Silk Road Economic Belt and Maritime Silk Road. The initiative to jointly build the Belt and Road, embracing the trend toward a multipolar world, economic globalization, cultural diversity, is designed to uphold the global free trade regime and the open world economy in the spirit of open regional cooperation. The initiative defines five major priorities encompassing policy coordination, infrastructure connectivity; unimpeded trade; financial integration and connecting people. The initiative and its core concepts have been written into documents from the United Nations, G20, APEC and other international and regional organizations. The "Belt and Road" construction is a long-term systematic project with far-reaching implications and an important platform for building a "community of responsibility", a "community of interests" that shares weal and woe, and a "community of shared future " for China, countries along the route and other countries in the world.

Keywords

Belt and Road Initiative · Connectivity and co-operation · Five major priorities · Community of shared future

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_2

2.1 Introduction

In September 2013, Chinese President Xi Jinping introduced the concept of the Silk Road Economic Belt during a visit to Kazakhstan. Just a few months later, China announced that the realization of the Silk Road Economic Belt would be seen as a key policy priority and also the concept of the Twenty-First Century Maritime Silk Road was declared. Both these concepts are part of the Chinese government's action plan called The One Belt, One Road (OBOR) initiative, or later also termed the Belt and Road Initiative (BRI).

The Belt and Road Initiative is a major concept put forward based on profound changes in the international and domestic situation and aims to coordinate the overall international and domestic situation. It is an important part of Xi Jinping Thought on Socialism with Chinese Characteristics for a New Era, and furthermore it is in line with world peace and development. BRI is in accordance with the pursuit of the "Chinese Dream" of the great cause of national rejuvenation. The joint construction of BRI has specific connotations, implications, and requirements of the era and has gradually become the general consensus and common expectation of the international community, and it has received positive responses from the vast majority of countries and international organizations.

2.2 International Background of BRI

Complex and profound changes are taking place in the world. The underlying impact of the international financial crisis keeps emerging; the world economy is recovering slowly, and global development is uneven; the international trade and investment landscape and rules for multilateral trade and investment are undergoing major adjustments; the contagious diseases in this globe are the paramount challenge to people's health; and countries still face big challenges to their development. The initiative to jointly build the Belt and Road, embracing the trend toward a multipolar world, economic globalization, and cultural diversity, is designed to uphold the global free trade regime and the open world economy in the spirit of open regional cooperation. It is aimed at promoting orderly and free flow of economic factors, highly efficient allocation of resources, and deep integration of markets; encouraging the countries along the Belt and Road to achieve economic policy coordination and carry out broader and more in-depth regional cooperation of higher standards; and jointly creating an open, inclusive, and balanced regional economic cooperation architecture that benefits all. Jointly building the Belt and Road is in the interests of the world community. Reflecting the common ideals and pursuit of human societies, it is a positive endeavor to seek new models of international cooperation and global governance, and it will inject new positive energy into world peace and development.

2.3 The Proposition of Belt and Road Initiative

2.3.1 One Belt

Silk Road Economic Belt is a new economic development area formed on the basis of the concept of Ancient Silk Road. The Silk Road Economic Belt, which links the Asia-Pacific Economic Circle to the east and the European Economic Circle to the west, is considered to be “the longest and most promising economic corridor in the world.”

This concept derives from the speech made by President Xi Jinping at the Indonesian Parliament On October 3, 2013; it goes, “China is willing to strengthen maritime cooperation with ASEAN countries, make good use of the China-ASEAN Maritime Cooperation Fund established by the Chinese government, develop maritime cooperative partnership, and jointly build the “Maritime Silk Road“ in the 21st century.”

2.3.2 One Road

Twenty-First Century Maritime Silk Road is based on history, focusing on the new historical starting point of the tenth anniversary of the establishment of a strategic partnership between China and ASEAN, a strategic vision for the well-being of the people of the region.

Just as President Xi Jinping pointed out on September 7, 2013, in a speech at Nazarbayev University in Kazakhstan, “In order to make the economic ties between countries closer, mutual cooperation deepen, and development space wider, we can use innovative cooperation models to jointly build the “Silk Road Economic Belt,” and gradually form regional cooperation from point to point, from line to film.”

Regarding the geological location of BRI, it encompasses two different routes which draw insights from China’s ancient history. The “Silk Road Economic Belt” referred to as “One Belt,” starts from China and ends in Europe. The “Twenty-First Century Maritime Silk Road” is referred to as “One Road” for short, and it is along the Maritime Silk Road, from the coastal ports of China to the Indian Ocean through the South China Sea, extending to Europe and Africa, or from the coastal ports of China to the South Pacific through the South China Sea.

2.3.3 Comprehensive Network

Along the land silk road, the route ramifies into two directions. One extends through Central Asia and Russia to Europe, and the other crosses Pakistan all the way to the Indian Ocean, Central Asia, and West Asia to the Persian Gulf and Mediterranean countries. China is trying to develop new comprehensive partnerships with these countries and regions and plan to strengthen the infrastructure along the road. Like the Shanghai Cooperation Organization, China, Russia, Kazakhstan, Kyrgyzstan, Tajikistan, and Uzbekistan are all on the Silk Road, and the other five Observer countries and three dialogue partners are also along the Silk Road. China's domestic core area of the Silk Road Economic Belt includes Xinjiang, Qinghai, Gansu, Shanxi, and Ningxia in the northwest, and Chongqing, Sichuan, Guangxi, and Yunnan in the southwest. The main waypoints of the Twenty-First Century Maritime Silk Road include Quanzhou, Fuzhou, Guangzhou, Haikou, Beihai, Hanoi, Kuala Lumpur, Jakarta, Colombo, Calcutta, Nairobi, Athens, and Venice with a purpose to develop economic cooperation between China and Southeast Asia, South Asia, the Middle East, North Africa, and European countries. Xinjiang and Fujian will become China's hub of the BRI and gain unprecedented development opportunities.

2.3.4 Policy Coordination

Policy communication is an important guarantee for the construction of the BRI. Under the premise of deepening the integration of interests, China endeavors to promote political mutual trust and reach a new consensus on cooperation in line with the principle of seeking common ground while reserving differences. Countries along the route are expected to build an exchange mechanism for inter-governmental national policy communication and discuss economic development strategies and countermeasures.

2.3.5 Facility Connectivity

Infrastructure interconnection is a priority area of the "Belt and Road" construction. Based on respecting the sovereignty and security concerns of relevant countries, BRI promotes countries along the route to strengthen the docking of infrastructure construction plans and technical standard systems, and joint construction of international backbone channels, aiming to form an infrastructure network connecting various regions in Asia and between Asia, Europe, and Africa. In the process of carrying out facility connectivity, special emphasis is placed on the green and low-carbon construction and operation management of infrastructure.

2.4 Integration with International Organization and Countries along the Routes

2.4.1 Continuous Expansion of Strategic Cooperation

The BRI has received positive responses from more and more countries and international organizations, and it has become a popular international public product and international cooperation platform in the world today. As of the end of 2022, China has signed more than 200 cooperation documents on the joint construction of the BRI with 145 countries and 32 international organizations, covering investment, trade, finance, technology, society, humanities, people's livelihood, and other fields. At the same time, China actively fulfills its international responsibilities, and under the framework of the joint construction of the BRI, deepens the connection with the development plans and policies of all parties. At the global level, the BRI is effectively aligned with the United Nations' 2030 Agenda for Sustainable Development, forming a policy synergy to promote global common development. At the regional level, the BRI is effectively aligned with regional development plans or cooperation initiatives such as the overarching plan of ASEAN Connectivity, the African Union's Agenda 2063, and the European Union's Eurasian Connectivity Strategy to promote connectivity. BRI is supportive of consensus on the process of regional economic integration.

2.4.2 Fruitful Communication at the Summit Forum

Various systems and mechanisms for the joint construction of the BRI have gradually taken shape. Under the principle of extensive consultation, joint construction, and shared benefits, parties involved strive to build an international platform for extensive consultation, and the International Cooperation Summit Forum of the Belt and Road Initiative has become the highest-level international cooperation platform. In 2017 and 2019, China successfully hosted two International Cooperation Summit Forums. During the first summit forum, 29 heads of state, heads of government, and other leaders attended the forum, and more than 1600 representatives from more than 140 countries and more than 80 international organizations participated in the forum, resulting in 279 specific and practical achievements in 5 categories. At present, all these agreements have been implemented according to the planned schedule, and some of them have been transferred to normal work and will continue to be put forward. The second summit forum attracted more countries and international organizations to participate and therefore achieved more fruitful results. China proposed to build a global connectivity partnership to start a new journey of high-quality joint construction of the Belt and Road. China has been preparing for the third summit forum since the zero-Covid-19 policy was lifted in September 2022.

2.5 The Implications of the Belt and Road Initiative

The Belt and Road Initiative originated in ancient China, but it has been endowed with a distinct connotation of the times. The "Vision and Actions for Jointly Building the Silk Road Economic Belt and the Twenty-First Century Maritime Silk Road" (hereinafter referred to as the "Vision and Actions") issued by the Chinese government clearly states, "Promoting the 'Silk Road Economic Belt' and the 'twenty-first Century Maritime Silk Road' the construction of the Silk Road is a major initiative and concept proposed by Xi Jinping to coordinate both domestic and international situations, conform to the trend of regional and global cooperation, and meet the development needs of countries and regions along the route. It is an initiative, not a strategy, and its goal is to build a community of responsibility, a community of interests, and a community of destiny in countries and regions along the 'Belt and Road'."(http://keywords.china.org.cn/index.htm n.d.) Xi Jinping emphasized that the joint construction of the "Belt and Road" initiative is "Combining the development of our country with the development of the countries along the route, combining the Chinese dream with the dreams of the people of the countries along the route, and giving the ancient Silk Road a brand-new era connotation."

The "Belt and Road" construction is a long-term systematic project with far-reaching implications. As President Xi Jinping pointed out, "jointly building the Belt and Road opens up new space for world economic growth, builds a new platform for international trade and investment, expands new practices for improving global economic governance, and contributes to improving people's well-being in all countries. New contributions have become a common road of opportunity and prosperity." Facts have proved that the joint construction of the Belt and Road is mutually beneficial.

(1) Forming a new pattern of comprehensive opening-up.

Deng Xiaoping, the chief architect of reform and opening-up, pointed out, "The current world is an open world, and one is for foreign countries and the other is for domestic ones, that is, one region vs. another region, one sector vs. another sector." Nowadays, both are closed. Today's world is facing trade protectionism, unilateralism, and severe challenges of anti-globalization and isolationism, a trend of anti-globalization and anti-globalization is intensifying, and it is eroding the political and economic mutual trust between countries. An open China and an open world are facing increasingly prominent new contradictions and challenges. Build a new system of comprehensive opening-up and form a new pattern of comprehensive opening-up. The joint construction of the Belt and Road initiative is a major measure for China to implement all-round opening-up under the new historical conditions, and it is an important platform for forming a new pattern of comprehensive opening-up. The joint construction of the "Belt and Road" will help to form a new pattern of domestic all-round opening to the outside world with mutual aid between the East, China, and the West, and coordination of land and sea. Since the reform and opening-up, my country has gradually expanded its opening to the outside world along the path of "special economic zones—coastal open cities—coastal economic open areas—riverside and inland open cities—border open cities—inland." Although fruitful results have been achieved, there are still problems such as the lack of coordination between "bringing in" and "going out," unbalanced development of opening-up between regions, and the overall level and overall level of opening-up is not high. Therefore, "we must focus on the 'Belt and Road,' insist on paying equal attention to bringing in and going global, follow the principle of extensive consultation, joint contribution, and shared benefits, and strengthen openness and cooperation in innovation capabilities.

The integration of national strategies such as the development of the Yangtze River Economic Belt, with the development of the West, the revitalization of the northeast, the rise of the middle, the development of the east, and the development of the border.

The combination of these two strategies and openness will lead to the formation of a situation of all-round opening-up and the joint development of the eastern, central, and western regions. Promoting the construction of the "Belt and Road" needs to follow an objective avenue. The economic law requires that we should pay equal attention to bringing in and going out and continuously improve the level of an open economy by cultivating new trade formats and models, innovating foreign investment methods, and optimizing regional opening-up layouts. The comprehensive opening of the new pattern provides a new platform and injects new vitality.

The joint construction of the "Belt and Road" will help to form a new pattern of all-round opening-up across the Eurasian continent and even the world. For a long time, the world open system has been dominated by a few Western countries such as the United States, and the rules of world trade, investment, and cooperation have also been established and implemented mainly by a few Western countries such as the United States. The role of status is extremely unbalanced, and there is a lack of fair voice and equal development rights. A small number of developed countries can take advantage of the right to formulate international rules, the right to price commodities, and the right to speak in international affairs to obtain huge profits, resulting in the ever-widening gap between the "North and South" in the world. Mutual respect, equal dialogue, wholehearted treatment, mutually beneficial cooperation, and win–win sharing among all parties involved in the joint construction of the "Belt and Road" fully tap the potential of economic growth through each party's best efforts, complement each other's advantages and share interests, and continuously expand economic exchanges and cooperation, to promote the common economic development of all countries, and strive to provide a new platform and inject new vitality for the formation of a new pattern of all-round opening-up across the Eurasian continent and even the world.

(2) Open up a new model of international cooperation.

President Xi Jinping pointed out, "From a historical perspective, human beings are in an era of great development, great change and great adjustment. The world's multi-polarization, economic globalization, social informatization, and cultural diversification are developing in depth, and the general trend of peaceful development is becoming stronger and stronger. The pace of innovation continues to move forward. The connection between countries has never been closer than it is today, the yearning for a better life of the people of the world has never been stronger than today, and the means for mankind to overcome difficulties have never been as rich as today." The "One Belt One Road" initiative complies with the requirements of the era of major development, transformation, and adjustment of human society and reflects the strong opposition of the international community to hegemonism and hegemony in international economic cooperation and exchanges. China has a strong desire to build a new type of international cooperative relationship with mutually beneficial cooperation, sharing, and win–win results as the core and to achieve common development.

The construction of the “Belt and Road” is not about starting from scratch and rebuilding, but to achieve strategic alignment and complementary advantages. Through the joint construction of the “Belt and Road” to build a new type of international cooperative relationship with mutually beneficial cooperation, sharing, and win–win as the core, it is necessary to strengthen cooperation with the United Nations Strategic alignment of multilateral and bilateral cooperation mechanisms such as the World Trade Organization, the World Trade Organization, and Free Trade Agreements; properly handle the strategies or plans formulated by relevant countries and regions that overlap with the “One Belt, One Road” radiation area, such as the “New Silk Road” of the United States, Russia’s “Eurasian Economic Union,” EU’s “Central Asia Partnership,” Japan’s “Silk Road Diplomacy,” Turkey’s “Brexit to Asia” strategy, India’s “Westward Strategy” plan, etc.; and handle national development strategies and policies established by countries within and outside the region. To this end, the joint construction of the “Belt and Road” needs to abide by the purposes and principles of the UN Charter and adhere to open cooperation, harmony and inclusiveness, market operation, and mutual benefit and win–win results. In particular, the humanity should jointly advocate trade liberalism and oppose trade protectionism; advocate multilateralism and oppose unilateralism; advocate the spirit of cooperation and oppose isolationism; and jointly resist any acts that wantonly trample and undermine international rules. The joint construction of the “Belt and Road” is an economic cooperation initiative, not a geopolitical alliance or military alliance; it is a process of openness and inclusiveness, not a closed-door clique or a China club. China welcomes all countries to play zero-sum games as long as they have the will. The joint construction of the “Belt and Road” initiative reflects the international community’s call for openness, equality, mutual benefit, and win–win cooperation and has created a new space for international economic cooperation. A new model of mutually beneficial cooperation, sharing, and win–win cooperation has been established. Countries regardless of size, strength, wealth, civilization, ethnicity, culture, religion, and differences, as long as they agree with the “Belt and Road”, they can participate in the discussion on an equal footing, co-construction, and sharing and can carry out extensive and in-depth equal cooperation to achieve a reasonable division of labor, sharing, and win–win and common development.

(3) Adding new impetus for common development.

As an open platform for equal and mutually beneficial cooperation, the “Belt and Road” not only provides new opportunities for China’s development but also adds new impetus to the countries participating in the “Belt and Road” co-construction to ride on the express train of China’s development and to promote the prosperity and common development of the world economy. After a long period of rapid economic growth in China, labor cost advantages and demographic dividends have been reduced to varying degrees, and structural imbalances such as overcapacity have become increasingly prominent. Whether it is traditional industries such as cement, steel, coal, textiles, home appliances, automobile manufacturing, and civil engineering and construction, or a number of emerging high-tech industries such as photovoltaics and wind power, the utilization rate of their production capacity is generally low, and overcapacity problems occur to varying degrees. However, for most countries within and outside the "Belt and Road" region, China's traditional industries and emerging industries have obvious advantages. In addition, many countries within and outside the "Belt and Road" region are still in the early stages of industrialization, with low levels of economic structure, lagging infrastructure construction, and backward industrial base development; there is huge potential for product demand and investment demand. Therefore, it is necessary to "actively promote the "Belt and Road" international cooperation, strive to achieve policy communication, facility connectivity, unimpeded trade, financial integration, and people-to-people bonds, create a new platform for international cooperation, and add new impetus to common development."(https://www.yidaiyilu.gov.cn/ n.d.)

The joint construction of the "Belt and Road" has distinct characteristics of openness, inclusiveness, and win–win results. More and more countries will inevitably participate in it, which will enable more and more countries to gain new impetus for development. The "Belt and Road" involves 65 countries with a population of 4.4 billion, accounting for 63% of the world's population, with huge market potential. Not only that, the "Belt and Road" routes are also the most dynamic regions in the world's economic development. The average annual growth of foreign trade and foreign capital inflows reached 13.9% and 6.5%, respectively, higher than the world average growth level. The joint construction of the "Belt and Road" aims at openness and inclusiveness and insists on facing the world. As long as they agree with the Silk Road spirit, more than 230 countries in the world can participate in the joint construction. Therefore, both for the countries along the "Belt and Road," and for some other countries in the world, they can share the development opportunities of the "Belt and Road" and reap the fruits of development. Not only that, in line with the new scientific and technological revolution and the new trend of industrial transformation, firmly grasp the development opportunities of networking, digitization and intelligence, in-depth exploration and active promotion of new technologies, new formats, and new models, and also enable participants to participate in the "Belt and Road" initiative. The establishment of a country has obtained a new path of development and new growth momentum, making it a powerful driving force for the economic growth and development of relevant countries and even the world.

(4) Provide new solutions for global governance.

The world today is facing profound changes unseen in a century. The world is increasingly multipolar, the international balance of power is changing profoundly, and global challenges are increasing day by day. This requires not only further strengthening of global governance but also the need to adapt to the new requirements of the times and promote the reform of the global governance system.

To jointly build the “Belt and Road” means to build the “Belt and Road” into a platform for establishing multiple cooperation, a multilateral trading system and realizing common development, a platform for conducting multilateral diplomacy and developing an all-round diplomacy, and an important practical platform for building a community with a shared future for mankind. Through exchanges and mutual learning, dialogue and consultation, and win–win cooperation, we will promote the development of global governance in a more fair and reasonable direction and help build a new type of international relations with mutually beneficial cooperation, sharing, and win–win results as the core. This reflects the interests of the vast majority of countries and meets the general requirements of people all over the world. As Comrade Xi Jinping pointed out, “The joint construction of the ‘Belt and Road’ complies with the inherent requirements of the reform of the global governance system, and demonstrates the need to help each other and share rights and responsibilities. The consciousness of a community with a shared future provides new ideas and solutions for improving the reform of the global governance system.”

At present, the instability and uncertainty of the world are becoming more and more prominent, economic growth is sluggish, the gap between the rich and the poor is intensifying, trade protectionism, unilateralism, populism, and isolationism are on the rise. “Jointly building the ‘Belt and Road’ is not only economic cooperation but also improving the global development model, 3-mode and global governance, and an important way to promote the healthy development of economic globalization,” which is related to the destiny of mankind and the bright future of world development.

The “Belt and Road” initiative is to make the “Belt and Road” a platform for equal communication, exchange, and cooperation between the people of the countries along the route and other countries in the world to promote the interconnection of the countries along the route and some other countries in the world, such as trade, investment, infrastructure, etc., and to promote science and technology. Cooperation and exchanges in education, culture, etc., effectively respond to global common challenges, solve common problems in the world, safeguard the common interests of all countries, adhere to the common values of mankind, accelerate the narrowing of the development gap between different countries and regions, and promote the common development of all countries in the world.

There is only one earth for human beings, and all countries coexist in the same world. They are interdependent and share weal and woe, becoming more and more a community with a shared future where you are in me. “To promote the building of a community with a shared future for mankind with the joint construction of the ‘Belt and Road’ as a practical platform is proposed from the perspective of my country’s reform and opening up and long-term development. Wanbang’s view of the world occupies the commanding heights of international morality.”(http://eng.yidaiyilu.gov.cn/ n.d.) Taking the “Belt and Road” as a practical platform for building a community with a shared future for mankind is to fully implement mutual respect, equal treatment, mutual consultation and mutual understanding, openness and innovation, tolerance and reciprocity, and fairness and justice. The requirements of co-construction and sharing, harmony but difference, inclusiveness, respect for nature, green development, etc., enable all countries to promote common development in planning their own development, take into account the legitimate concerns of other countries when pursuing their own interests, and jointly build lasting peace, openness and inclusiveness, and common prosperity. The joint construction of the "Belt and Road" initiative essentially advocates peace and development, mutual benefit, and win–win results and enables participants to achieve common development. Therefore, all parties should take "hello, hello to me, hello to everyone" as the common concept of international cooperation and move forward together toward building a community with a shared future for mankind.

(5) A new platform to enhance the well-being of all countries.

The "Belt and Road" originated from the ancient Chinese Silk Road, but it faces the future and belongs to the world. Historically, the ancient Silk Road was a road that brought well-being to the people of China and the countries along the route. The recovery of the ancient Silk Road will certainly help the rejuvenation of the Chinese nation and enhance the well-being of all countries in the world. The Swedish explorer Sven Hedin predicted more than 80 years ago: "It is no exaggeration to say that this transportation line (the Silk Road) is the longest road through the whole old world. From a cultural-historical point of view of China, this is the most important link connecting all nations and continents that have ever existed on the earth . . . . If the Chinese government can revive the Silk Road and use modern means of transportation, it will surely help mankind."

The Belt and Road Initiative proposed by the Chinese government not only inherits the spirit of the ancient Silk Road, absorbs the essence of the ancient Silk Road, but also enriches and deepens it, endows it with a specific era connotation, and injects new momentum into it. Seeking happiness for the people, rejuvenation for the nation, and great harmony for the world are the original aspiration, mission, and responsibility of the Communist Party of China. In 2012, Comrade Xi Jinping proposed the Chinese dream of the great rejuvenation of the Chinese nation, and in 2013, he proposed the joint construction of the "Belt and Road" initiative. This is not a historical coincidence but a mission. The joint construction of the "Belt and Road" makes the "Chinese Dream" and the "World Dream" closely linked and mutually beneficial. It is not only a road of trade and friendship, but also a road of win–win and mutual prosperity. The joint construction of the "Belt and Road" can not only further reproduce the prosperous scene of the ancient Silk Road, "envoys meet each other, business travel is endless" and "ships are in the sea, I don't know how many," but also through the joint efforts of all countries in the world to create "people Yin Yin." To this end, "We must adhere to dialogue and consultation, joint construction and sharing, win-win cooperation, and exchanges and mutual learning, seek the greatest common denominator of cooperation with countries along the route, and promote countries to strengthen political mutual trust, economic integration, and cultural exchanges, and advance the implementation one step at a time, grasp the results bit by bit, and promote the joint construction of the 'Belt and Road' to go deeper and more solid, and benefit the people of the countries along the route, promote the building of a community with a shared future for mankind."

The development opportunities and achievements brought by the joint construction of the "Belt and Road" initiative belong not only to China, but also to the world. In order to better promote the construction of the "Belt and Road," allow countries and people around the world to fully share the development opportunities and achievements of the "Belt and Road," and make the achievements of the "Belt and Road" truly benefit all parties, the Chinese government has successively issued the "Vision and Actions" Policy documents such as "Jointly Building the "Belt and Road": Concepts, Practices and China's Contributions" and Assumptions for Maritime Cooperation in the Construction of the "Belt and Road Initiative" have made arrangements for the construction of the "Belt and Road" and have made solid progress in practice. Since the Belt and Road Initiative was put forward, it has not only expanded China's trade and investment, promoted China's economic development, and enhanced the well-being of the Chinese people but also injected new momentum into the recovery of the world economy since the outbreak of the international financial crisis and has provided new impetus for the countries along the Belt and Road and some other countries in the world. Economic development has radiated new vitality and made new contributions to the continuous improvement of the well-being of people around the world.

2.6 Conclusion

BRI not only provides new opportunities for the development of countries around the world but also opens up new horizons for China's opening-up and development. The initiative is of great significance to the economic development of China and the entire world and will certainly play an important role.

The "Belt and Road" is an important platform for building a "community of responsibility," a "community of interests" that shares weal and woe, and a "community of destiny" for China, countries along the route, and other countries in the world. It is an important platform to promote mutually beneficial cooperation and achieve win–win symbiosis. Due to the different economic development conditions, levels, and quality of different countries, as well as different cultures, systems, ethnic groups, and religions, each country faces considerable differences in development issues and interest demands. Therefore, promoting the construction of the "Belt and Road" requires upholding the spirit of cooperation and understanding. In accordance with the requirements of mutual respect, equality and mutual benefit, and win–win sharing, actively respond to the practical concerns of economic and social development of all parties and strive to come up with a rational, pragmatic, and feasible cooperation plan, strengthen communication and coordination between governments of various countries, and sign through equal consultation. The memorandum of understanding on the construction of the "Belt and Road" and the active implementation of relevant regulations and requirements will jointly create a good atmosphere for the construction of the "Belt and Road"; strategically connect the existing multilateral and bilateral cooperation and exchange mechanisms, establish and improve the “Belt and Road” cooperation and exchange mechanism, and effectively perform common responsibilities and obligation; strive to enhance the consensus on the construction of the “Belt and Road,” and jointly respond and cooperate to solve various contradictions, problems, and challenges faced by globalization. As Xi Jinping pointed out, “Human history tells us that it is not scary to have problems. What is scary is that we are afraid to face them and cannot find a solution to them. Facing the opportunities and challenges brought about by economic globalization, the correct choice is to make full use of all opportunities, cooperate to meet all challenges, and guide the direction of globalization in various arenas.”

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Economic Development and Health Care Status in Silk Road Countries

3

Yiming Wu and Liwen Xiao

Abstract

The Belt and Road (B&R) Initiative, proposed by China in 2013, has grown into one of the most promising platforms for international cooperation, forging a new pathway toward inclusive globalization that delivers shared benefits. In addition to to cooperate in infrastructure construction and economy and trade, the B&R construction is still expanding its cooperation fields. It is also a core component of the B&R initiative in ecological environment protection, health governance, security cooperation and other aspects. In order to carry out international cooperation in disease prevention and control, it is important to know the epidemic situation of diseases, medical and health resources in countries along the B&R. This chapter introduces the economic development and health care status of some B&R countries and regions, such as ASEAN, Japan and South Korea, South Asia, Middle East countries and Northeast Africa, to provide a reference for medical cooperation.

Keywords

Silk Road Countries · Economic development · Health care status

3.1 Introduction

In 2013, when President Xi Jinping visited Kazakhstan and Indonesia, respectively, he proposed the construction of the "Silk Road Economic Belt" and the "Twenty-First Century Maritime Silk Road" initiative, which is now referred to as the Belt and

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_3

Road initiative (i.e., BRI). Geographically, the BRI runs through Eurasia, connects the Asia-Pacific economic circle in the east and the European economic circle in the west, and radiates the North American economic circle. It reflects the good wishes of inheriting the spirit of the Silk Road, jointly building an open cooperation platform, and providing new impetus for the cooperation and development of various countries.

The core feature of the BRI lies in the “five links,” among which, financial integration, as the fulcrum for leveraging the grand blueprint of the BRI, is the starting point and necessary condition for enterprises to make transnational investments in the host countries along the route. Since 2014, China has signed cooperation agreements with countries along the BRI in batches, and strengthened the support of multinational enterprises for investment in countries along the route. With the support of various funds, China’s top 100 enterprises have gradually invested in more than ten fields such as energy, infrastructure, communications, and the Internet in the countries along the route.

In addition to cooperation in trade and investment, the BRI is also an important guarantee for deepening the coordinated development of regional health industries. In terms of cooperation mechanism construction, talent training, and infectious disease prevention and control, China is policy-oriented and has better introduced the health industry into the strategic layout of the BRI to form development momentum. On the one hand, the cooperation and development of the BRI have been continuously promoted, and the support policies introduced and implemented at the national level have provided policy guarantees for the great development of the health industry. On the other hand, the medical and health services in the countries along the BRI are unevenly developed, and the overall development is in a state of underdevelopment. In 2015, the National Health and Family Planning Commission formulated and implemented the *Three-Year Implementation Plan for Promoting the “Belt and Road” Health Exchange and Cooperation (2015–2017)* to promote the development of the health industry under the BRI from a national strategic perspective.

The reference to the “Healthy Silk Road” first appeared in a speech delivered by President Xi Jinping during his state visit to Uzbekistan on June 22, 2016. He called for joint efforts to build a “Healthy Silk Road,” deepen cooperation in medical and health care, and strengthen cooperation in the fields of infectious disease epidemic notification, disease prevention and control, medical rescue, and traditional medicine. The “Healthy Silk Road” has thus become a new concept in the construction of the BRI. On March 21, 2020, in a message of condolences to French President Emmanuel Macron, President Xi Jinping proposed for the first time the concept of building a “human health community” to improve global public health governance. On June 17 of the same year, Xi Jinping proposed the new concept of a China-Africa health community at the China-Africa Solidarity Anti-epidemic Summit. This has provided new impetus and injected new connotations to the joint construction of the “Healthy Silk Road” between China and Africa.

The spread of COVID-19 continues to pose serious threats to the lives and health of people in various countries. The deficiencies in the medical and health systems of some countries and regions have not been repaired, and the global public health prevention and control mechanism still needs to be improved. In the new stage of development, the high-quality joint construction of the "Belt and Road" will further broaden the healthy road to safeguard people's health and safety, and the global public health governance cooperation mechanism will continue to be improved.

The following section shows the economic development and health care status of some Silk Road regions such as ASEAN, Japan and South Korea, South Asia, the Middle East, and Northeast Africa.

3.2 ASEAN Countries

ASEAN countries are located in the southeastern part of Asia, bordering China to the north, Australia to the south, the Pacific Ocean to the east, the Indian Ocean to the west, and Bangladesh and India to the west. It is located at the "crossroads" between Asia and Oceania, the Pacific Ocean and the Indian Ocean, with a total area of 4.4356 million square kilometers. There are 10 ASEAN member countries in total. Laos is a landlocked country, Vietnam, Malaysia, Cambodia, Thailand, Myanmar and Brunei are coastal countries, and Singapore, the Philippines, and Indonesia are island countries (Fig. 3.1).

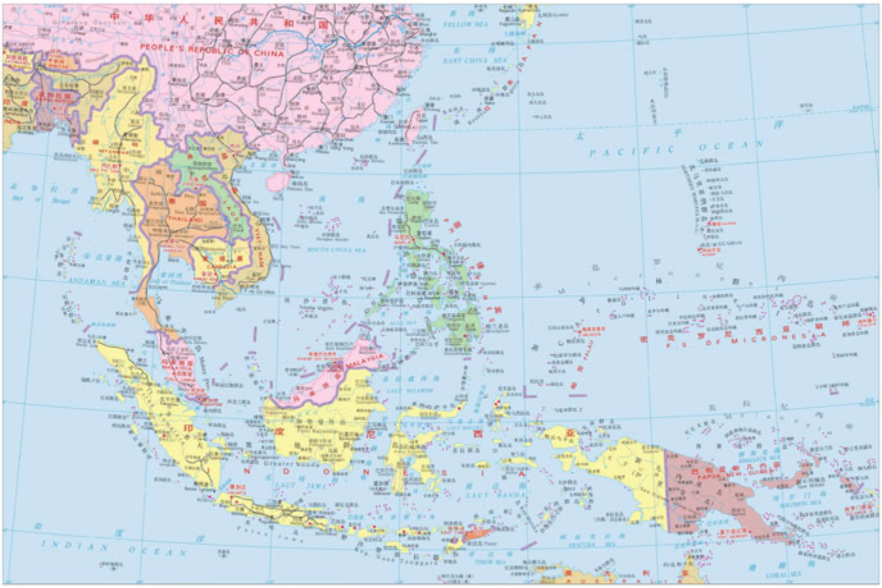

Fig. 3.1 Chinese version of the map of Southeast Asia, http://ditu.ps123.net/world/11340.html1.1 Economic development

3.2.1 Economic Development

In 2019, the total economic volume of the ten ASEAN countries reached US$3.17 trillion, making it the fifth largest economy in the world. There are two high-income countries in ASEAN, Singapore, and Brunei. However, as an economic community, it belongs to emerging economies as a whole. Indonesia is the country with the largest GDP. In 2019, the total economic volume reached 1.12 trillion US dollars, accounting for 35.26% of the entire ASEAN. It is also the only country in ASEAN with a GDP exceeding 1 trillion US dollars. In recent years, the economic growth rates of Cambodia, Myanmar, the Philippines, Vietnam, Indonesia, and Malaysia have all maintained a rapid growth rate of more than 5%. ASEAN is one of the most dynamic regions in the world economy today.

The development of countries in the region shows the characteristics of "rich in the south and poor in the north," and the level of development is inconsistent. At the first level, Singapore is a developed country in the region, and Brunei is an oil-rich country. At the second level, Malaysia, Thailand, the Philippines, and Indonesia are newly industrialized countries. At the third level, Vietnam is developing rapidly. At the fourth level, Cambodia, Laos, and Myanmar have lower levels of development. Most of the ten ASEAN countries are not large in territory, and each has its own characteristics in resource endowment.

3.2.2 Current Status of Medical and Health Care

As a high-risk area for emerging infectious diseases, Southeast Asia has a wide variety of diseases, which brings a heavy health and economic burden to low-income countries. The public health risks facing the region have two dimensions. First, in the context of globalization, public health events in other regions, especially the influx of transnational infectious diseases, have an impact on ASEAN countries. The second is the unique health challenges posed by the specificities of the region.

ASEAN countries have close economic and cultural exchanges with other regions, especially neighboring regions. ASEAN has signed free trade agreements with China, Japan, South Korea, India, Australia, and New Zealand, and the volume of trade with countries outside the region is much higher than within ASEAN (ASEAN Secretariat 2015). The close economic exchanges have also increased the frequency of people's movements, and the increasingly developed international traffic has made Southeast Asia extremely vulnerable to transnational infectious diseases. For example, the fatality rate of SARS in Singapore, the Philippines, Thailand, and Malaysia is higher than the world average. Although Singapore is small, the number of confirmed cases is second only to China and Canada (World Health Organization [WHO] 2003). Influenza A (H5N1) spread further after entering Southeast Asia, and the impact far exceeded the area where the epidemic first broke out, and it has not yet completely subsided. In the COVID-19 outbreak, about 60% of the confirmed cases in Singapore are foreign workers, and the virus infection rate in foreign worker dormitories is about 0.83%, which is nearly 40 times higher than the infection rate in the general community in Singapore (Clement 2020).

The natural environment and level of regional development in Southeast Asia also pose some particular public health challenges. One is the frequent occurrence of infectious diseases closely related to the tropical climate. For example, the intensity of El Niño is one of the predictors of dengue outbreaks in Thailand (Mathuros 2009). When the rainy season comes, mosquitoes will multiply rapidly and in large numbers in places with a lot of standing water. Hot and rainy weather conditions such as in southern Vietnam and the local residents' habits of storing rainwater provide breeding grounds for mosquitoes. Moreover, the outbreak cycle of this disease in Southeast Asia has been shortened from an average of 10 years to 3–5 years, with an average annual number of cases reaching 2.9 million, and the economic loss caused by it in 2010 alone was as high as 950 million US dollars (Caballero-Anthony 2015). Another mosquito-borne disease, malaria, is also prevalent in large strips around the equator in tropical and subtropical regions. The natural environment in Southeast Asia is very suitable for the breeding of Anopheles mosquitoes, and the number of confirmed cases and deaths is second only to Africa.

In terms of natural disasters, earthquakes and tsunamis are also common in Southeast Asia, leaving survivors vulnerable to infectious diseases or deteriorating health conditions. Floods and stagnant water are prone to mosquito breeding, and in conditions of overcrowding and lack of public health products can increase the risk of individual and group disease. Second, Southeast Asia is dominated by developing countries. Unbalanced development has caused rural areas to face greater public health threats than urban areas. For example, the urban areas of the Mekong region are almost free of malaria epidemics, but the disease is quite prevalent in rural areas, including borders and forest fringes (Cui 2012). At the same time, the threat posed by diarrheal diseases cannot be underestimated due to the high proportion of people using unimproved sanitation and drinking water systems in the region. Only 25.8% and 16.1% of Cambodian and Laotian populations have access to safely treated drinking water, and the rural population is only one-third of the urban population (Sustainable Development Goals, n.d.). The latest global outbreak of cholera is beginning in Southeast Asia. Visitors to Southeast Asia are also often plagued by dysentery and diarrhea. In addition, the problem of zoonotic infectious diseases in the region is also very prominent. In recent years, the intensive poultry production system has gradually developed in Vietnam, Laos, Thailand, and other countries, but it has also led to breeding bases becoming potential outbreak sites. Moreover, there are widespread cases of mixing animals in the market to reduce costs, which objectively leads to an increase in the possibility of cross-species transmission of the virus (Weiss and McMichael 2004).

Finally, the absence of an effective surveillance system further magnifies public health risks in Southeast Asia. Surveillance systems are the foundation of disease control. An effective surveillance system can detect outbreaks in a timely manner, respond to disease spread, and facilitate the evaluation of disease control methods. Many infectious diseases in Southeast Asia have zoonotic origins, but as in other resource-poor regions, the capacity of countries to monitor animal health is underdeveloped (Butler 2006). Coupled with the existence of a large number of private hospitals in countries such as Vietnam, they often fail to report malaria and other infectious diseases in a timely manner, resulting in the spread of the epidemic in the country is often seriously underestimated (Delacollette 2009). The failure of disease surveillance systems not only makes disease prevention and control more difficult, but also makes it extremely challenging to develop policies and strategies that balance public health and socioeconomic realities.

To sum up, Southeast Asia faces high regional public health risks due to the characteristics of the geographical environment and the level of socioeconomic development. This not only makes the region a key node for maintaining global health security, but also the frequent occurrence of diseases has become an unfavorable factor for regional economic development. It can be said that Southeast Asia has a strong impetus to carry out coordination and cooperation in the field of public health.

3.3 Japan and South Korea

Japan and South Korea are both located in East Asia and are important economies in Asia. The two countries and China face each other across the sea and have a long history of cultural exchanges. In the past 30 years, the scale of trade and investment between China, Japan, and South Korea has been expanding, and financial and industrial cooperation has become increasingly close. It is an important partner country on the Twenty-First Century Maritime Silk Road (Fig. 3.2).

3.3.1 Economic Development Status

The total economic volume of Japan and South Korea in 2019 reached 6.8 trillion US dollars. Japan reached $5.15 trillion, and South Korea reached $1.65 trillion. Among them, Japan is the first Asian country to enter the ranks of developed countries, and it is the third largest economy in the world, with a per capita GDP of more than 41,000 US dollars. After the “Han River Miracle,” South Korea’s economy has developed rapidly, with a per capita GDP of more than 32,000 US dollars. It has been officially recognized as a developed country in 2021. The real GDP growth of Japan and South Korea has been slow in recent years, especially in Japan, which has been below 2% since 2011, but the unemployment rate has remained low. South Korea’s economic growth rate remained at around 3%, and the unemployment rate was slightly higher than that of Japan.

3.3.2 Current Status of Medical and Health Care

After World War II ended in 1947, Japan’s population health was poor (Japan SBOJ 2016). The health status of Japan’s population has improved since 1950, and the

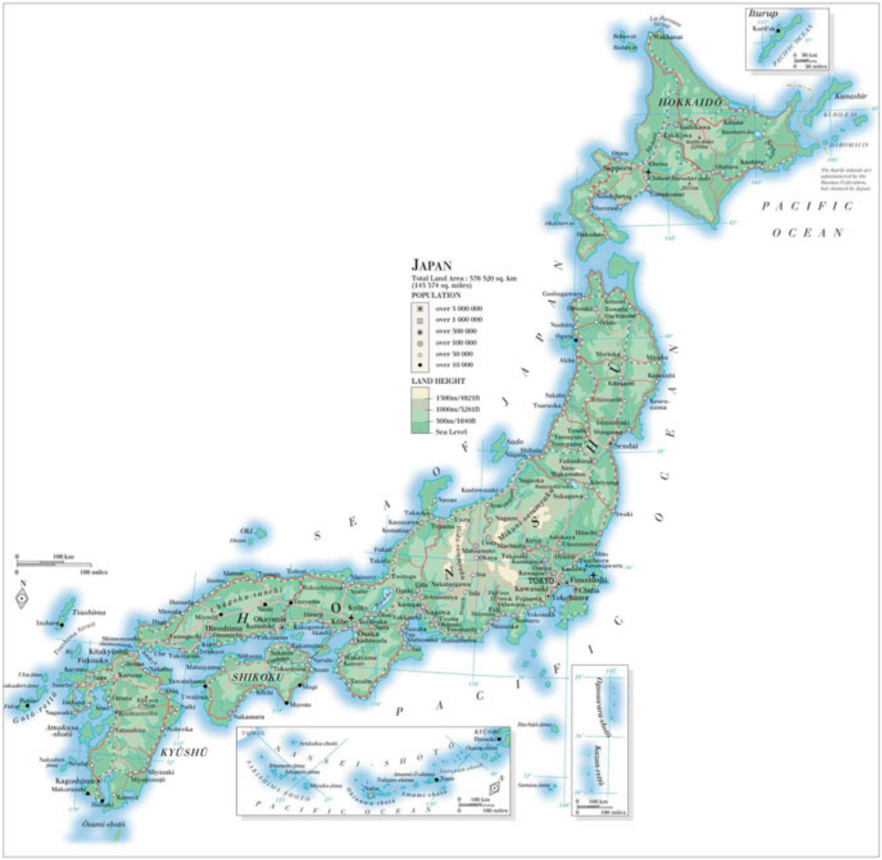

Fig. 3.2 English version of the map of Japan, http://ditu.ps123.net/world/10999.html

decline in mortality was mainly due to Japan's investment in public health in the early post-war period. In the post-war 10 years, 32 health-related laws and regulations were successively promulgated. Japan conducts community-based public health interventions on key factors affecting maternal and child health and the provision of clean water. The Japanese government has taken different measures to deal with the main domestic health problems in different periods. For example, in the 1950s, the main problem was infectious diseases. In 1952, the Japanese government implemented free treatment for tuberculosis patients. With socioeconomic development, noncommunicable diseases have become a major health problem in Japan. In 1969, the Japanese government implemented the strategy of intervening stroke and controlling hypertension, which was extended to the whole country in 1982. In addition, Japan has taken a series of measures to increase the quantity and quality of its health workforce, laying the foundation for Japan to realize UHC (Universal Health Coverage) (Akashi et al. 2015). Japan achieved UHC in 1961, giving its citizens equal opportunities for health promotion. Japan has one of the longest life expectancies in the world. However, Japan's investment in hygiene is not the highest. In 2008, Japan's health expenditure accounted for only 8.5% of GDP, ranking 20th among OECD (Organization for Economic Co-operation and Development) countries (Ikeda et al. 2011). Entering the twenty-first century, health problems caused by population aging, changing disease spectrum, and bad living habits have become increasingly prominent. Therefore, the Ministry of Health, Labour and Welfare of Japan promulgated the "Healthy Japan 21" campaign (Liu et al. 2002). The Japanese government began to implement Long-term Care Insurance (LTCI) in 2000 to deal with increasingly serious aging (Tamiya et al. 2011). In 2016, the elderly population aged 65 and over accounted for 27.28% of the total population (American CIA 2017).

Due to the development of medical technology, the overall quality of life of South Koreans has been improved. The average life expectancy of South Koreans in 1970 was only 61.9 years old, ranking last among the four countries compared with the United States, Japan, and China. The average life expectancy of South Koreans surpassed that of China in 1986, rising to 69.1 years, and surpassed that of the United States in 2002, rising to 77.0 years. The average life expectancy rose further to 81.9 years in 2013. Infant mortality and fertility rates have also fallen sharply, along with a growing elderly population, which has changed South Korea's family structure. The proportion of the population aged 65 and above in the total population in South Korea has increased year by year, while the proportion of the population aged 0 to 14 in the total population has decreased in recent years. It is estimated that in 2050, the proportion of the population over the age of 65 in South Korea will reach 35.9%, making it the second largest population aging country in the world after Japan (40.1%). At the same time, South Korea will also usher in a sharp decline in its population. In 2050, South Korea's population will decrease by 5.7 million, making it the seventh-largest population decline country in the world (Fig. 3.3).

It is worth noting that the average life expectancy of Koreans has increased significantly, but the healthy lifespan is not so long. Healthy lifespan refers to the time free from disease and accidents. In order to improve the national health level, the Korean government is committed to the establishment and improvement of the medical security system. The scale of government medical expenditure has grown rapidly. After the implementation of universal medical insurance in 1989, the growth rate of medical and health expenditure reached the highest level in history, which also stimulated the total medical expenditure in South Korea. In 1977, the Korean medical insurance system was established, and initially only employees of large companies were required to participate in compulsory insurance. In 1980, health insurance spending accounted for only 20% of total health care spending, the lowest level among OECD countries. In 1988, medical insurance achieved universal coverage, allowing any citizen to enjoy medical and health services at any time and at any institution on the premise of sharing a part of the cost. Incorporating a wider population into the medical security system will help improve the overall health of the nation, and it will also contribute to a significant increase in medical investment. In 1960, South Korea's per capita life expectancy ranked second to last among OECD countries. After only 28 years, it reached the average level of OECD

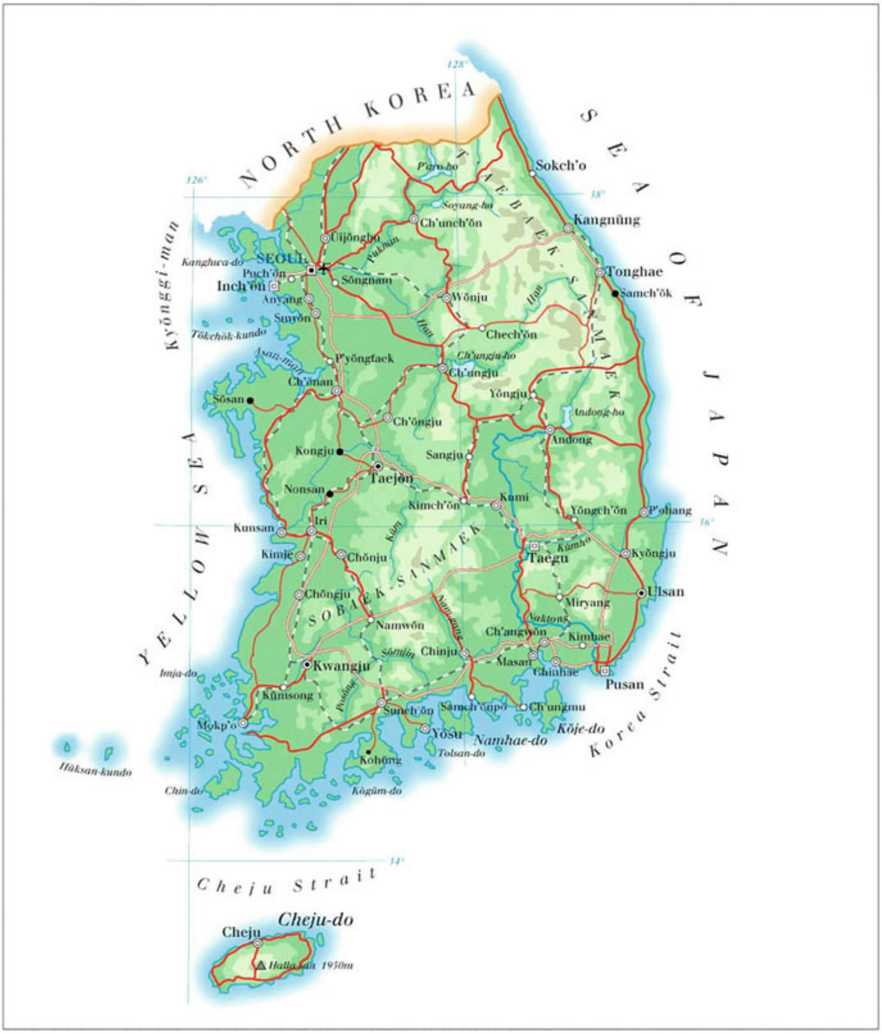

Fig. 3.3 English version of the map of Korea, http://ditu.ps123.net/world/10654.html

countries, while South Korea's per capita income ranked only 22nd among OECD countries. South Korea's achievement is partly due to a reduction in infant mortality and a change in the causes of death. The cause of death due to disease has changed from previous infectious diseases to current chronic diseases and diseases caused by unhealthy lifestyles.

3.4 South Asian Countries

South Asia refers to the vast area between the central and western sections of the Himalayas in southern Asia and the Indian Ocean. It borders the Bay of Bengal to the east and the Arabian Sea to the west, with a total area of about 4.3 million km^2. There are seven countries in South Asia. Nepal and Bhutan are landlocked countries, India, Pakistan, and Bangladesh are coastal countries, and Sri Lanka and Maldives are island countries. Among them, India, Pakistan, Bangladesh, and Sri Lanka are the key countries along the Maritime Silk Road (Fig. 3.4).

3.4.1 Economic Development Status

In recent years, South Asia has been one of the regions with the fastest economic growth in the world, and regional cooperation has developed steadily. On December 7, 1985, the heads of seven South Asian countries adopted the Declaration on South Asian Regional Cooperation and the Charter of the South Asian Association for Regional Cooperation and established the South Asian Association for Regional

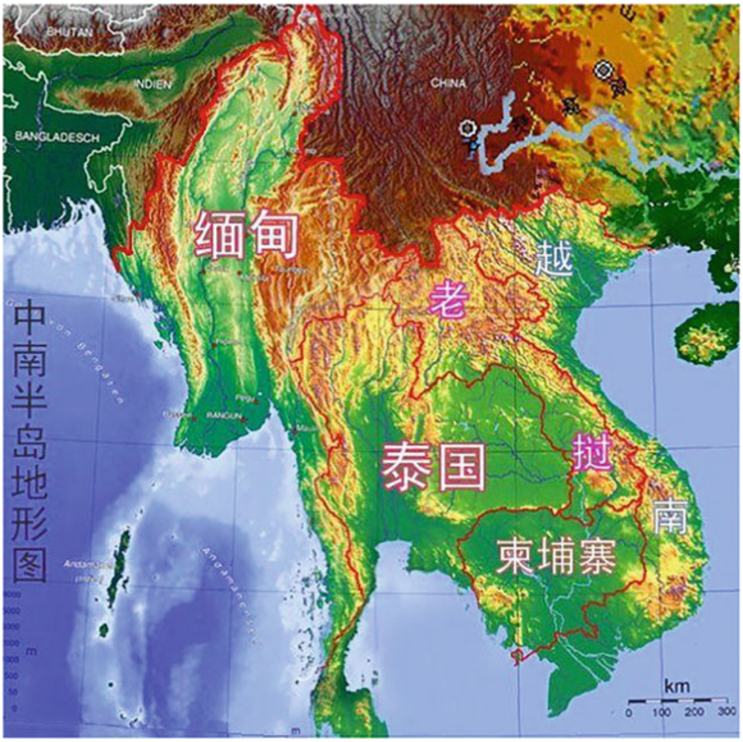

Fig. 3.4 Topographic map of Indochina Peninsula in Asia, http://ditu.ps123.net/world/12975.html

Cooperation (SAARC). Afghanistan joined in November 2005. In April 1997, India, Bangladesh, Nepal, and Bhutan announced the establishment of a sub-regional cooperation organization, named "South Asia Growth Corners." The organization aims to strengthen the development and utilization of natural resources in the economic field of the four countries and promote the overall economic development of the region. At present, all SAARC member states have ratified the South Asia Free Trade Area Agreement and are preparing to establish the South Asian Customs Union and the South Asian Economic Union. With the gradual implementation of measures to simplify visa procedures and reduce tariffs, the flow of people and goods in South Asia is expanding.

There are regional differences in economic growth among countries in South Asia. Among them, India, Pakistan, and Sri Lanka are developing countries, while Bangladesh, Nepal, Bhutan, and Maldives are least developed countries. According to the economic growth rate of each country in 2017 from high to low, South Asian countries can be divided into three gradients. The first gradient has the highest economic growth rate, including Bhutan, Bangladesh, India, and Nepal, with an economic growth rate of 6%–8%. The second gradient economic growth rate is second, including Pakistan and Maldives, whose economic growth rate is between 5% and 6%. The third gradient has the worst economic growth rate, including Sri Lanka, which has an economic growth rate of 4% and below.

3.4.2 Current Status of Medical and Health Care

India is one of the countries most affected by infectious diseases in the world. According to the statistics of the World Health Organization (WHO), the proportion of India's basic health indicators in the world is infant mortality accounted for 23%; leprosy patients accounted for 68%; and tuberculosis patients accounted for 30%. Infectious diseases are a major cause of high infant and child morbidity and mortality, as well as high hospital admissions. Tuberculosis and malaria are currently the two deadliest diseases in India. The budget of the Ministry of Health and Family Welfare of India for the prevention and control of epidemic diseases accounts for about 55% of the total departmental budget. According to World Bank estimates, 29% of India's population lives below the poverty line, and India's agricultural population accounts for about 72% of the total population. Most of these poor people are located in rural areas, their education level is lower than that of other groups in society, and they have a higher prevalence rate. Compared with other groups, poor people have less access to health equipment, and there are also many problems in drinking clean water and sanitation. Not only does India have a large number of poor people, but there are also huge differences in health status between regions and states. The health status of some states is much higher than the national average and can be on par with developed countries, while others are far behind. At the same time, the health priorities considered by each state are also different.

Although there is still a gap between India's various public health indicators and developed countries, India has made remarkable progress in reducing mortality and eliminating other diseases since independence. Since the independence of India, the Indian constitution stipulated a national free medical care system and established a free universal immunization plan and a free treatment project in public hospitals. A government-led public health service system has been established. After more than half a century of improvement, India's medical and health system has achieved great development, which has promoted the development and stability of Indian society.

The infant mortality rate in Pakistan is extremely high, the infant mortality rate is as high as 11%, and the child mortality rate is also 8.33%, mainly related to the high incidence of infectious diseases and childhood diseases. The common and frequently-occurring diseases in Pakistan are cardiovascular disease, chronic hepatitis, and anemia, which indirectly shows that Pakistan's living standards and health and epidemic prevention conditions are poor. This may also have a certain relationship with the mortality rate of infants and young children (Zhang and Liu 2007). Currently, Pakistan's medical field is continuously improving. These medical systems include the national plan for primary medical care, the immunization plan, the state aid control plan, the malaria control plan, the tuberculosis control plan, the cancer treatment plan, and the women's health plan. The implementation of these medical plans has effectively reduced epidemics and infectious diseases, fostered public awareness of health, and promoted sound medical system reforms.

Bangladesh is one of the signatories to the Asian Health Charter and the Almaty Declaration on Primary Health Care. The national constitution stipulates that improving the living conditions of the people, including food, clothing, housing, education, and medical care, is the basic duty of the state. Bangladesh's health policy is aligned with the Health for All Strategy 2000, which has resulted in a health development strategy focusing on primary health care. The government's policy of providing health services for the entire population, 90% of whom live in rural areas, is the basis for the establishment of a national primary health care network, so the focus has accordingly shifted to rural primary health care. Although more than 50% of the health budget is allocated to primary health care and related services, due to the rising cost of health care, Bangladesh is doing everything possible to mobilize the resources of the whole society for medical services. Steps it has already taken include charging some hospital services to secure income and developing traditional and homeopathic medicine systems to make better use of local resources.

3.5 Middle East Countries

The Middle East is the region with the most complex security situation in the world today. The Middle East is the place where East and West meet, and it is also the region where Christianity and Islam clash most fiercely. Among the more than 20 countries in the Middle East, there are five major powers: Saudi Arabia, Iran, Turkey, Egypt, and Israel. The complex geopolitics and doctrinal politics, as well as the domestic turmoil of major powers in the Middle East, have brought new opportunities and challenges to the implementation of the Belt and Road Initiative in the region (Fig. 3.5).

Fig. 3.5 Map of the Middle East (geomorphic map), http://ditu.ps123.net/world/5166.html

3.5.1 Economic Development Status

In 2019, the population of the Middle East was about 500 million, accounting for 7.1% of the world's total, but its gross domestic product was only US$2.81 trillion, accounting for only 3.3% of the global total. The growth rate of the Middle East economy was 1.3%, far below the global average growth rate of 3.7%. The trade volume of the Middle East accounts for only 4.7% of the global total. In the total foreign direct investment stock of the United States, the share in the Middle East only accounts for 1.5%, and the trade value only accounts for 3.7%.

At present, the world is undergoing profound changes unseen in a century, and the international structure and system are undergoing profound adjustments. The majority of developing countries have greatly improved their voice in global political life, and the diversity of world civilizations has become more prominent. The Middle East countries straddle the Asian and African continents and are the core area of the global energy supply. China and the Middle East countries are both important political forces on the international stage. As one of the important participants and founders of the Silk Road civilization in history, the Middle East countries are located at the intersection of the "Belt and Road" and are natural partners for China to jointly build the "Belt and Road." As of December 2020, China and 13 countries in the Middle East have signed cooperation documents on the joint construction of the "Belt and Road." In 2020, China's foreign direct investment reached 917 billion yuan, a year-on-year increase of 3.3%, and its foreign nonfinancial direct investment was 759.8 billion yuan, a year-on-year decrease of 0.4%. The overall scale of foreign investment remained basically stable. Among them, China's direct investment in the Middle East in 2019 was 19.81 billion yuan, and the main investment countries were the United Arab Emirates, Iraq, Saudi Arabia, and Israel, which were 7.85 billion yuan, 5.77 billion yuan, 4.25 billion yuan, and 1.25 billion yuan, respectively. The Middle East market mainly includes Israel, Kuwait, Saudi Arabia, Iran, the United Arab Emirates, Turkey, and other Gulf countries.

3.5.2 Current Status of Medical and Health Care

The shortcomings of government governance in Middle Eastern countries are prominent, especially the long-term marginalization of the medical and health sector. In the field of health care, the Middle East has been underinvested for many years, the degree of modernization is not high, and there are great differences between rich and poor countries. In particular, the medical and health departments of developing countries in the Middle East are faced with the problems of low budget expenditure, insufficient professionals, and lack of medical supplies. Most Middle Eastern countries spend far less per capita on health care than countries of the same income, and the ratio of medical personnel per 1000 people is far below the WHO-recommended level of 4.5 medical personnel per 1000 people, a figure in Morocco 0.72, and 0.79 in Egypt. Thankfully, about 60% of the population in the Middle East is under the age of 30, and the population structure is younger (Jeremy 2020). Precautionary measures to limit the spread of disease in countries such as Syria, Yemen, Libya, and other countries whose health facilities have been devastated by war are difficult. These countries are unable to cope with the crisis of medical facilities, supplies, and personnel shortages brought about by the sudden outbreak. In Syria, the World Health Organization predicts that 70% of health workers have fled the country, and only 64% of hospitals and 52% of primary health centers are functioning properly.

As the COVID-19 outbreak spirals out of control and accelerates in the Middle East, the humanitarian disaster and political consequences will be unimaginable (Jonathan 2020). The number of refugees and homeless people in Iraq, Syria, Lebanon, and Turkey alone exceeds 12 million. The real situation of cross-infection is unimaginable. The NGO Doctors Without Borders (MSF) has warned that the virus will spread rapidly in the region, especially in refugee camps, where people are highly concentrated and lack necessary sanitation facilities. The recent outbreak of the epidemic in the Middle East has repeatedly shown that the region faces the dual dilemma of preventing and controlling the epidemic and restarting the economy.

3.6 East and North African Countries

East Africa, from Eritrea in the north, to the Rovuma River in the south, the Indian Ocean in the east, and Lake Tanganyika in the west, usually includes Ethiopia, Eritrea, Djibouti, Somalia, Kenya, Uganda, Rwanda, Burundi, Tanzania, and Seychelles.

North Africa, the northern part of the African continent, is customarily the vast area north of the Sahara Desert. It covers an area of 8.37 million square kilometers, including Egypt, Libya, Tunisia, Algeria, Morocco, Sudan, etc. China's medical and health cooperation with African countries, especially with Egypt, Tanzania, and Kenya, is still relatively close. Therefore, this part mainly introduces the economic development and medical and health status of these three countries (Fig. 3.6).

3.6.1 Economic Development Status

On July 1, 2020, Tanzania was included in the middle-income country category by the World Bank, which means that Tanzania achieved this target 5 years ahead of schedule. Tanzania is the second country in East Africa to be included in the middle-income category. According to World Bank criteria, countries with per capita income between US$1006 and US$3955 are middle-income countries. In 2019, Tanzania's economic growth rate reached 7%, which is one of the fastest growing economies in Africa. In the past 10 years, the average annual growth rate of Tanzania's GDP has been about 6.5%. According to data released by the Central Bank of Tanzania, in the 2018/19 fiscal year, Tanzania's total GDP was 129 trillion shillings (57.15 billion US dollars), a growth rate of 7.0%, and per capita GDP was 2.5 million shillings (1104 US dollars).

Kenya implements a "mixed economy" system dominated by the private economy, with the private economy accounting for more than 70% of the overall economy. Agriculture is the largest foreign exchange earning industry in Kenya. Kenya has a relatively developed tourism industry and is the second largest foreign exchange earning industry. Remittances are Kenya's third largest source of foreign exchange. Kenya's industry is relatively developed in East Africa, and domestic consumer goods are basically self-sufficient. According to the latest "2020 Economic Survey" released by the Kenya National Bureau of Statistics (KNBS), Kenya's economic growth rate in 2019 was 5.4%, down from 6.3% in 2018. The rapid growth of the finance and insurance industry and the real estate industry has driven the good performance of the service industry.

In March 2018, President Sisi was successfully re-elected. In April 2019, the amendment to the constitution was passed, and the term of President Sisi can theoretically be extended to 2030, which will help Egypt's long-term political stability and play a strong leading role in economic development. Egypt's infrastructure construction has achieved remarkable results, the economic structural reform has achieved initial results, the investment and business environment has been greatly improved, and the economic growth momentum has been good. Foreign

Fig. 3.6 Map of Africa, http://bzdt.ch.mnr.gov.cn/browse.html?picId=%224o28b0625501ad13015501ad2bfc0455%22

exchange reserves, the level of foreign investment attraction, industrial production capacity, and export capacity have been continuously enhanced, and the tourism industry has recovered strongly. In addition, Egypt has also taken some positive measures to alleviate the development difficulties of small and medium-sized enterprises.

3.6.2 Current Status of Medical and Health Care

In recent years, the epidemic of infectious diseases in East Africa has been contained to a certain extent, but it still faces multiple health threats. In addition to common AIDS, malaria, tuberculosis, and other infectious diseases, East Africa and the whole of Africa also face the threat of chronic noncommunicable diseases and emerging infectious diseases. Chronic diseases account for one-third of all deaths in Tanzania each year, and by 2030, chronic disease-related deaths are projected to surpass infectious diseases (Christopher et al. 2016). In addition, East Africa and even Africa are also facing the threat of a variety of emerging infectious diseases that first appeared in developing countries such as Africa. Among the ten known emerging infectious diseases pointed out by the World Health Organization, five kinds first appeared in Africa, and six kinds have been or are raging in many places, mainly including Rift Valley fever, Lassa fever, Ebola, and so on (Nathan et al. 2020).

Currently, Tanzania and Kenya do not have a systematic public health system; they are all integrated into the health care system under the overall national framework, which can be roughly divided into the following four categories according to different implementation entities: first, the government-led public health system; second, international organizations and social organizations that focus on the prevention and control of certain infectious diseases; third, disease and health research institutions that focus on scientific research; and fourth, a small number of private public health agencies and faith-based organizations (FBOs). On the whole, the development of medical and health services in Tanzania and Kenya is constrained by huge financial funding gaps, and receiving external aid has become the main channel to fill the gap. The two countries have a high degree of similarity in receiving external aid funds and aid content. African countries such as Tanzania and Kenya already face multiple health threats, especially chronic diseases, but external aid has not systematically addressed the wider prevalence of chronic diseases. Existing public health systems and governance practices in Tanzania and Kenya take into account the fact that infectious diseases are a major health threat and have achieved remarkable results. At the same time, the East African public health system, which relies heavily on external aid, is rife with the over-commercialization of the medical and health sector spawned by neoliberalism, further increasing the disease burden on the local people.

According to statistics from the World Health Organization, in 2015, Egypt's national recurrent health care expenditure accounted for 4.2% of GDP. According to purchasing power parity, Egypt's per capita recurrent health care expenditure is 495.2 US dollars. In 2016, the average life expectancy in Egypt was 61.1 years.

According to data released by the Egyptian Central Public Mobilization and Statistics Agency (CAPMAS), the average life expectancy of Egyptian women in 2017 was 73.6 years, and the average life expectancy of men was 70.8 years. By comparison, in 2006, the average life expectancy for women in Egypt was 69.1 years and for men was 66.5 years.

In 2017, the Egyptian Parliament passed the "Comprehensive Medical Insurance Law," taking the lead in establishing a comprehensive medical insurance system in Port Said Province, which will be gradually expanded to Suez and Ismailia (the first phase of implementation). Egypt plans to fully establish a medical insurance system within 15 years (in 6 stages). In 2017, 46.9% of women participated in health insurance, and the participation rate of men was 54.6%.

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Traditional Medicines Along the BRI Countries

4

Xiaoying Wu

Abstract

Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illness. All kinds of folk medicine and traditional medical systems all over the world are also within the scope of traditional medicine. Traditional Chinese medicine (TCM) is a complete system of healing that developed in China about 3000 years ago, and includes herbal medicine, acupuncture, moxibustion and massage, etc. Indian traditional medicine, named Ayurveda, is Sanskrit, which is translated into "Ayurveda" or "life Veda medicine". Ayurvedic traditional medicine can be traced back to the Vedic era in 5000 BC. Mongolian traditional medicine and Arab traditional medicine are also an important part of traditional medicine in the world. Traditional medicines in history was also exchanged and spread along the BRI counties. It has made a great contribution to the development of modern medicine. To date, TCM in China have a high level of support from the government. The disciplinary development of TCM should embrace inheritance and innovation, and explore the scientific research and transformation of clinical experience. With the development of BRI, the traditional medical exchanges and cooperation will be more frequently, and make greater benefit to local people.

Keywords

Traditional Chinese medicine · Indian traditional medicine · Mongolian traditional medicine · Arab traditional medicine · Exchange, BRI

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_4

In 2013, China proposed its Belt and Road Initiative (BRI) to promote trade, infrastructure, and commercial associations with 65 countries in Asia, Africa, and Europe, including East Asia (Mongolia), 18 countries in West Asia, 8 countries in South Asia, 5 countries in Central Asia, 7 countries in CIS, and 16 countries in central and Eastern Europe. This initiative contains important health components (Tang et al. 2017). Since ancient times, the Belt and Road has been a road for communication and exchange. The ancient Silk Road is not only a road of commerce and trade but also a road of cultural communication and integration. It promoted the exchange and integration of civilizations and became an important chapter in the history of human civilization's exchanges and mutual learning.

It is reported that 80% of the population in the developing world relies on traditional medicine, and 70–80% of the population in developed countries utilized complementary therapies. Traditional medicine of various countries in history was also exchanged and spread along the BRI. It has made a great contribution to the development of modern medicine, such as anti-malaria drug artemisinin (Zhang 2016; Chang 2016; Yang et al. 2020). The World Health Organization (2008) defines traditional medicine as "the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses." Two examples of widely known traditional systems of medicine include traditional Chinese medicine (TCM) and Ayurvedic medicine. Traditional Chinese medicine (TCM) is recognized as a traditional medicine in the world. In addition to traditional Chinese medicine, traditional medicine also includes Indian medicine and Arab medicine. All kinds of folk medicine and traditional medical systems all over the world are also within the scope of traditional medicine (Raja Ikram et al. 2015; Othman and Farooqui 2015).

4.1 Traditional Chinese Medicine

Traditional Chinese medicine (TCM) is a complete system of healing that developed in China about 3000 years ago and includes herbal medicine, acupuncture, moxibustion, massage, etc. (Tang et al. 2008; Zhou 2010). There is a long history for current TCM. It is generally believed that the term of traditional Chinese medicine came into being after the introduction of Western medicine (Wang et al. 2008). TCM is used exclusively to refer to the original medicine or medical practitioner in China. "Zhongyi" first appeared in Hanshu Yiwenzhi. It refers to doctors with medium medical abilities. There are two kinds of usages: verb object phrases and nouns. When used as verb-object phrase, "Zhongyi" means according to the principles of Chinese medicine. As a noun, "Zhongyi" contains two kinds of meanings: ancient and modern. Ancient meaning refers to the middle level of doctors or medical techniques and extends to ordinary doctors or medical techniques. Modern meaning refers to the original Chinese medicine or people engaging in original Chinese medicine. TCM was earliest recorded in 1857 before the introduction of Western medicine. There are variant names of TCM, such as Qihuang, Hua medicine, Old medicine, Guoyi, Han medicine, etc. Guoyi was first proposed by ZHANG Tai-yan in 1923 (Zhu 2017). After the founding of the People's Republic of China, ethnic medicine and "traditional Chinese medicine" went from coexisting to gradually being included in the category of "traditional Chinese medicine." "Traditional Chinese medicine" derives the two meanings of "Chinese traditional medicine" in the broad sense and "Han national medicine" in the narrow sense. With the promulgation and implementation of the of the People's Republic of China on Traditional Chinese Medicine Law, the term "traditional Chinese medicine" officially contains the collective meaning of the national medicine of all ethnic groups in the legal level (Bi and Zhang 2022).

TCM is one of the earliest medical/healing systems developed and matured more than 2000 years ago. TCM includes herbal medicine, acupuncture, moxibustion, etc., which is a fully institutionalized part of the Chinese healthcare system. It is known that the basic theories of TCM were formed more than 2000 years ago. Many distinguished classical books (e.g., Huangdi's Classic of 81 Medical Problems, Treatise on Cold-Induced and Miscellaneous Diseases, Shennong's Herbal, The Pulse Classic and Treatise on Cause and Symptoms of Diseases) in Chinese have been written to decipher the basic TCM theories and concepts. The basic TCM concepts and theories include qi, yinyang, five phases, the human body channel system, zang fu, organ and syndrome, etc. Qi is a very important concept in Chinese philosophy. In TCM, it is considered that the qi is the fundamental substance that constitutes the human body, and the regular movement of qi is essential to maintain human life. Thus, various pathological changes in the human body are attributed to abnormality in the qi. The essence of TCM diagnosis is to understand where the flow of qi has been disturbed and, once known, the aim of treatment is to re-balance the harmonious flow of qi. The theory of yin and yang holds that the world is a material wholeness and the result of the unity and opposition of yin qi and yang qi. The interaction between yin and yang is fundamental for the occurrence, development, and change of things. TCM believes that yin and yang always exist in the human body, and when yin and yang are out of balance, the human body will get sick. Therefore, the core treatment principle of TCM is to restore the proper balance of yin and yang. It has been said that all Chinese medical physiology, pathology, and treatment have been developed based on yin and yang. In TCM theories, five phases or five elements (Wu Xing in Chinese) refer to metal, wood, water, fire, and earth. According to the nature, motion, and interaction of things, the five-phase theory was used to explain the nature of things and the relationship between them. It is believed that there are two equilibrium cycles: a generating cycle and an overcoming cycle. The yin-yang and five phases theories are the fundamental theories in TCM, which lays a general foundation for the specific theories, including the theories related to diagnosis, such as zang fu theory, syndrome differentiation theories, pathology and pathogeny theories, and treatment-related theories like the therapeutical principle, herb prescription compatibility and herb nature, etc. (Li 2008; Oravecz and Mészáros 2012; Xu et al. 2013; Liu et al. 2021).

TCM has many advantages in clinical practice, particularly the knowledge of the phenotypic regularities of the human body and the interaction between the human body and the natural environment. The findings of the meta-analysis suggest that TCM can effectively relieve symptoms, boost patients' recovery, cut the rate of patients developing into severe conditions, and reduce the deterioration rate (Dai et al. 2020; Xu et al. 2022).

The development and inheritance of TCM have a long history in China. Ancient Chinese medicine classics, such as "Neijing," "Nanjing," "Compendium of Materia Medica," and "Treatise on Febrile Diseases and Miscellaneous Diseases" are listed as must-read classics by contemporary TCM scholars. The government pay attention to the construction of TCM institutions and talents, including establishing lots of TCM school and hospitals, vigorously training TCM doctors by combining medical school training, and actively promoting the integration of TCM and Western medicine. Now, TCM has become an important part of China's healthcare system. On October 11, 1958, Mao Zedong pointed out that "Chinese medicine is a great treasures, and should be explored and improved." The central government will give full play to the unique advantages of traditional Chinese Medicine, including improving the service capacity of TCM, developing TCM healthcare and preventive care services, and promoting inheritance and innovation of TCM. For example, China will implement the project of cultivating the clinical advantages of TCM, strengthen the research on the prevention and treatment of dominant diseases with TCM, strengthen the integration of TCM and Western medicine, and improve the clinical efficacy of major difficult and critical diseases (Outline of the Healthy China 2030 Plan).

TCM, as a traditional medicine, has a far-reaching impact on the countries in the Chinese character cultural circle as well as Western countries. It has spread to various countries and derived from it, such as Japanese Han Medicine, Korean medicine in South Korea, Korean medicine in North Korea, Vietnam traditional medicine, etc. The use of TCM has been widely embraced in many developed countries under the name of traditional, complementary, and alternative medicine (TCAM) and is now becoming the mainstream in the UK and the rest of Europe, as well as in North America and Australia (Dashtdar et al. 2016).

4.2 Traditional Indian Medicine

Traditional Indian medicine is one of the oldest medical systems and remains popular worldwide, which includes Ayurveda, Yoga and Naturopathy, Unani, Siddha, Sowa Rigpa, and Homoeopathy. Ayurvedic medicine has some similarities to TCM (Mohammad 2010). Ayurvedic medicine, also named Ayurveda, is Sanskrit, which is translated into "Ayurveda" or "life Veda medicine." Ayurvedic traditional medicine can be traced back to the Vedic era in 5000 BC. The earliest medical textbook, Atreya Samhita, is still used in real life. It is known for being the world's oldest documented comprehensive medical system. In history, Ayurveda was first recorded in Rig Veda, an ancient collection of Indian poetry in 6000 BC. Ayurvedic medicine holds that nature and human body are composed of earth, fire, water, and wind. The three major energies in the human body are also composed of these five elements: ether and air combine to form vata, fire and water combine to form pita, and water and soil combine to form kapha. Once these three vital energy are too much or not enough, people will get sick (Mukherjee et al. 2017; Sen and Chakraborty 2016).

In the Ayurvedic system of medicine, it is considered that a living system is made of panch-mahabuta, in the form of vata, pitta, and kapha at the physical level and satwa, raja, and tama at the mental level. This covers the psychosomatic constitution and is commonly known as the Tridosh theory. The imbalance in these body humors is the basic cause of any type of disease manifestation. To date, several objective parameters have been proposed to monitor the level of these basic humors, but none of them is complete. In this exercise, it is now proposed to consider the free radical theory of diseases as one of the objective parameters. To be more specific, vata can be monitored in terms of membrane-bound signal transduction, pitta as the process of phosphorylation and de-phosphorylation of different proteins (signaling moieties and enzymes), and kapha can be viewed as the degree of gene expression as protein synthesis. This can be correlated with the ojas of the body or total body defense mechanism. Ayurvedic medicine is not only a medical system but also a healthy lifestyle. Ayurveda consists of two words: Ayur refers to life and Veda means knowledge and science. Therefore, Ayurveda means the science of life. According to Ayurveda, human beings should coexist harmoniously with nature, And the disease is because this harmony is broken. The main purpose of Ayurvedic medicine is to restore this basic balance through the use of nature and its products. This concept not only runs through the process of treating pain but also runs through the process of disease prevention (Vyas 1982; Tripathi 2000; Agrawal et al. 2017).

There is evidence that Ayurvedic medicine has enriched almost all medical systems in the world. Through maritime trade with India, Egyptians learned about Ayurvedic medicine. The invasion of Alexander the great brought the Greeks and Romans into contact with Ayurveda. Traditional Unani medicine is formed in this communication. In the early part of the first millennium, with the spread of Buddhism to the East, Ayurvedic medicine also spread to the East and had a great impact on traditional Chinese herbal medicine.

The Indian government is also encouraging evidence-based medicine research to play the more important role of traditional medicine in the healthcare system (Monika Pathania et al. 2020).

The Government of India through its Ministry of AYUSH is responsible for policy formulation, development, and implementation of programs for the growth, development, and propagation of Ayurveda. Different programs have been taken up toward increasing visibility, acceptability, and usage of Ayurveda vis-a vis its integration in the health system. Strategies to globalize and promote Ayurveda are being taken up through AYUSH clusters focusing on the safety-efficacy-quality aspects and rational use of Ayurveda (Katoch et al. 2017).

4.3 Arab-Islamic Traditional Medicine

Arab-Islamic medicine was born in the eighth century A.D. It was formed in the tenth century A.D. on the basis of inheriting the philosophical principles and medical theories of ancient Greek and Roman medicine and integrating the various nationalities around the Mediterranean and Persian and Indian medicine. From the seventh century A.D. to the next one or two hundred years, the Arabs initially established a worldwide empire, the Arab Empire, which stretches from the Spanish Pyrenees in the west to the western border of the Tang Dynasty and the Sindh region of India in the East. The civilization of this empire reached a very high level, and its scientific, technological, and cultural achievements, including medicine. Abu Bakr Muhammad ibn Zakariya Razi (AD 865–925) was not only an outstanding chemist and philosopher, but also a famous physician (Zarrintan et al. 2013, 2014). He has profound knowledge and extensive knowledge. He wrote more than 200 books in his life, especially in medicine (and chemistry). He is known as "the Arab Galen" and "the father of Muslim medicine." In particular, he has rich clinical experience and theoretical knowledge in surgery (such as hernia, kidney and bladder stones, hemorrhoids, joint diseases, etc.), pediatrics (such as infantile dysentery), infectious diseases, and difficult and complicated diseases.

The book named Chahar Maghaleh (Four Discourses) is written by Nizami Aruzi Samarqandi, a Persian writer in the twelfth century. The book records 12 stories that can be regarded as medical records. Through the analysis of the 12 cases, we can get a lot of Arabia-Islamic medical information before and after the twelfth century, including basic concepts, medical academic origin, diagnostic methods, treatment methods, and other content. That reflects the medieval Arabia-Persian society's medical level. Compared with traditional Chinese medicine, ancient Arabia-Persian society had distinct features in medicine, food therapy, external therapy, psychotherapy, and other fields; in the treatment of ideas and methods of diagnosis, they share some similarities with traditional Chinese medicine (Jin 2019). Recently, the term Traditional Arabic and Islamic Medicine (TAIM) was proposed. As a therapeutic system practiced in the Arab world under the influence of the Islamic religion since ancient times, TATM consists of herbs, eating habits, physical and mental exercises, psychotherapy, and applied therapy, many elements of which reflect the lasting interrelationship between Islamic medicine and prophetic influences and regional therapeutic practices derived from specific geographical and cultural origins (Azaizeh et al. 2010).

The development of Arab medicine has gone through three stages. The first phase, in the eighth century, entailed the translation of the medical works of Hippocrates and Galen, philosophical works by Plato and Aristotle, and mathematical works of Euclid and Archimedes into Arabic. Hospitals and medical schools were booming in the Arab world, and several Muslim scholars reached a stature in medical sciences that exceeded that of their predecessors. Among these famous scholars, Rhazes (Al Razi, 846–930) and Avicenna (Ibn Sina, 980–1037), played an important role in commemorating this period as the Golden Age. The final stage of the development of Arab medicine began in the twelfth century when European scholars studied Arab works and translated them into Latin. The most noteworthy example is the translation of Avicenna's Medical Classics, which dominated European medical teachings until the sixteenth century, except for Raz's book Synthesis (Saad et al. 2005; Alrawi and Fetters 2012).

Until recently, TAIM was used in many of the primary books in libraries throughout Europe. Many Arab countries, such as Syria, Morocco, Yemen, Egypt, and others, have studied the TAIM herbs. Ethnopharmacologists recently investigated the potential use of plant species in the Mediterranean, recording 250–290 plant species belonging to different families still in use. The remedies are administered by practitioners in forms of standard decoction prepared by boiling plant parts in hot water, infusion in water or oil, or inhale essential oils. It is also used as juice, syrup, roasted material, fresh salad or fruit, macerated plant parts, oil, milky sap, poultice, and paste. In recent years, remedies based on TAIM herbs have been tested in cooperation with physicians and have begun to prescribe routine prescriptions for patients in Europe and Mediterranean countries (Goldberg 1990; Azaizeh et al. 2010).

Arab traditional medicine has a great influence on the development of world medicine. Arab medicine has also had a great influence on Chinese traditional medicine. There is a dominant opinion in the Western sources of the history of medicine that the roots of modern clinical trials and methodology of experimental medicine first started in the Renaissance. Avicenna's medical canon has influenced Eurasian medicine in history. However, this opinion has been disputed with the thorough study of the rich medical literature of the medieval Islamic era. In the current review, the roots of clinical trial methodology have been traced back to the medieval Islamic tradition and the contribution of Islamic scholars in this field is discussed. The importance of experimental versus theoretical reasoning, the need for a control group, a statistical approach to interpreting trial results, appreciation of uncertainty in medical practice, and the difference between human and animal trials all can be traced back to the rich medieval Islamic medical literature. Despite their history and growing population, knowledge about Arab and Muslim traditional practices as it relates to health and wellness is limited. A better understanding of TAIM and its elements will enhance the ability of clinicians caring for Arab and Muslim patients to provide culturally sensitive care as it relates to their patients' perception of health and well-being, as well as rituals and customs pertaining to the view of healers and the value of traditional therapies (Zarvandi and Sadeghi 2019).

4.4 Exchange of TCM with Other Traditional Medicines

At the beginning of the ancient "Silk Road," traditional Chinese medicine resources (TCM resources) have long been integrated into it, and it was once the "important part" of the ancient "Silk Road" in Chinese history; benefited from this, the political connections were strengthened, the economic trade was developed, and Chinese medicine culture was spread. Before Qing Dynasty, people took out the "silk" and brought back "herbs" on the "Silk Road," which enriched China's medicinal resources. In the later Qing Dynasty and the period of the Republic of China, more scientific and technological methods were brought back from abroad, and this in turn enriched medical research methods, with more than 2000 years' development (Zhang et al. 2018).

Traditional Indian medicine was introduced into China along with Buddhism along the Silk Road. Buddhist medicine is a medical and pharmaceutical system based on the ancient Indian "medical prescription" and guided by Buddhist theory. Early Buddhist medicine was mainly introduced into China through the ancient Silk Road. The introduction of Buddhist medicine through the ancient Silk Road had a great influence on traditional Chinese medicine at that time. Many ancient Chinese medical experts, such as Tao Hongjing in the southern and northern Dynasties, chaoyuanfang in the Sui Dynasty, Sun Simiao in the Tang Dynasty, and so on, have introduced the Buddhist medical theory in their works. After being introduced into China, Buddhist medicine gradually integrated with traditional Chinese medicine. For example, Sun Simiao's "preparation of a thousand gold prescriptions for emergency treatment" said: "where the great treatment of disease, we must be calm and determined, no desire, no demand, the first great compassion, vowing to save the suffering of spirit." This expression reflects the integration of Buddhism and traditional Chinese medicine. This integration promoted the formation of Chinese Buddhist medicine. Since the Tang Dynasty, traditional Chinese medicine has become a part of Chinese traditional medicine (Canton-Alvarez 2019; Li and Lin 2017; Sacamano and Paproski 2020; Wu et al. 2021).

The earliest medical exchanges between Arabia and China can be traced back to the Han Dynasty. The historical records once recorded the "floating Yicao" of Kang juguo and the "Mercury, tulip, Styrax, green wood incense, Coriolis, benzoin" and other drugs of Persia. In the Han Dynasty, Zhang Qian sent envoys to the western regions and brought back walnuts, garlic, beans, pomegranates, safflower, and other medicinal plants. The Ming Dynasty was an era when traditional Chinese medicine absorbed a large amount of Islamic medicine. Islamic medicine also has an important influence on the medical classics of traditional Chinese medicine. In the early Ming Dynasty, both Puji Fang and Li Shizhen's Compendium of Materia Medica recorded back to the medical prescriptions. Islamic medicine also has a certain impact on the medicine of 10 ethnic groups who believe in Islam in China (Na Guangshun 2007); for example, borneol was widely used in Arabia in medieval times. In the Tang Dynasty, borneol has been officially included in the Chinese materia medica works (Xiong and Song 2020).

China advocates the construction of a human health community, and the utilization and development of traditional medicine will play an important role.

Artemisinin shows the contribution of traditional Chinese medicine to global health, and the role of traditional Chinese medicine in the prevention and treatment of infectious diseases has been affirmed. The Chinese government made the development plan for traditional Chinese medicine along "the Belt and Road," which plan proposes that during the "fourteenth five-year plan" period, it will cooperate with countries that jointly build the "the Belt and Road" to build 30 high-quality overseas centers of traditional Chinese medicine, issue 30 international standards for traditional Chinese medicine, create 10 overseas brand projects for the dissemination of traditional Chinese medicine culture, build 50 international cooperation bases for traditional Chinese medicine and a number of national export bases for traditional Chinese medicine services, strengthen the construction of overseas registration service platforms for traditional Chinese medicine products, organize and send medical teams for foreign aid of traditional Chinese medicine, and encourage social forces to explore the construction of Sino foreign friendly traditional Chinese medicine hospitals in a market-oriented manner. These will deepen cooperation in global health governance and strive to build partnerships in traditional medicine (the development plan for promoting the high-quality integration of traditional Chinese medicine into the joint construction of the "the Belt and Road" (2021–2025)).

Understanding the knowledge of our ancestors: "knowledge of our ancestors and learning from nature" should be the paradigm for the coming years. Dr. Rob Verpoorte says, "the support from the medical field should stimulate all researchers in the field to start new collaborations and further improve our efforts in building cases for evidence-based use of traditional medicines. This could build a platform on which in the coming years a further Nobel Prize might be awarded to our field" (Rob Verpoorte 2017).

Today, the silk road has played an immeasurable role in promoting the integration of Eastern and Western cultures. Traditional medicine is an important part of human civilization. As China's unique health resources, economic resources with great potential, scientific and technological resources with original advantages, excellent cultural resources, and important ecological resources, traditional Chinese medicine and medicine of countries along the "Belt and Road Initiative" have complementary and certain comparative advantages. Chinese medicine is going international. We should adhere to the principles of friendly cooperation and peaceful development, actively carry out exchanges and cooperation with countries and regions along the "Belt and Road Initiative" line in medical care, healthcare, medical education, medical research, medical culture, and the health industry, and promote the "two-way integration" of Chinese medicine culture with the international community.

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Part II

Parasite and Disease Spread Along the Silk Roads: A Review to Date

Infectious Diseases in Belt and Road Initiative (BRI) Countries

5

Xiaoying Wu and Zhongdao Wu

Abstract

Infectious disease is the most ancient and common human diseases. In China and BRI countries, there are a variety of infectious diseases. People and animals on the ancient Silk Road have been threatened and tortured by infectious diseases. With the development of the RBI, we are faced with the risk of the spread of various infectious diseases. According on the WHO report, the top 5 of the most serious infectious diseases were tuberculosis, pertussis, tetanus, leprosy and AIDS. Except the central and eastern Europe countries, the standardized disability adjusted life years(DALYs)of BRI counties is higher than China. In addition, mosquito is a vector of many infectious diseases.It is one of important public health problem for controlling mosquito. After the BRI, the risk of imported infectious diseases is increasing, some mosquito-borne diseases are more risky (eg. Malaria). It's necessary to strengthen control of infectious diseases while improving international exchanges and co-operation with B&R countries. Of course, China's formula for success in parasitic and neglected tropical disease control might translate to BRI countries.

Keywords

Infectious diseases · Imported diseases · Disability adjusted life years(DALYs) · Mosquito-born diseases · BRI

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_5

In 2013, China proposed its Belt and Road Initiative (BRI) to promote trade, infrastructure, and commercial associations with 65 countries in Asia, Africa, and Europe, including Southeast Asia, the South Asia region, Central Asian countries, Western Asia, Central and Eastern Europe, Commonwealth of Independent States (CIS) countries, and other regions. This initiative contains important health components (Tang et al. 2017), for example, infectious diseases control.

Infectious diseases of man, animals, and birds are caused by the entry of pathogenic microorganisms into organisms that are susceptible to the given infection. Due to factors such as extreme heat, drought, and war, people and animals on the ancient Silk Road have been threatened and tortured by infectious diseases (Qitao 2017). With the development of the RBI, exchanges between China and foreign countries have become increasingly frequent. At present, we are faced with the risk of the spread of various infectious diseases, including zoonotic infectious diseases such as Brucellosis (Liu et al. 2021) and some unknown diseases such as Behçet disease (Alpsoy et al. 2021).

5.1 Current Status of Infectious Diseases in RBI Countries

Through a systematic review of information and literature of authoritative websites such as the World Health Organization (WHO), the paper summarized and analyzed the regional characteristics of infectious diseases in areas and countries along the China-Proposed Belt and Road Initiative(B&R) from 2009 to 2013 by using literature induction analysis and expert consultation measures. The morbidity rate of 16 kinds in 23 kinds of infectious diseases reported by WHO is higher than that in China. The top 5 of the most serious infectious diseases were tuberculosis, pertussis, tetanus, leprosy, and AIDS (Man et al. 2019).

In Southeast Asia, there are 14 diseases, including diphtheria, endemic treponema, rubella, tuberculosis, leprosy, measles, tetanus, congenital rubella syndrome, neonatal tetanus, pertussis, cholera, malaria, and AIDS, accounting for 60.87% of the common reported infectious diseases. Among them, the incidence of 14 infectious diseases in this area is more serious than in China (Chenchen et al. 2019). In the South Asia region, there are 14 diseases, including diphtheria, pertussis, rubella, cholera, poliomyelitis, tuberculosis, leishmaniasis, mumps, leprosy, measles, malaria, tetanus, neonatal tetanus, and AIDS, and their incidence was higher than that in China. Furthermore, more than half of all countries in South Asia have a higher incidence rate of seven kinds of infectious diseases, such as leprosy, tuberculosis, malaria, AIDS, tetanus, pertussis, and diphtheria, than China (Zhenhong et al. 2019). Also, 16 diseases were reported in the six countries of Central Asian countries in 2013—diphtheria, pertussis, rubella, yellow fever, cholera, poliomyelitis, tuberculosis, leishmaniosis, epidemic parotitis, leprosy, measles, malaria, tetanus, congenital rubella syndrome, neonatal tetanus, AIDS, etc. Compared with China, the incidence of ten diseases, such as AIDS, malaria, cholera, polio, leprosy, tetanus, and neonatal tetanus, is higher in Central Asia (Long et al. 2019). Furthermore, 14 are reported in Western Asia. The morbidity of 12 infectious diseases is higher than that in China. The prevalence of pertussis, leishmaniosis, tetanus, and measles in West Asia is common. For the high potential infectious disease risk from West Asia, it is important that prevention and control systems be improved, such as people who would go to these areas need to pay attention to these infectious diseases and get the vaccine in advance. For these people back from the areas, the epidemic was put under control through isolated treatment, personal protection, medical observation sterilization, and so on to prevent epidemics outside our country (Anjiang et al. 2019). Moreover, 14 kinds of infectious diseases were reported in Central and Eastern Europe, including pertussis, diphtheria, rubella, yellow fever, polio, tuberculosis, leishmaniasis, mumps, jaundice, measles, tetanus, congenital rubella syndrome, neonatal tetanus, and AIDS. Among them, pertussis, tetanus, measles, rubella, and tuberculosis are more serious. The incidence of pertussis in 13 countries was higher than that in China, and tetanus and measles had a pandemic in 2011 (Man et al. 2019). Also, 12 kinds of diseases were reported in CIS countries in 2013, accounting for 52.17%, such as diphtheria, pertussis, rubella, yellow fever, poliomyelitis, tuberculosis, parotitis, measles, tetanus, congenital rubella syndrome, neonatal tetanus, AIDS, etc. Compared with China, the incidence of four diseases, such as pertussis, tuberculosis, AIDS, and diphtheria, is higher in CIS countries. The incidence of four diseases, such as rubella, mumps, measles, and neonatal tetanus, is lower in CIS countries (Chenchen et al. 2019).

5.2 The Disease Burden of Infectious Diseases in RBI Countries

The disease burden refers to the loss caused by illness and early death to the patient, society, and family, including economic loss, deterioration of quality of life, loss of life year, etc. The selected indicator of disease burden is disability-adjusted life year (DALY), which refers to all health life years lost from onset to death, including health life years lost by disease death and health life years lost by disease disability (Murray and Lopez 1994).

Based on the data from WHO, the disease burden of infectious diseases in RBI countries was estimated. In Southeast Asia, the standardized disability-adjusted life years (DALYs) of infectious diseases in 11 countries are 1273–21,132 DALYs/100000. Among them, Cambodia, Myanmar, Laos, and Timor Leste have higher age-standardized burden of infectious diseases, which are 12,889 DALYs/100000, 13,566 DALYs/100000, 21,052 DALYs/100000, and 21,132 DALYs/100000, respectively, higher than the global average (11,315 DALYs/100000), The age-standardized mortality rate of infectious diseases in the other seven countries (Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei, and Vietnam) is lower than the global average. Only Brunei (1273 DALYs/100000) and Singapore (1527 DALYs/100000) have a lower disease burden than China (1858 DALYs/100000). Among the seven countries in South Asia, the age-standardized burden of infectious diseases is 2173–20,789 DALYs/100000. Among them, Pakistan has the highest disease burden, reaching 20,789 DALYs/100000, ranking 122 in the world, followed by India and Nepal, 13,613 DALYs/100000 (119 in the world) and 11,880

DALYs/100000 (116 in the world), respectively. The burden of Maldives is 217.8 million, which is the lowest in the world. The burden of infectious diseases in all countries in the region is higher than that in China. In the six Central Asian countries, the burden of infectious diseases is relatively serious, and the age-standardized burden of infectious diseases is 3834–31,128 DALYs/100000, which is much higher than that in China. Among them, the two countries with the most serious burden are Afghanistan and Tajikistan, with 31,128 DALYs/100000 (139 in the world) and 14,692 DALYs/100000 (120 in the world), respectively. Among the 18 countries in West Asia, the age-standardized burden of infectious diseases is 635–21,708 DALYs/100000. Among them, Yemen is the most serious, followed by Iraq, Azerbaijan, and Jordan. The age-standardized burden of infectious diseases is 7823 DALYs/100000 (106 in the world), 4926 DALYs/100000 (95 in the world), and 3691 Da Lys/100000 (78 in the world). The country with the lightest burden is Qatar, ranking ninth in the world. The burden of infectious diseases in Georgia, Turkey, Armenia, Jordan, Iran, Azerbaijan, Oman, Iraq, and Yemen is higher than that in China. The overall burden of infectious diseases in 16 countries in Central and Eastern Europe is low. The age-standardized delays of 16 countries are far lower than the global average (11,315/100000). Among them, Latvia (2076 DALYs/100000, 57 in the world) and Albania (1927 DALYs/100000, 55 in the world) have a relatively high burden. Except Latvia and Albania, the DALYs of other countries are lower than the average level of Europe (2191 DALYs/100000) and China. Among the four CIS countries, Moldova, Ukraine, and Russia, the death burden of infectious diseases exceeded 3000 DALYs/100000, reaching 3150 DALYs/100000, 3734 DALYs/100000, and 3877 DALYs/100000, respectively, all higher than that of China. Mongolia and Egypt have 5357 DALYs/100000 and 4268 DALYs/100000, respectively, ranking 100th and 85th in the world, much higher than China (Haitao et al. 2019).

5.3 Translation of China's Experiences to Other BRI Counties

The incidence of infectious diseases in BRI counties is very serious, especially for tuberculosis, pertussis, tetanus, leprosy, and AIDS, and other infectious diseases are also in a similar situation. In addition, mosquitos are vectors of many infectious diseases, and they are recognized the leading killers of humans in the world. After the Belt and Road Initiative launches, more countries are involved and international communication and cooperation are significantly growing in China. Therefore, the risk of imported infectious diseases is increasing as well, and some mosquito-borne diseases, which have been well controlled or seldom seen in China, will be more risky to cause local transmission from imported cases and become a threat to people's health in China. It's necessary to strengthen the prevention and control of infectious diseases while improving international exchanges and cooperation with B&R countries (Yaling et al. 2020; Yan et al. 2020; Shengqiang et al. 2018). During his visit to Central Asia and Southeast Asia in 2013, President successively put forward the great strategic initiative of jointly building the Silk Road Economic Belt and the Twenty-First Century Maritime Silk Road (referred to as “the belt and road initiative”). This initiative gives the ancient maritime Silk Road a brand-new connotation of the times (Oliveira et al. 2020).

Before the founding of the People’s Republic of China 70 years ago, parasitic infections and other neglected tropical diseases were highly prevalent. Owing to social development, particularly economic reforms since the 1980s, China’s economic transformation translated into similar and remarkable reductions in neglected tropical diseases. The elimination or near elimination is a public health problem of lymphatic filariasis, malaria, trachoma, soil-transmitted helminth infections, schistosomiasis, and other neglected tropical diseases (Qian et al. 2019, 2020). Of note, neglected tropical disease control and poverty reduction appear to reinforce the other (Wang and Zhou 2020). China’s formula for success in parasitic and neglected tropical disease control might translate to other parts of the world, such as in southeast Asian, through China’s new Belt and Road Initiative(Li et al. 2021).

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6 Disease Details on Plague (Black Death), Cholera, Brucellosis, and Tick-Borne Encephalitis Along the Silk Road(s) of Former and Recent Times

Heinz Mehlhorn

Abstract

The so-called Silk Road connected during the Middle Ages regions of China of our days to Southern regions in Europe, passing countries like Iran, Iraq, Kazakhstan, etc., of our days, since European people wanted materials and products based on silk. These East-Western connections led to cultural connections as well as to the exchange and transfer of severe bacterial diseases like plague and cholera as well as viral diseases like Spring-summer-meningo-encephalitis/tick-borne encephalitis (Fig. 6.1).

Keywords

Plague · Spreading of diseases · Control measurements

6.1 Plague (Black Death): History

Humans spread themselves over all continents on earth. This occurred at different speeds on single continents (like Africa), but reached higher speeds of spreading in the giant regions between Europe of our days and the giant Asia, where many different cultures had grown up, dropped down, and arose again in further cultures around the globe. Neighboring countries started mutual contacts and increased exchange of goods, which were wished/needed by neighbors. These business contacts became more and intensive over the following centuries until today, where transports are done on land, via sea and airplanes.

Since humans, animals, and plants had been transported constantly in former time along these streets, it is clear that not only goods and culture were transported along

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_6

these “streets” but also agents of diseases. Since silk—being developed in China—was and still is today a wanted luxury product in Europe, the name Silk Road was and is also used for several so-called “streets” on land and sea, where over plants, products and disease are constantly spread in increasing amounts.

However, the recent name *Silk Road* was not used for very long times before today, but it was created just in the year 1877 by the German geographer Ferdinand von Richthofen, who apparently also knew the reports of the Venetian businessman Marco Polo, who traveled together with his father and uncle for about 17 years in China and stayed and worked later at the court of the famous Chinese emperor Kublai Khan in different positions before returning to Europe (Italy), where he was blamed at home to have participated in various local cheats. Thus, this name became more and more familiar many years after the Second World War, when international trade became more and more common, so that today transportation lines exist using trains, planes, and very large ships.

Genetic studies of 3800-year-old human bodies showed that these bodies contained two different *Yersinia pestis* genomes that induce the disease plague (black death). Further related detections supported the fact that the so-called Justinian plague, which started in the year 1347 in the regions of the recent countries of Ethiopia and Sudan, endangered Mediterranean Europe and parts of Eastern countries in the years of the sixth century. Further widespread outbreaks and serious plague occurred in Europe in the years 1347–1353 (in Europe passing from along the silk road to other countries), 1910, and 1921. It took until the year 1884 when the French scientist Yersin and the Japanese Kitasato detected at the same time the agent of plague disease (a bacterium). Since then, the disease has been described in many countries by different names (e.g., Black Death). It took until 1898 when the French scientist Paul Louis Simmond published that rat fleas (e.g., *Xenopsylla cheopis*) may transmit the agent of disease. Today it is known that many other flea species (e.g., *Pulex irritans*, *Nosophyllus fasciatus*) may act as vectors, too (Figs. 6.1, 6.2, 6.3, 6.4, 6.5 and 6.6). Intense, worldwide studies documented that the agents of plague may survive and reproduce inside a broad spectrum of hosts (e.g., in total at least 200 mammal species, e.g., dogs, cats, rats, and mice). Besides these animals, humans may also act as direct vectors of the agents of the primary lung plague by coughing.

Fig. 6.1 External aspects of a flea (*Pulex irritans*) seen by a light microscope

6.1.1 Plague (Disease)

1. *Agents of disease: Yersinia pestis* strains (bacteria) belong to the family of Enterobacteriaceae. They are pleomorph, aerobic, Gram-negative, nonmotile, and rod-shaped and can become cultured rather easily using different agar media. Worldwide exist various strains, which all have relationships with *Yersinia pseudotuberculosis*. In former times, several outbreaks with millions of human death cases have occurred worldwide due to the peculiar species (*Yersinia pestis*) being spread all over the earth and thus was also spread along the Silk Road. The discovery of this agent of disease was published at the same time (1884) by two young scientists:
   (a) Alexandre Émile Jean Yersin in the laboratory of Louis Pasteur (Paris).
   (b) Kitasato Shibasaburō in Hong Kong, a co-worker of Robert Koch.

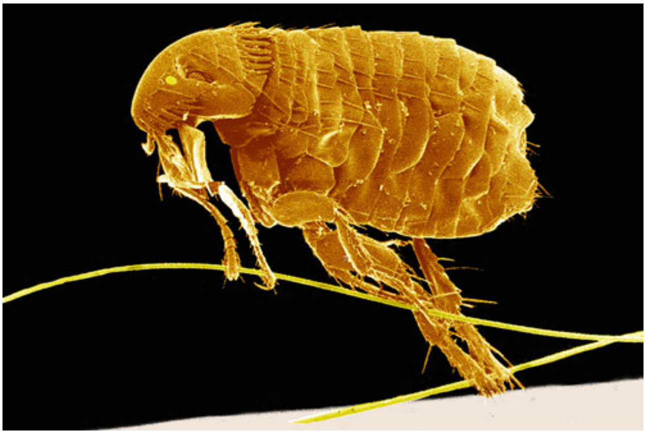

Fig. 6.2 Scanning electron micrograph of the lateral side of the cat flea *Ctenocephalides felis*

Fig. 6.3 Macrophoto of a cat flea bite site on a human arm at three sites

2. *Different clinical types of plague*.
   By mass investigations of infected persons (and infected rodents), it was noted that in principle three different types occur:

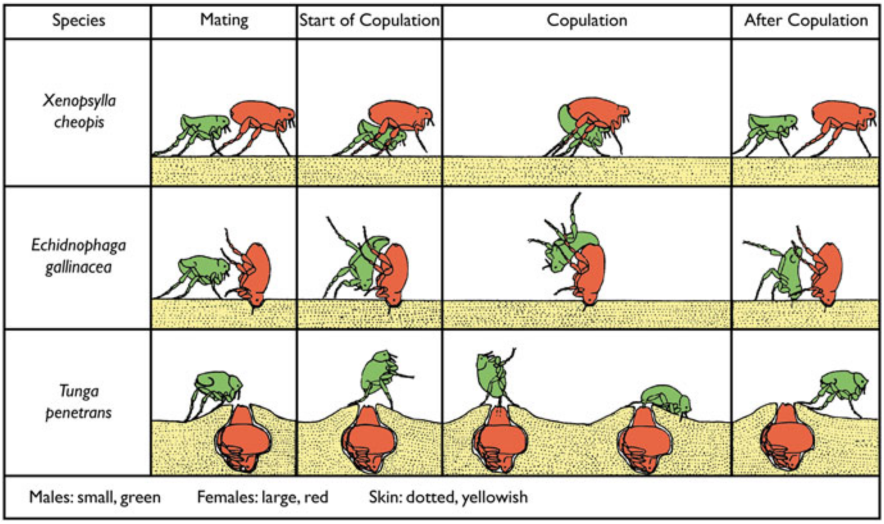

Fig. 6.4 Diagrammatic representation of the features of three flea species during copulation on human skin (above: *Xenopsylla cheopis*, tropical rat flea; middle: *Echidnophaga gallinae*, chicken flea; below: *Tunga penetrans*, sand flea)

Fig. 6.5 Scanning electron micrographs of a male and female *Tunga penetrans* flea

   (a) *Bubonic plague:* This type was found in 40–90% of the cases studied.
   (b) *Septemic cases:* In up to 30% of the cases.
   (c) *Pneumonic cases:* In 5–10% of infected persons.

3. *Transmission:* The plague bacteria are transmitted to humans by a very broad spectrum of fleas during their blood-sucking activity (Table 6.1).

Fig. 6.6 Photo of human skin showing three fleas having entered human skin

Table 6.1 Important flea species (see Figs. 6.1, 6.2, 6.3, 6.4, 6.5 and 6.6)

Species	Size (mm)	Characteristics	Hosts
Pulex irritans	♂ 2–2.5 ♀ ~4	Neck without comb-like protrusions, ocellar bristle below eye	**Humans**, pet animals
Ctenocephalides canis, C. felis	♂ 2 ♀ 2.5	1 comb each at head and pronotum	Dogs, cats, **humans**
Xenopsylla cheopis	♂ 1.4 ♀ 2.5	Without any combs, ocellar bristle crosses the eye	Rats, mice, **humans**
Ceratophyllus gallinae	♂ 3 ♀ 3.5	1 comb at the pronotum	Chickens, **humans**
Echidnophaga gallinacea	♂ 1.5–2 ♀ 2–2.5	Without combs; female becomes attached at the skin of birds and humans	Chickens, dogs, **humans**
Tunga penetrans	♂ 0.5–0.7 ♀ 0.5–1.0	Pronotum without comb, female penetrates skin, male free running	**Humans**, any animals, especially rats

3.1 *The agents of plague are transmitted to humans by the following:*
  (a) By inhaling infected fluids of exhaled infectious material of infected humans or animals.
  (b) By bites of infected fleas.
  (c) By spreading of infected flea feces into skin wounds.
  (d) By contact of wound contents.

3.2 *Incubation period.*

In general, different times occur, ranging from a few hours up to 2–3 days, depending on the masses of injected agents of plague during the sucking of infected fleas. However, in several cases, it took 5 days, in others only one day.

3.3 *Death cases during epidemics.*
  a. Bubonic plague: 40–60%.
  b. Pneumonic and septemic plague: ~90% and more.

   Adult fleas may starve for long (up to 1 year) since it waits for soil shakings, which announce the arrival of a potential host. This is important to know for people who move into an apartment, which was the home of dog or cat owners and was empty for a longer time. The newcomers may become attacked by large numbers of suddenly hatching fleas. The same behavior is described by bird fleas, which rest inside their pupa cover until another bird enters the nest or they attack when humans start cleaning bird cages. Fleas leave dead bodies as soon as the body cools down. This is important in the transmission of the agents of plague—the bacterium *Yersinia pestis*. If infected rats die, the fleas leave them and attack humans and other uninfected animals (e.g., rats), where they transmit the plague bacteria during blood sucking. This transmission may occur by regurgitation of the bacteria into a human host. This occurs in the following steps:

   1. The flea ingests the bacteria from an infected rat.
   2. This flea then changes the host and attacks after a while a human being.
   3. Then, this flea starts to suck hastily human blood, which is mixed in its prestomach with remnants of rat blood containing plague bacteria.
   4. The non-stretchable anterior portion of the flea's gut becomes overfilled, and as a consequence, the flea vomits (regurgitates) the whole infected blood mixture (containing the bacteria) into the wound of the human skin.
   5. Then, the bacteria may start propagation inside human blood. In particular, the tropical rat flea (*Xenopsylla cheopis*, Table 6.1) is a very important vector of the agents of plagues since it is worldwide common in rats living in human slums. From time to time, outbreaks of plague occur even today in regions of India, East Africa, and the USA and thus the agents of disease are transported to many countries inducing local outbreaks, which at first might be misinterpreted.

4. *Bite reactions:* Fleas are often disturbed during blood sucking. Thus, they stop it and start a new approach at a different site or at a different vertebrate host. Therefore, often, real rows of bites can be found on human skin. The injected saliva, which blocks clotting of the blood, initiates itching, which is often repeated and thus rather nasty. Reactions on bites may range from none to extremely intense depending on the allergic status of a host—but in any way, the reactions are very nasty and remain for several days.
5. *Transmission of agents of disease:* The history of mankind is full of examples where fleas have influenced the fate of single persons but also that of whole nations since they are vectors of agents of different diseases.

(a) *Plague (Black death):* This disease, which has killed millions of humans in times before the invention of antibiotics, is due to infections with the bacterium *Yersinia* (*Pasteurella*) *pestis*. This Gram-negative, stab-like bacterium was detected at the same time (1884) by a former co-worker of Robert Koch (Kitasato 1853–1931) and by Alexandre Émile Jean Yersin, a co-worker of the French scientist Louis Pasteur (1822–1895) during an epidemic in Hong Kong. These bacteria are transmitted by regurgitation of bacteria during the blood sucking of fleas. These bacteria reach via blood the lymph nodes, which increase their size extremely within 3–5 days after the flea bite and appear in a hemorrhagic red color. These swollen regions occur in about 90% of all infections and are named *bubones*. Via regular blood transportation, the agents of disease then may also enter the lung, where they reproduce themselves enormously so that during coughing slime masses with millions of bacteria are expectorated and thus may infect other close-by standing persons. This phase—called *pneumonic plague*—is lethal without treatment. Thus, it is understandable that in pre-antibiotic times plague had extremely reduced human populations for many centuries worldwide. For example, after the European so-called 30-Year War (1618–1648), many people were killed that only five million humans remained alive in the region between Breslau and Paris (a distance of about 1200 km). But even today plague is still present in many regions of India, Africa, and North America. For example, in 1994, there was a breakout of plague in India close to a monastery (where "holy" rats were kept), leading to thousands of human cases, which caused big problems, since the needed supply of antibiotics was too slow and led to thousands of death cases.
   - *Treatment:* Actual measurements of treatment are products containing streptomycin (most efficacious), doxycycline, and tetracycline, being all applied under strict clinical control in order to avoid the spreading of plague.
   - *Vaccination:* Vaccines are available, but WHO as well as STIKO (Standing Vaccination Committee in Germany) recommend vaccinations only in case of an outbreak.

(b) *Murine spotted fever:* The agents of this and related fevers (*Rickettsia typhi* = *R. mooseri*) are common in rats and are still spread today in many tropical and subtropical regions. Today treatment is done by application of tetracyclines and chloramphenicol. However, extremely important is the intense control of plague hosts such as rats and fleas in regions with a high human population with international contacts.

(c) *Erysipeloid:* This disease is often found, e.g., in Russia and related countries. It is induced by the bacterium *Erysipelothrix rhusiopathiae*, which leads to severe skin damages in many species of animals and immune-compromised humans.

(d) *Further viruses:* The groups of Mehlhorn and Mencke (Germany) proved that fleas may transmit, besides the agents of plague, a broad spectrum of viruses (e.g., Caliciviruses), which are stable enough to survive for a while in the stomach of fleas (Mencke et al. 2009). These agents were found in flea saliva as well as in flea feces, where they remained infectious for up to 60 days, thus endangering large amounts of further hosts.

6. *Flea elimination:* In order to avoid the transmission of agents of disease by flea bites or flea feces, the pet animals should be protected by insecticidal collars and pour-on preparations containing insecticides (e.g., Advantix®). The latter, however, do not act against flea larvae. However, these larvae might be killed by MiteStop®, an extract of neem seeds, which dries up the surface layer and thus kills the larvae. Humans can be kept free from fleas by spraying products based on icaridin (like Viticks®) onto legs and trousers. This compound repels a broad spectrum of blood-sucking insects and ticks.

6.1.2 Vectors of Plague Bacteria

6.1.2.1 Human Flea (*Pulex irritans*) (Fig. 6.1)

1. *Name: Latin: pulex* = flea; *irritans* = annoying. *English:* Human flea; *German:* Floh; *French:* puce.
2. *Geographic distribution/epidemiology:* Today, this flea species occurs worldwide; however, in early times, it was restricted to North America. It is apparently absent in tropical regions of Asia. Humans, their dogs, and other animals helped to distribute this flea worldwide, starting increasingly about around 1700 due to enlarged worldwide transportation facilities. For size and morphology, see Table 6.1.
3. *Transmission of agents of disease: Pulex irritans* transmits the agents of plague and erysipeloid and is an intermediate host of the tapeworm *Dipylidium caninum*.

6.1.2.2 Cat Flea (*Ctenocephalides felis*) (Fig. 6.2)

1. *Name:* Greek: ctenos = comb; cephalon = head. Latin: *felis* = cat.
2. *Geographic distribution/epidemiology:* Today worldwide.
3. *Biology, morphology:* This flea has developed several races, which now occur worldwide. Main hosts of this species are still today cats. However, this flea is also very common on dogs and humans, where it represents 80% of the infestations. It is also common on rats, mice, and several other free-living mammalians, which may harbor many agents of diseases. Even birds were found bearing this flea. It has its origin in regions of North Africa and Asia and was imported to Europe, especially in times of the Roman Empire. Its spread increased in Central Europe when cats became "house animals" in the thirteenth–fourteenth century. Actually, its reproduction is considerably increased in human dwellings. This is understandable since it originates from "warm" countries. The recent occurrence relation of cat fleas to the human fleas is 18:1, underlining its dominance in human dwellings.
4. *Transmission of agents of disease:* Worldwide: fleas are vectors of agents of plague and potentially help with the mechanical transmission of several further

viruses. Furthermore, this flea may become an intermediate host of the tapeworm *Dipylidum caninum*.

6.1.2.3 Dog Flea (*Ctenocephalides canis*)

1. *Name:* Greek: ctenos = comb; cephalon = head. Latin: canis = dog.
2. *Geographic distribution/epidemiology:* Worldwide.
3. *Biology, morphology:* Both sexes of this flea species look rather similar to *C. felis* and suck blood at a very large spectrum of animals and humans. In southern European countries, about 50% of the fleas on humans are dog fleas. It needs microscopical investigation to differentiate dog fleas from cat fleas. Dog fleas can be differentiated from cat fleas by the help of the length of the first tooth at the lower side of the head. The first tooth is half as long as the second one, while in cat fleas the first and second teeth are identically long.
4. *Transmission of agents of disease:* Worldwide: plague; in Europe and East USA: the tapeworm *Dipylidium caninum*.

6.1.2.4 Rat Fleas (*Nosopsyllus fasciatus*)

1. *Name:* Greek: nosos = disease; psyllos = flea. Latin: fasciatus = striped. English: Northern rat flea.
2. *Geographic distribution/epidemiology:* This flea is distributed worldwide and acts as a mechanical vector of several agents of disease.
3. *Biology, morphology:* Main host is the so-called migrating rat (*Rattus norvegicus*). In addition, other hosts may be used: e.g., rodents and carnivores, which feed such rodents. Occasionally also *humans* are infested. Thus, it is not astonishing that the mouse flea *Leptopsylla* (*Ctenopsyllus*) *segnis* is found also on cats. These fleas also attack easily humans. The tropical cat flea *Ctenophyllus cheopis* is one of the main vectors of the agents of plague.
4. *Transmission of agents of disease:* Plague bacteria in the USA; worldwide: agents of pseudotuberculosis and erysipeloid.

6.1.2.5 Further hosts

Besides main hosts (rats), more than 200 species of mammals may harbor plague species, including those who live close to humans like those of dogs and cats or guinea pigs. This contributes to the quick spreading of the disease as soon as the agents of the disease have entered a special region.

6.2 Cholera

This disease, which has got its name using the Greek term *cholé*, which means bile, has its origin in the Indian subcontinent and is spread worldwide from there to other continents following sea straits and land straits. Until today seven *pandemics* have occurred, wherefrom the last one is still active, although drugs are available and may be used if financially available.

This agent of disease (*Vibrio cholerae*) was first described in the year 1854 by the Italian scientist Filippo Pacini, but it remained mostly unknown until the German physician Robert Koch (1843–1910) studied this agent of disease in India in the year 1883 and described it as "Kommabakterium" (comma bacterium) based on its shape. He also noted that this agent of disease is able to reproduce itself in water when human feces have been spread therein. This important result was confirmed in the year 1859 by the Spanish scientist Joaquim Pascual and the Portuguese scientists Augusto da Costa Simoes as well as by José Ferreira de Macedo Pinto in the year 1850.

Cholera induces typical symptoms starting after an incubation period of 2–3 days after humans have ingested infectious stages within contaminated food or water. There are in general three phases of the disease before death:

1. *Nausea and diarrhea.*
2. *Exsiccosis* (excretion of fluid intestinal contents).
3. *Severe body reactions:* dizziness, coma, lung infections, etc.
4. *Death* in case of huge loss of water and lack of (recent) medication.

6.2.1 Important treatment

Replacement of fluids, sugar (glucose 13.5 g/l) and salts (sodium citrate 2.9 g/l, sodium chloride 2.6 g/l, potassium chloride 1.5 g/l) orally, respectively, via intravenous injection. Children should get erythromycin (12.5 mg/kg body weight four times per day). If treatment and an increase of water supply are not done, death rate may increase especially in young children and old persons.

6.2.2 Selected important cholera pandemics, which had also been spread along the Silk Road system in many regions of the globe

1. *Pandemic 1817–1824*, which occurred in Asian regions and Eastern regions of Africa; and 1823 beginning in Asia, Russia, and later in Europe.
2. *Pandemic 1826–1841*, which started in Mekka, was spread by pilgrims to Egypt and from there to Europe and from there by emigrants to the United States and always caused high numbers of human deaths.
3. *Pandemic 1852–1860*, which was spread in parts of Asia (Arabia: Maghreb, e.g., Algeria) and in Europe. During the Crimean War (1853–1856), both counterparties lost more soldiers due to the pandemic than during the fights. In particular, huge numbers of deaths occurred especially in big cities like London, Munich, Vienna, and Zurich.
4. *Pandemic 1863–1876.* The starting of significant pandemics occurred in Northern Europe, swept to Belgium in the year 1866, and from there to Germany and France and finally reached North and South America.

5. *Pandemic 1883–1996.* This pandemic had its origin in India and swept from there to Afghanistan and from there via the pathways of the different tracks of the former Silk Road to Russia, to towns like Hamburg (Germany), Istanbul, and from there to many towns being involved in international cooperations.
6. *Pandemic 1899–1923.* This pandemic had its origin in Russia and spread from there to Central and Western Europe.
7. *The last pandemic* in recent years started around *1961* and is still active today *(2022)* on its way from Indonesia via Russia to Western Europe and other continents. The agent of the disease is the subtype ElT or of the agent *Vibrio cholerae*.
8. Local outbreaks currently occur worldwide due to a broad spectrum of variations of agents of disease, but the numbers of human death cases are reduced due to the existence of active drugs for treatment. However, people in poor countries are still today highly endangered.
9. *Symptoms of disease.* Infections start mostly by the occurrence of vomiting and excretion of fluid feces containing flock-like inclusions. Due to fluid feces, symptoms of exsiccosis occur followed by algor. Very intense infections may follow by a variety of body reactions such as dizziness, confusion, lung inflammation, etc.
10. *Treatment.* Most important is to replace fluids, sugar, and salts with the help of intravenous injections. The WHO recommends using antibiotics only in very severe cases, while children under 12 years should be treated for 3 days by application of erythromycin (15 mg/kg body weight, 4 times per day).
11. *Prevention.* Most important is to keep high hygienic standards like clean hands and clean tableware and to cook food in endemic regions. If plans are made to visit regions with high infection rates, it is recommended to check the current status of diseases and recommended prevention measurements at the different embassies.
12. *Attention:* In Germany and many other countries, several diseases are strictly notifiable and omission is a criminal conduct. Thus, information should be obtained ahead of travel.

6.3 Brucellosis

This disease is initiated by rod-shaped or coccoid, rather small Gram-negative, pleomorphic bacteria of the genus *Brucella* (named honoring the English scientist David Bruce). They are found *worldwide* inside sheep, goats, pigs, cattle, dogs, camels, etc., but also in horses and humans. Thus, these bacteria are also found along the different straits of the Silk Road in Northern China, Kazakhstan, and Mongolia and thus become constantly spread via contaminated food. Since there occur mostly subclinical infections of humans after the oral uptake of these bacteria, the following symptoms may occur mostly only in 10–20% of the infections: intermitting or undulating high fever shivers interrupted by fever-free phases of 2–5 days. Severe damage may occur due to hepatomegaly and lymphadenopathy, especially in persons with a reduced immune system.

Due to these potentially undiagnosed infections, this disease was and often remains today mostly unnoted, but is still spreading today along the different straits and/or along ship routes to many countries.

However, in contrast to former times, therapy is possible and successful today when these agents of the disease have been spread in trains, ships, or airplanes. It turned out that combinations of doxycycline, rifampicin, and gentamycin are highly effective (however, the current status should always be checked in recent literature before use).

6.4 Spring-Summer Meningoencephalitis/Tick-Borne Encephalitis

This disease was first described by an Austrian scientist (Schneider 1931) and was diagnosed as an infection due to viruses. Intensive studies showed that this disease has its origin in the Far East, where a so-called Far East subtype is dominant, while its occurrence is decreased in countries around Mongolia and even more in Russia, where the Siberian subtype has been shown to be dominant. In Russia and Europe, the so-called Western subtype has apparently reached a higher grade of distance compared to the Siberian and Far East type.

A. The agents of disease belong to the following groups of viruses (occurring from East to West):

   1. *Far Eastern subtype.*

   Far Eastern tick-borne encephalitis virus (Far Eastern TBEV) replacing the former name Russian Spring-Summer encephalitis virus (RSSEV). This disease is characterized by severe symptoms inducing lethal cases of up to 20%. In particular, 50% of people of an age of at least 60 years suffer from encephalitis; 25% of younger ones suffer from encephalomyelitis.

   2. *Siberian subtype.*

   This subtype induces the so-called Siberian tick-borne encephalitis. In former times, the virus was called West Siberian virus.

   3. *Western European subtype.*

   This virus is actually named Western tick-borne encephalitis virus (WTBEV). In former literature, the name Central European encephalitis virus (CEEV or FSMEV) was used. Actually, the abbreviation FSME (German: Frühsommer-Meningoenzephalitis) is used in common literature.

B. *Transmission:* The viruses of TBE have been spread from the East of Japan and China to Europe in the West. The most common vectors in the East are ticks of the species *Ixodes persulcatus*, while in Western regions the most common vectors belong mainly to the species *Ixodes ricinus*, although *I. persulcatus* has already reached regions in Germany and is spreading the virus also by infecting mice, sheep, cattle, and dogs. Transmission may also occur by mother milk.

6.4.1 Incubation period

It is difficult to determine the date of an infection of humans by tick-transmitted agents of disease since the bite is not noted because the injected tick saliva contains anesthetic substances in various amounts. Thus, the actual data for incubation periods are based on calculations reaching from 2 to 28 days.

6.4.2 Symptoms of disease

FSME and related diseases may produce different symptoms at different intensities. Often was noted that in 60–70% of the infections only slight subclinical symptoms/feelings occur.

6.4.3 Severe symptomatic cases

- Meningitis.
- Meningoencephalitis (may have lethal follow-up).
- Meningoencephalitic symptoms over months: lethal in 1–2% of cases.

6.4.4 Therapy

There are no special drugs available. Thus, "treatment" should be done by supporting general body fitness.

6.4.5 Prevention

Use of tick repellents (e.g., those based on icaridin). These products should also be sprayed on shoes, naked skin, and trousers. The protection time covers 6–7 h but should be repeated in cases of sweating (Fig. 6.7).

6.4.6 Vaccination

Available are vaccines like Encepur N, FSME-Immun CC, Ticovac, and others; the vaccination scheme is provided by the physician. *Note:* it takes time until the vaccination acts. The starting of the protection is product specific and thus vaccination should be done early before the start of the travel in endemic regions.

Important: All activities should be done only by experienced persons (Tables 6.2, 6.3, 6.4 and 6.5).

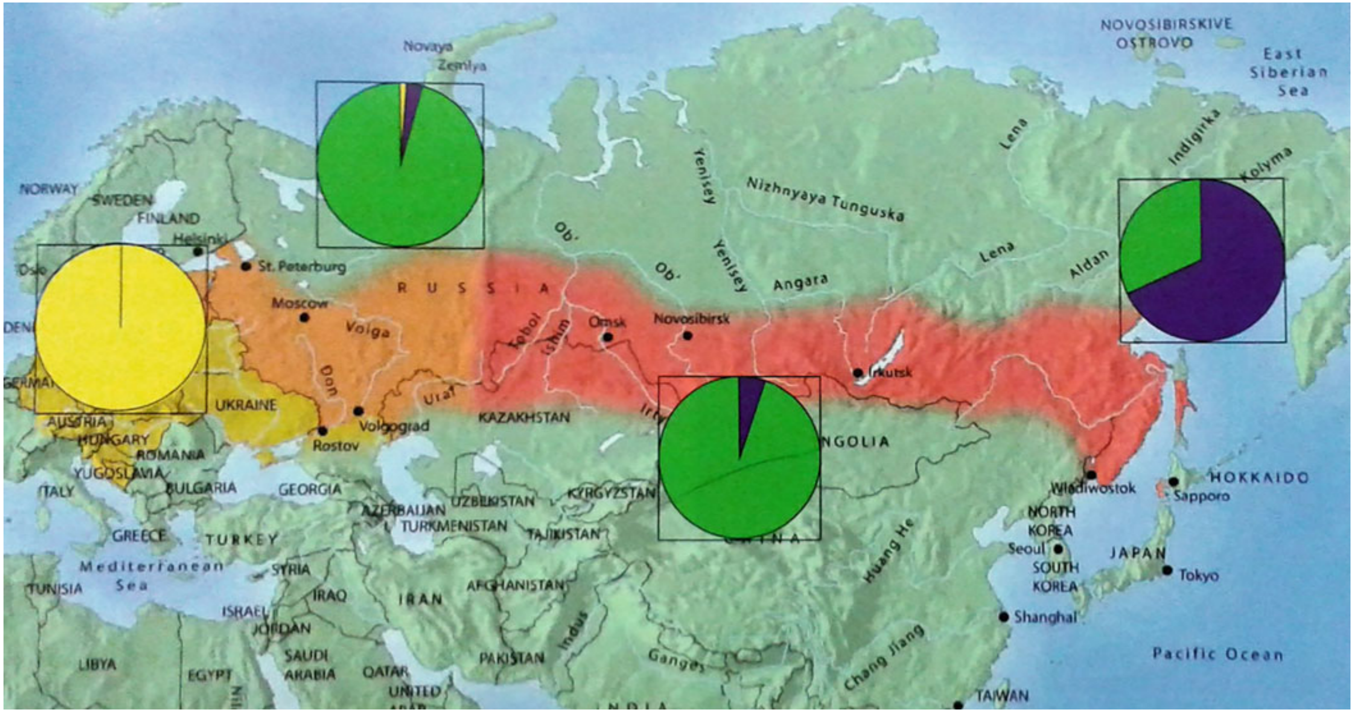

Fig. 6.7 Diagrammatic representation of the subtypes of the spring-summer meningoencephalitis, which actually covers four subtypes (Far East, Siberian subtypes 1 and 2 and the absence in Central Europe). Amounts are shown in colors: yellow = Western subtype; green = Siberian subtype; blue = Far East subtype

Table 6.2 Virological and/or serological proofs of documented occurrences of disease due to FSME and RSSE starting in the *East* and stretching into *Western Europe* (Authors Aspöck and Dobler)

Country	Focal proof of the presence of FSME and/or RSSE infecting humans
Japan	Human infections are especially high on the island Hokkaido
China	Proofs of subtypes at the borders to Russia and Mongolia
South Korea	Proofs of infected rodents by viruses of the Western subtype
Mongolia	Proofs of viruses of the Siberian subtype at the border to Russia
Kazakhstan	Large amounts of RSSE viruses are spread in the North and Northeast regions
Kyrgyzstan	Huge amounts of viruses occurring in Northern and central regions along the borders to Kazakhstan and Uzbekistan
Uzbekistan	FSME and RSSE viruses are found in people in regions North and West of borders to Kazakhstan, Tajikistan, and Turkmenistan
Russia	Occurrence of infected humans and animals in forest regions of the taiga between the 40th and 60th latitude North. **Proven:** large amounts of *Ixodes persulcatus* ticks are main vectors.
Estonia, Lithuania, Latvia	All three countries are hotspots of FSME viruses, which is spread by *Ixodes ricinus* and *I. persulcatus*
Finland	Focal infectious zones around towns; vectors are *Ixodes ricinus* and *I. persulcatus*
Sweden	Intense spreading of FSME along the East coast, low-graded ones in/around big towns
Norway	Few, if at all, sites with the spreading of FSME
Denmark	Few cases, e.g., on Isle of Bornholm
Poland	FSME is spread along the Russian border and often (documented) close to towns
Greece	Rather few cases of FSME, probably due to low-graded testing
Albania	Rather few cases of FSME, probably due to low-graded testing
Serbia/ Bosnia-Herzegovina	Rather few cases of FSME, probably due to low-graded testing
Croatia	Large spreading regions in the North at the borders to Hungary, Slovenia, and close to Zagreb
Slovenia	Large spreading in the whole country
Hungary	Large spreading in regions close to surrounding countries
Italy	Rather few cases, apparently due to rather few checks
Slovakia	Regions with many spread diseases in regions between the towns of Zilina and Levice and along the border to Hungary
Czech Republic	Large regions around Pilsen, Budejovice, Brno, Ostrava, and small regions all over the countries
Germany	Large forest regions in Bavaria, Baden-Wuerttemberg, smaller regions in other regions over the country; huge amounts along the border to Austria
Austria	Hotspot regions all over the country up to elevations of 1200–1500 meters
Switzerland	Proven regions stretch from Zurich to Basel and around Bern to Thun and along Neuchatel Lake
Liechtenstein	Single cases—apparently imported

Table 6.3 Important tick-transmitted flaviviruses

Flaviviridae of the tick-borne encephalitis group	Human diseases	Geographic distribution
Far East type (RSSE)	Meningoencephalitis	Japan, Russia
Negishi virus	Meningoencephalitis	Japan
Siberian subtype (RSSE)	Meningoencephalitis	Eastern Europe, Northern Europe, Central Europe, Western Russia
Central European encephalitis virus (FSME)	Meningoencephalitis	Western Russia, Eastern and Central Europe
Omsk hemorrhagic fever virus	Hemorrhagic fever	Russia
Tyuleniy	Hemorrhagic fever	Russia, Norway, Alaska
Powassan virus	Meningoencephalitis	Russia, Canada, USA
Louping ill virus	Meningoencephalitis	Norway, England
Kyasanur forest fever	Hemorrhagic fever	India, Arabia
Meaban virus	Fever	France

Table 6.4 Important clinical symptoms of different variations of Spring-Summer meningoencephalitis as follow-up of three groups of tick-transmitted agents of diseases

Meningitis	Encephalitis	Encephalomyelitis
Headache Fever Dizziness Nausea Stiff neck pharyngitis	Ataxia Tremor Nystagmus Unconsciousness Symptoms of meningitis Vocal disturbances Hyperkinesia Dysregulations Psychic disturbances	Symptoms of encephalitis Paralysis symptoms of extremities Bulparal paralysis

Table 6.5 Natural host spectrum of FSME and their natural hosts

Natural vectors	Natural hosts (mice)
Ixodes ricinus	*Apodemus flavicollis*
Ixodes persulcatus	*Myodes glareolus*
Ixodes ovatus	*Apodemus sylvaticus*
Ixodes hexagonus	*Microtus arvalis*
Haemaphysalis sp.	Broad spectrum of vertebrates
Dermacentor reticulatus	Broad spectrum of vertebrates

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Plague Disease: From Asia to Europe and Back along the Silk Road

7

Günter A. Schaub and Patric U. B. Vogel

Abstract

In the past, plague disease resulted in the most disastrous pandemics, killing in total about 200 million people. The etiologic agent, the bacterium *Yersinia pestis*, is transmitted by fleas or by human-to-human contacts. The rat flea *Xenopsylla cheopsis* is the main vector. The main hosts are rodents, but *Y. pestis* also develops in pets, farm animals, and humans, the latter also infected by the common human flea *Pulex irritans*. Declines in the population densities of rodents initiate the fleas to suck blood of other mammals, thereby possibly causing an infection. The waves of pandemics are classified into the Justinian plague (sixth–eighth century) and the second (fourteenth–eighteenth century) and third pandemics (1894–early twentieth century), but *Y. pestis* infected humans even thousands of years before these pandemics. The origin of the first and second pandemics presumably lies in the Central Asia steppes from where it seems to have been distributed by caravans via the Silk Road to Europe. The strains of *Y. pestis* causing the late epidemics of the second pandemic were presumably transported back several times to Asia. The third plague pandemic was spread by steamships to all major ports. There, improved hygiene strongly reduced the number of deaths, especially in Europe. Nowadays, local infections are still present in Asia, Africa, and North America.

Keywords

Yersinia pestis · Fleas · Rodents · Justinian plague · Black Death · Third pandemic

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_7

7.1 Introduction

Plague—this name symbolizes one of the most frightening threats to humanity in the past. The disease had a fatality rate of about 60%, dependent on the form of the disease. Summed up over the centuries, it worldwide presumably has killed 200 million people (Glatter and Finkelman 2021). At a time when nothing was known about the causative agent and its transmission, the only effective measure was to run away, and outbreaks in villages initiated inhabitants to leave. However, this was just an illusion because plague followed and reached many regions of the world. It raged over centuries, often with recurring outbreaks and epidemics after its first introduction to new areas. Considering the devastating effect of plague on human populations, it is surprising that humans are not the primary host for *Yersinia pestis*, the etiologic agent of the disease. Instead, it is a disease that typically circulates within populations of rodents and is transmitted by respective flea species (Perry and Fetherston 1997; Eisen et al. 2015). The circulation in sylvatic enzootic cycles between fleas and mammals that are partially resistant is the key to the longevity and persistence of *Y. pestis* in some areas (Perry and Fetherston 1997). The effect that plague had on humans goes far beyond the historic impact on economic and social aspects and is even noticeable on a molecular level, e.g., by triggering a natural selection of human immune genes involved in the defense of infectious diseases (Immel et al. 2021).

Even nowadays, plague has not been completely eradicated. It is still endemic in several regions of the world, with occasional human infections up to smaller outbreaks. It persists in local enzootic cycles, mainly between rodents and their fleas. In the first decade of the twenty-first century, about 20,000 cases with about 1600 deaths have been recorded, mainly in Africa, inclusive Madagascar (Dillard and Juergens 2022). Surveillance systems are established, and a coordinated response of isolation, treatment, and elimination of possible causes resulted in an appropriate control of these outbreaks. In addition, improved hygiene measures contributed to the control of this once-devasting disease. However, as several other infectious diseases have shown, poverty, armed conflicts, climate change, ceasing health focus, and other socioeconomic changes bear the risk of an increased resurgence.

7.2 *Yersinia pestis*

Y. pestis is a Gram-negative nonmotile bacterium. It was identified late in 1894 by Alexandre Yersin during an outbreak of the disease in Hong Kong (Zietz and Dunkelberg 2004). The genus *Yersinia* comprises several nonpathogenic and pathogenic species, of which only a few have medical importance for humans. Based on molecular analyses, *Y. pestis* evolved about 6000 years ago from the species *Yersinia pseudotuberculosis* (Demeure et al. 2019), which causes a gastrointestinal disease in many regions of the world (Vogel and Schaub 2021). However, the molecular clock analysis estimating this first emergence has a vast range of uncertainty and, thus, should be taken with care (Benedictow 2013). The earliest appearance of *Y. pestis*, as verified by *Y. pestis* DNA in human bones, dates back to the Neolithic or Bronze age, up to 5000 years BC (Andrades Valtueña et al. 2017; Spyrou et al. 2018). Also, a recent molecular analysis of a *Y. pestis*-genome in the 5000-year-old remains of a human hunter indicates the spin-off of *Y. pestis* from *Y. pseudotuberculosis* about 7400 years ago (Susat et al. 2021). Newer molecular studies analyzing ancient *Y. pestis*-DNA indicate the evolution of two genetically different forms of *Y. pestis* at that time (Andrades Valtueña et al. 2022).

In the past decades, research revealed several adaptations that contributed to the rise of *Y. pestis* and its biological differences from its predecessor. The transmission by fleas is no innate feature of species of the genus *Yersinia*. It developed after divergence from the predecessor, *Y. pseudotuberculosis*, which is still transmitted by feces and contaminated water and not by insect vectors (Chouikha and Hinnebusch 2012; Vogel and Schaub 2021). The adaptation of *Y. pestis* to flea transmission is estimated to have evolved about 4000 years ago (Barbieri et al. 2021). The genetical adaptations that conferred the bacteria new biological properties and increased its virulence have evolved in a stepwise process with early ancestral *Y. pestis*-strains presumably capable of inducing pneumonic plague by just a single gene acquisition (Zimbler et al. 2015). However, the virulence and transmission modes of ancestral strains are unclear (Demeure et al. 2019), and plague might have been limited to a few human infections caused by zoonotic transfers during the handling of hunted animals (Susat et al. 2021). Hence, the ancient *Y. pestis* strains found in the Bronze Age were presumably not transmitted by fleas (Drancourt and Raoult 2016). The continuous evolutionary adaption of *Y. pestis* to flea transmission comprised an arsenal of bacterial biomolecules that have been increasingly discovered and characterized in recent years (Hinnebusch et al. 2021). On a molecular level, this included gene loss as well as the acquisition of new genes, including plasmid-encoded ones, by lateral gene transfer (Hinnebusch et al. 2016). Ultimately, *Y. pestis* pathogenicity relies on diverse virulence factors that are distributed across its chromosomal DNA and three acquired plasmids (Demeure et al. 2019). One of these plasmids, pFra, encodes for a phospholipase that enables *Y. pestis* to survive the unfavorable microenvironment in the flea's digestive tract (Chouikha and Hinnebusch 2012; Barbieri et al. 2020). This enzyme is not absolutely necessary, as *Y. pestis* survives in fleas after feeding on brown rats but seems to have broadened the host range by helping *Y. pestis* to resist in fleas that are fed on black rats and humans (Bland et al. 2021). Another evolutionary adaptation of *Y. pestis* to fleas is associated with a loss-of-function mutation of a gene encoding for urease. While this gene is intact in *Y. pseudotuberculosis*, it results in high mortality rates of fleas. In *Y. pestis*, this gene is silenced due to mutations paving the way for flea transmission (Chouikha and Hinnebusch 2014). After these adaptions, *Y. pestis* was already transmissible by fleas, but not very efficiently. Later, additional mutations conferred the ability to form biofilms in the flea foregut (Sun et al. 2014; Hinnebusch et al. 2016). In fact, the clonal evolution of *Y. pestis* is not limited to ancient strains but also found in current geographically isolated strains of the same region (Lowell et al. 2015).

7.3 Clinical Manifestations of Plague and Reservoir Hosts of *Yersinia pestis*

Plague disease appears in several clinical manifestations, depending on the route of transmission. The short period of sickness and high lethality rate in most plague forms is mainly mediated by the fast dissemination of the bacteria from the entry site within the body (Gonzalez and Miller 2016). The pathogen achieves this by blocking immune signaling, evading immune components, and intracellular multiplication (Chung and Bliska 2016). The main plague form, associated with many of the known pandemics, is the bubonic plague. It starts within a few days up to a week after the infection by flea bites with swollen lymph nodes, so-called buboes, e.g., under the armpits. Further symptoms include headache, fever, and vomiting. The bubonic plague is lethal in over 50% of cases and is the main form observed in most known epidemics. The septicemic form is similar to the bubonic form, but without visible buboes. It is further associated with septic shocks and organ failure. It was the name-giving form of the Black Death as infected people also developed violet-to-black coloration of the skin (Rakin 2003), which was caused by subcutaneous hemorrhages (Duncan and Scott 2005). The pneumonic plague is another frequently observed form but differs in transmission. It can develop from other forms when *Y. pestis* disseminates into the lungs or is inhaled, causing bloody sputum. In this form, infected people can directly infect others by droplets or aerosols (Rakin 2003).

More than 200 mammalian species are susceptible to infections with *Y. pestis* and can serve as reservoirs. Among those, rodents represent the main reservoir (Barbieri et al. 2020). For example, black rats play a major role as reservoirs in plague foci that persist today in Madagascar (Andrianaivoarimanana et al. 2013a). In other geographical areas, marmots are the dominating reservoir for *Y. pestis* (He et al. 2021). Furthermore, even domesticated predator animals such as cats and dogs can be infected with *Y. pestis* (Barbieri et al. 2020), of which the former were already kept as domesticated animals in urban settings in locations along the Silk Road (Haruda et al. 2020). Many of these carnivores are resistant to plague bacteria but can carry the pathogen during latent infections (Perry and Fetherston 1997). The same applies for other mammals, including mice, gerbils, and dogs, which are moderately resistant to plague, probably due to the long endemic circulation of the pathogen within their population. Even camels can be infected with *Y. pestis* (Barbieri et al. 2020). This is of particular interest as this livestock was dominantly used to carry goods in huge caravans along the Silk Road (Benedictow 2013). Besides the traditional animal reservoirs and its ability to survive in the environment in soil, *Y. pestis* can even survive intracellularly in protozoan ameba (Markman et al. 2018).

7.4 Fleas as Vectors of *Yersinia pestis* and Bacterium–Vector Interactions

Fleas are obligate bloodsucking insects and live in close proximity to their hosts (Schaub and Mehlhorn 2016a). After three detritus-feeding larval stages, they pupate. If a host approaches the wingless, laterally flattened and about 1–6 mm long adults emerge (Schaub and Mehlhorn 2016a). About 80 flea species can transmit *Y. pestis* to rodents, including the rat flea *Xenopsylla cheopsis* (Barbieri et al. 2020). Another flea, the common human flea *Pulex irritans*, is also capable of transmitting *Y. pestis* (Fig. 7.1). The role of *X. cheopsis* as the main vector in plague epidemics since the nineteenth century is commonly accepted. However, it has only a low transmission efficiency compared to other flea species, and its role as a vector during the Black Death, a frequent assumption, is questionable due to its poor ability to adapt to the colder European environment (Barbieri et al. 2020).

For the maintenance of a flea-rodent infection cycle, e.g., during epizootics, *Y. pestis* needs to cause massive bacteremia in its rodent host. In some rodents, levels of 10^9 bacteria per mL of blood develop. Once ingested with the blood, the bacterium multiplies in the midgut for about one week, leading to aggregate formations. In an advanced stage of flea infection, *Y. pestis* induces a biofilm formation within the foregut that impairs blood feeding but can also cause a blockage there. Thereby, fleas cannot suck blood efficiently and tend to regurgitate intestinal contents along with *Y. pestis* into the wound of the host (Hinnebusch and Erickson 2008; Chouikha and Hinnebusch 2012). Plague is just one of several infectious diseases in which a pathogen-triggered change, e.g., an increasing blockage of the

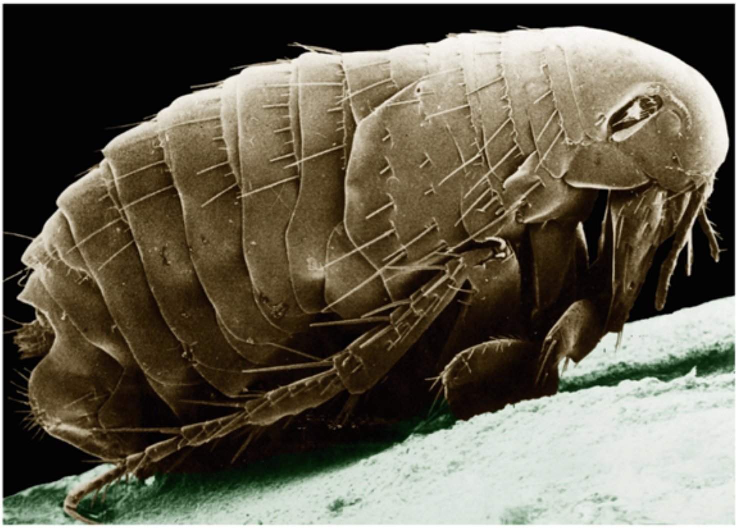

Fig. 7.1 Scanning electron micrograph of *Pulex irritans* (photo: H. Mehlhorn; Schaub and Mehlhorn 2016a)

foregut, facilitates the transmission (Schaub 2006). However, the blockage of the foregut by *Y. pestis* is species-dependent and strong in *X. cheopsis*, the flea of black rats, but less pronounced in other fleas such as the human flea *P. irritans* (Eisen and Gage 2009) that was found in many outbreak settings. The vector competence is also affected by host factors. For example, transmission efficiency increases when *P. irritans* feeds on experimentally infected rat blood compared to infected human blood, which causes foregut blockage at a much lower rate (Miarinjara et al. 2021).

Interestingly, the human flea is by now ascribed to have had a bigger role in transmission during plague epidemics (Dean et al. 2018). The human flea is not only capable of transmitting *Y. pestis* during bloodmeals but can also quickly digest and defecate viable *Y. pestis* cells, which can then infect new human hosts, e.g., through skin lesions. In fact, this route is now considered to have been important in former pandemics (Barbieri et al. 2020). A second transmission associated with blood sucking is called early phase transmission, which renders fleas infectious within hours and days without biofilm formation. This mechanism resembles a mechanical transmission through the reflux of portions of the infectious blood meal from the midgut to the foregut, which contaminates the wound during the next blood meal (Eisen et al. 2015; Bland et al. 2018).

7.5 Historic Plague Pandemics

Historically, three plague pandemics are classified: the Justinian Plague, the second pandemic with the first wave called the Black Death, and the third pandemic. Each of the pandemics was associated with different biovars of *Y. pestis*: Antiqua, Medievalis, and Orientalis (Bramanti et al. 2019a). Biovars are strains of bacteria differing in phenotypic properties in the form of biochemical features such as glycerol fermentation, and some authors suggest that *Y. pestis* classification should be done instead based on molecular signatures of biovars (Achtman et al. 2004). Currently, the Orientalis biovar causes human infections worldwide, while the Medievalis and Antiqua biovars exist mainly in enzootic cycles in Africa and Asia (Lemon et al. 2020). The concept of three large long-lasting pandemics is largely accepted within the scientific community albeit some historians give to consider that this might just be a simplistic view of the past, which has been established retrospectively to frame the historic sequence into a tangible concept rather than truly representing three distinct pandemics (Benedictow 2013). Furthermore, the knowledge is mainly based on written documents and, therefore, fragmented.

Another pandemic of bubonic plague, the Egyptian plague, mentioned in the bible and described as one of the “Ten plagues of Egypt” (Fig. 7.2), might have occurred even before the Justinian Plague (Rakin 2003; Zietz and Dunkelberg 2004). However, it cannot yet be proven that *Y. pestis* was the causative agent. The last years witnessed findings of *Y. pestis* in remains from a farmer of the Neolithic age in Sweden, which might point to epidemics or pandemics long before the Justinian Plague pandemic (Rascovan et al. 2019), but the severity of these early circulating strains is hard to estimate, and it might have been a few zoonotic spillovers to

Fig. 7.2 The “Ten plagues of Egypt” including an indication for bubonic plague (Boils) (source: Adobe Stock, file-no. 295990382, modified)

humans (Susat et al. 2021). Also, human remains of the Neolithic and Bronze Age tested positive for ancient *Y. pestis*-strains, were found in other places, including Germany, Croatia, and Baltic regions, and indicated an early circulation in Europe, coinciding and possibly introduced by massive human migration from the Pontic-Caspian steppes (Andrades Valtueña et al. 2017). In line with the early presence, another study also dated *Y. pestis* back to humans in Eurasia approx. 3000–5000 years, also long before any pandemic was recorded in ancient writings (Rasmussen et al. 2015). Other ancient epidemics called plagues are recorded in historical writings before the Justinian Plague, e.g., the plague of Athens or the Antonine plague, but it is unlikely that these have been caused by *Y. pestis* (Huremović 2019; Sampath et al. 2021).

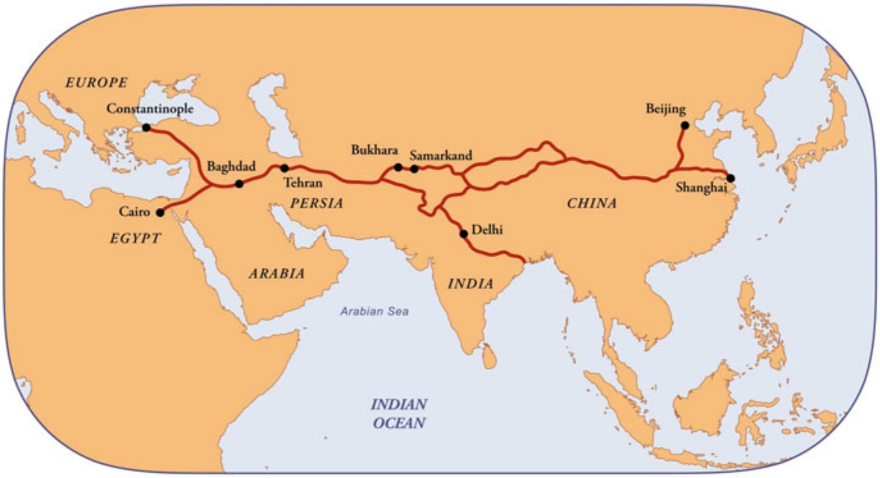

Fig. 7.3 Main Silk Road paths (source: Adobe Stock, file-no. 488663198, modified)

7.6 Silk Road and Spread of Plague

7.6.1 The Silk Road

The Silk Road was a network of caravan routes with interspersed hubs connecting Asia in the east and Europe in the west (Fig. 7.3). The Silk Road spanned roughly 4000 miles (beeline). Starting in Xi'An in north-central China, the route went westwards through the province Xinjiang in the northwest, which represented China's main entry and exit node of the Silk Road and ended in Turkey with a connection to the Mediterranean Sea. The historic central role of Xinjiang for trade and migration is still highlighted by the vast cultural and genetic diversity of its population even today, with around 50 ethnic groups living in that area (Adnan et al. 2021). Eastwards, Xi'An had further connections to Beijing and Shanghai (Fig. 7.3). The Silk Road network was lined by towns and resting places, roughly a day apart. Goods were traded in both directions with traders selling their goods stepwise at intermediate local hubs instead of taking the full distance of the Silk Road. The immense trade and intercultural exchange is also evidenced by the analysis of an excavated Chinese mummy from the second century AD in the Xinjiang region that had grave goods and symbols from China, Persia, Russia, Greece, India, and Central Asia (Wang et al. 2022). Besides the use of existing paved road sections, e.g., built by a Persian sovereign, newer archaeological findings indicate that early nomads in the Asian steppes facilitated the usability of distinct sections by periodically driving their sheep herds from the dry steppes to mountain areas, even thousands of years before the Silk Road became a popular trade route (Frachetti et al. 2017). Also, ancient nomads from the Alay Valley region in Kyrgyzstan, which contains one main route of the Silk Road and represents the connection to China, used the routes for sheep herds (Taylor et al. 2018). Thereby, they seem to have paved the way for the latter caravan routes, which were then increasingly used by travelers and traders (Frachetti et al. 2017). Before the Silk Road gained its full importance, there were already long-distance transports between the West and China maintained by pastoralists, but also a profound human migration occurred even in the second millennium BC. For example, millet consumption was a dietary practice that was presumably brought from North China through the Xinjiang region to Europe at that time (Wang et al. 2019).

The Silk Road enabled kingdoms and empires to trade and exchange valuable items, such as silk and spices from China, to grains or ivory from the Gupta Empire in antique India (Cassel 2006). The heyday of the Silk Road as the central trading route started in the second century and lasted until the end of the fifteenth century. Archaeological analyses discovered tea in Tibet, roughly at the time of the rise of the Silk Road in the second century. As tea does not grow in Tibet and is known to have been historically imported from China, the authors suggested an active side strand of the Silk Road through Tibet at that time (Lu et al. 2016). However, not all routes of the network became frequently used at the same time. For example, the route through Yunnan connecting South and West China became prosperous in the seventh century (Lu et al. 2016). These routes were then canalized through Xi'An to the West, but Yunnan also adjoins Tibet, which probably included a side strand. In addition to trade, the Silk Road was also associated with profound human migration. This resulted in a mixture of European and Asian genetic structures in inhabitants of many regions and former hubs flanking the ancient Silk Road. The causative migration presumably occurred at the time when the Silk Road was controlled by the Mongols (Mezzavilla et al. 2014). This migration can also be resembled by analysis of the Y-chromosomes of inhabitants of South Kazakhstan and dated back to the thirteenth–fourteenth century, consistent with the period of Mongolian leadership (Zhabagin et al. 2020). This is also in line with a high frequency of the specific haplogroup C2-M217, found in the present population along the southern Kazakh border, which included the former Silk Road and also corresponded to the way the Mongols took for their invasion (Khussainova et al. 2022).

7.6.2 The Silk Road and Spread of Diseases

The spread of infectious diseases, affecting both humans and animals, is strongly related to travel and trade even nowadays. Numerous examples indicate an early spread of infectious diseases along the Silk Road and are based on advanced genetical analyses. Exacerbations at several regions surrounding the Silk Road and genomic analyses of remains dating back to that ancient time also indicate that infectious diseases might have spread along the precursors of the Silk Road.

Recent genomic studies performed on DNA retrieved from human remains in the Xinjiang province proved *Salmonella enterica*-infected humans in Eastern Eurasia roughly 3000 years ago. Therefore, this bacterium might have spread through precursors of the Silk Road (Wu et al. 2021). In addition, single nucleotide polymorphism analyses of about 200 ancient samples indicate a spread of *Bacillus anthracis*, the causative agent of anthrax, from Xinjiang westwards through the Silk Road (Simonson et al. 2009). But the spread was not limited to human diseases. Bacteria of the genus *Brucella* cause an animal disease, primarily in sheep called brucellosis. Genetical analyses of Chinese strains indicate a presumed origin in North China. Furthermore, genetically similar strains are also found in close proximity to the former Silk Road in other Asian regions, including Kazakhstan, Mongolia, and Russia (Zhu et al. 2020; Liu et al. 2021). At the rise of the Silk Road, even parasites seem to have been distributed by traders and travelers, such as the Chinese liver fluke whose 2000-years-old eggs were found in an ancient latrine close to the Silk Road far outside its endemic region (Yeh and Mitchell 2016).

There are several arguments against and for a spread of plague along the Silk Road (Benedictow 2013). Considering the high tenacity of *Y. pestis* including survival of up to 6 months on clothes, over a month on corn, and in cadavers for up to 2 months even under hot conditions (Rakin 2003), there are plenty of opportunities for *Y. pestis* to reach local nodes, establish local infection cycles, or become endemic in wildlife rodents that feed on remains left behind by caravans. Considering all these potential opportunities for *Y. pestis* to survive and spread, coupled with the need for massive supply movements for the Mongolian troops stationed from the East to the West, it is likely that these favoring conditions spread plague (Green 2020a).

The spread of infectious diseases through this route occurred even before the heyday of the Silk Road in the second century. Plague seems to have been present in some Asian regions for several thousands of years, presumably causing all known pandemics (Harbeck et al. 2013). These ancestors of *Y. pestis* persisted in Central and East Asia, causing human infections at a time, when *Y. pestis* was not even transmitted efficiently by fleas (Spyrou et al. 2018). For example, Mongolia belongs to the regions where plague is still endemic in the twenty-first century and disposes persistent plague foci. However, recent phylogenetical comparisons indicate that these foci are not descendants from ancestral *Y. pestis* strains. Instead, a recolonization of Mongolia by strains from China at the time of the second pandemic or later is more likely (Riehm et al. 2012). Perhaps, sheep played a role in the zoonotic transfer of *Y. pestis* to humans in Asia not only today but also before the establishment of the Silk Road, sometimes as a host infected via rodents such as marmots (Dai et al. 2018). The early presence of *Y. pestis* in Eurasia was further underpinned by the discovery of *Y. pestis* strains in human remains in the Volga river region in Russia similar to the ancient strains and dating back about 4000 years, or another even earlier strain, found in the 5000 years old remains of a hunter from Latvia (Spyrou et al. 2018; Susat et al. 2021). In fact, the source from Latvia represents the most basal *Y. pestis* lineage known to date, which emerged just a few centuries after *Y. pestis* diverged from *Y. pseudotuberculosis* (Susat et al. 2021). Even though suitable intact archaeological samples are scarce, further studies also verified the presence of *Y. pestis* in the same period across Europe (Andrades Valtueña et al.

2017). Likewise, a basal *Y. pestis* strain was verified in human remains from different European regions, which might have been ancestral strains to the one that caused the accepted pandemics AD (Rasmussen et al. 2015; Rascovan et al. 2019). In particular, the presence of 5000–6000-year-old *Y. pestis* DNA dental samples of a Swedish farmer let the authors suggest a possible prehistorian pandemic by an already extinct *Y. pestis* strain might have ended the Neolithic age (Rascovan et al. 2019). This would be consistent with earlier mentions of plague, as the one mentioned in the bible and considered to be one of the "Ten plagues of Egypt." Unfortunately, these historical descriptions cannot be reliably associated with plague due to missing evidence. Furthermore, *Y. pestis*-infected rodents with occasional spillovers to humans, without outbreaks or huge enough to be found in historic writings, cannot be ruled out considering the approximate emergence of *Y. pestis*. In contrast, other studies suggest that plague could have affected only a few individuals at that time through single zoonotic transfers (Susat et al. 2021). Based on current data, the exact geographical origin of *Y. pestis* at the time of divergence from its predecessor is difficult to be determined. However, it is suggested that *Y. pestis* was introduced into Europe either once during the Neolithic Age or multiple times from sources in Central Eurasia (Andrades Valtueña et al. 2017).

7.6.3 The Silk Road and the Justinian Plague

Little is known about the exact origin, causative factors, and the spatiotemporal spread of the first accepted pandemic, the Justinian Plague. It might have originated in Asia facilitated by climatic changes (Kausrud et al. 2010). The ancient descriptions of the clinical signs documented by eyewitnesses, including buboes at the armpits, matched the typical symptoms of bubonic plague (Barbieri et al. 2020). However, for a long time, the identity of the causative agent has been the subject of controversial scientific discussions. The theory of *Y. pestis* to be the etiologic agent has recently been solidified by the identification of *Y. pestis* DNA in skeletons dating back to the sixth century (Harbeck et al. 2013). The Justinian Plague started in the sixth century and recurred in the form of outbreaks and epidemics until the eighth century. In this period, 14–21 plague waves are supposed to have hit Europe and the Mediterranean region (Barbieri et al. 2020). It also reached Southern Germany during the early waves as verified by *Y. pestis* DNA extracted from the teeth of two humans that were radiocarbon dated with a narrow window pointing at the very beginning of the Justinian Plague (Feldman et al. 2016). Interestingly, recent research revealed a profound diversity of *Y. pestis* strains found at different regions which were affected by this pandemic in Europe and showed multiple distinct *Y. pestis* strains, which scourged Europe between the sixth and eighth century. This indicates the broad spread of *Y. pestis* at that time and clonal adaptions in different areas (Bos et al. 2012; Keller et al. 2019).

The Justinian Plague pandemic reached Constantinople in 541/542 AD and rapidly spread to other European countries, including Germany and France, in just a few years until 545/546 (Zietz and Dunkelberg 2004). It also reached Britain as recently verified by *Y. pestis* DNA found in human remains on an excavated cemetery (Keller et al. 2019). According to one theory, it emerged in Africa, either in Ethiopia in East Africa followed by the spread to the Mediterranean region or in Egypt during 541 to 544 AD (Cassel 2006; Feldman et al. 2016). Other theories suggest an origin in the Central Asian steppes from where it was distributed by caravans to the Mediterranean region by the main trading routes (Huremović 2019). At the time of the Justinian Plague, the Silk Road was thriving and the most important trade route. Perhaps the spread was facilitated by the switch from caravan routes to further transport of goods by seaways in the Mediterranean Sea especially hitting ports with devastating effects (Huremović 2019). The heavy grain trade across the Mediterranean Sea might have accelerated the dispersal as stored sacks of grain are preferred by, and can easily be afflicted by rodents, and served as a source for infected fleas (McCormick 2003; Barker 2021).

The Asia theory assumes an origin either in China, Russia, Mongolia, or Kazakhstan (Li et al. 2009). However, the origin in China is not clear-cut as huge epidemics similar to plague have not been mentioned in historical Chinese documents (Benedictow 2013; Slavin 2019). In this regard, the continuous recording of epidemics together with other natural catastrophes started in China generally after the first waves of the Justinian Plague (Sussman 2011). The spread might have been associated with border expansion and human migration in the Asian and European regions. In the fifth century, preceding the Justinian Plague, the Huns expanded their territory and invaded Europe (Kausrud et al. 2010). Consistently, the impact of human migration on plague dispersal is also considered to be likely for prehistorian *Y. pestis* strains in Eurasia (Andrades Valtueña et al. 2017) and also for the Black Death (see Sect. 7.6.4). Consistent with the Asian theory, *Y. pestis* strains isolated from marmots and their fleas over a period of 50 years in the mountains of Tien Shan, which connects Kyrgyzstan and the Xinjiang region in China, were genetically related to ancestral strains and with the lineage 0.ANT5 and also the most closely relevant to the *Y. pestis*-lineage 0.ANT4 that caused the Justinian Plague (Eroshenko et al. 2017).

Besides goods for trade, animal herds were kept in the Asian steppes and moved along trade routes and could initiate infections with *Y. pestis*. For example, sheep herds are still causing human infections in the Qinghai-Tibet plateau, mostly from meat processing such as skinning, and the primary source are marmots passing *Y. pestis* to these sheep herds (Dai et al. 2018). The same applies to the Alay Valley in Kyrgyzstan, which flanks one of the former main routes of the Silk Road. Based on archaeological findings, nomads relied primarily on sheep herds for even about 2000 years BC (Taylor et al. 2018). This in general increased the risk of human infections from eating infected meat or hunting rodents. In this regard, bubonic plague can be transmitted by blood-to-blood contact with infectious body fluids of animal carcasses (Jullien et al. 2021) and should therefore not be underestimated. In addition, domesticated cats were kept in places on the Silk Road even before its rise in the second century (Haruda et al. 2020). Cat fleas can also transmit *Y. pestis*, albeit with low efficiency, and are frequently found in human housings in plague foci, which further increases the risk of human infections (Bland and Hinnebusch 2016).

Therefore, a zoonotic transmission by predators is not unlikely and known from corsac foxes that transmit *Y. pestis* between marmot populations (Fijn and Terbish 2021). Furthermore, camels were used for transportation on long distances on the Silk Road. These animals can also be infected with *Y. pestis* and develop clinical signs (Barbieri et al. 2020).

Although the length of the Silk Road, with exchange and storage of goods at intermediate hubs, makes it unlikely that the disease reached Europe by this infection route (Benedictow 2013), at least through a single transfer, the biological properties of *Y. pestis* are peculiar. For example, the infection source of dead corpses restarting sylvatic cycles or facilitating zoonotic events to humans is also consistent with current knowledge on the post-mortem tenacity of *Y. pestis*. It synthesizes specific compounds in response to stress factors, such as low temperature or pH shifts, which help preserve *Y. pestis* cells. As a result, they are rendered into a viable but nonculturable state, which allows them to persist in their dead host for long periods of time (Easterday et al. 2012). Even the high tenacity in soil poses a risk for the re-infection of mammals (Drancourt and Raoult 2016). However, in experimental settings, the infection rate of mice by contaminated blood in soil is low, and, therefore, contaminated soil is unlikely to be a major infection source (Boegler et al. 2012).

Just like the Silk Road represented the perfect distribution route for infectious diseases between Europe and Asia, the further inland spread of the Justinian Plague in Europe followed main trade routes until it reached Germany and then England (Barbieri et al. 2020). The initial epidemic and recurring outbreaks presumably killed about 40% of the Roman's empire population (Huremović 2019). Furthermore, the Justinian Plague is often described as one of the main drivers of economic, social, and political changes which reordered the society at that time in the Mediterranean region and might have caused the decline of the Roman Empire and the transition from antiquity to the Medieval Age (Sabbatani et al. 2012). However, both aspects, the mass mortality and the social impact, are still discussed as controversial as some studies did not find clear evidence for this assumption, and mortality rates and their contribution to radical social changes might be overestimated (Mordechai et al. 2019; White and Mordechai 2020). Thus, an accurate estimation of the gravity of this pandemic in all means is difficult. Regarding the continued poor hygiene standards in urban regions and the lifestyle of poor populations, it is surprising that the plague literally disappeared for many centuries in Europe (Kausrud et al. 2010), but it did not disappear completely as evidenced by several reports of outbreaks in Russia and Asia (Zietz and Dunkelberg 2004).

7.6.4 The Silk Road and the Second Pandemic including the Black Death

The second pandemic was initiated by *Y. pestis* strains belonging to other genetic clades than the strains that caused the Justinian Plague (Wagner et al. 2014; Drancourt and Raoult 2016; Piret and Boivin 2021). The second pandemic reached

Europe in 1346 and recurred periodically until the eighteenth century. The death rates varied widely according to different sources, but the first wave, called Black Death, might have killed more than 25 million people in Europe between 1347 and 1352 (Huremović 2019; Glatter and Finkelman 2021). These numbers alone indicate what a massive impact this pandemic has had on public health, social structures, and the economy. Particularly serious, the disease hit Europe hard as it encountered a weakened population that suffered under decades of poor agricultural harvests and the feudal system (Redish 2013). In particular, in England, the population was starving and malnutritioned for decades due to bad harvests and a bovine plague that preceded the spread of the Black Death (DeWitte and Slavin 2013). Interestingly, the Black Death seems to have displayed strong regional differences in mortality, as recently reconstructed by palaeoecological data (Izdebski et al. 2022).

In 1346, plague appeared first in the Golden Horde located at the Black Sea and Azov Sea, including the major trade ports Tana and the surrounding area of Caffa on the Crimea (Barker 2021). In 1346, the seaport Caffa was besieged by the Tartars. At this time, this seaport was mainly used by Italian traders from Genua who originally founded the seaport less than a century before with the approval of the ruling Mongols (Wheelis 2002). In the Tartarian troops, an outbreak of plague occurred. A favoring factor might have been that this area is densely colonized by plague reservoirs, gerbils (Cesana et al. 2017). According to the prevailing opinion, tartars used catapults to throw dead corpses into the town, followed by an outbreak of plague in Caffa. The Italians fled back to Italy in their ships, carrying infected rats that resulted in a spread of the Black Death to Italy (Rakin 2003). These historical events are based on memoirs of the Italian de' Mussi (Wheelis 2002) and most widely accepted, even though other historical records indicate a closely related origin such as Tana in Russia (Nam 2021; Barker and Chen 2022). On their way back to Italy, the Italian traders presumably also brought the Black Death to Athens and Constantinople. The traders could have been infected, but more likely, Y. *pestis* was carried through infected rats onboard. However, some historical dogmas such as the Caffa theory are not only questioned by historians, but also by newer molecular insights into the genetic evolution of *Y. pestis*, which currently indicate an earlier circulation. The emergence of the Black Death might date back to the end of the twelfth century until the mid-thirteenth century, and therefore, long before the assumed first outbreaks of the Black Death. This is also supported by some historical records from different areas (Barker and Chen 2022). However, the strength and intensity of possible outbreaks preceding the events in Europe in 1347 cannot be fully evaluated and might have been weaker in magnitude. Taken together, even if the bioterroristic attack of the tartars had never happened and the Black Death originated earlier, plague likely took its route through the maritime grain trade. At that time, Genoa and other Italian regions covered a substantial percentage of their grain demand through shipments from the Black Sea ports (Barker 2021).

The first outbreak in Italy brought by the ships occurred in a seaport in Sicily (Glatter and Finkelman 2021). Italy with its powerful seaports was hit particularly hard by the Black Death. For example, in Venice, about 100,000 people died (Zietz and Dunkelberg 2004). However, Genoa, the home of most Italian traders operating in the Black Sea area, is believed to be the place that gave rise to the inland spread of plague, again through main trade routes. This assumption is based on *Y. pestis* detected in human remains from a cemetery of a hospital which was a main node for travelers leading to Rome and other areas. Furthermore, Italy depended on imported grain, and a profound grain and flour trade throughout the routes of Europe might have also contributed to the fast spread (Cesana et al. 2017). Recent findings of *Y. pestis* DNA in dental samples from graves in coastal South Italy from the fourteenth century also verify the presence of the Black Death (Raele et al. 2021). As a consequence of the devastating effects of the Black Death, quarantine was implemented as a preventive isolation first in the seaport Ragusa in Croatia, and then adopted by other towns including Venice in Italy in subsequent decades (Sehdev 2002). This practice might have helped to stop or delay some plague outbreaks. However, the low living standards at that time and the involvement of rats as reservoirs reduced the effects. From Italy, the disease further spread to France, Germany, and other European countries (Rakin 2003).

Once the disease was introduced in Europe, it quickly spread within a few years, again via main trade routes, according to model calculations (Yue et al. 2017). The average spread of the disease was estimated at 4 km per day (Duncan and Scott 2005; Barbieri et al. 2021). The role of the black rats and their main flea, *X. cheopsis*, is controversially discussed. Although frequently postulated as the main driver of the Black Death, environmental conditions in Europe are also seen as a great constraint for the settlement of this vector–rodent pair (Barbieri et al. 2020). The lack of ancient samples affected the discussion (Bramanti et al. 2019b), but a recent identification of *Y. pestis* DNA in a rat skeleton in Poland from the fifteenth or sixteenth century supports the traditional theory, at least, that the black rat was a reservoir during the second pandemic (Morozova et al. 2020). Furthermore, the black rat can be, under ideal conditions, the main reservoir of *Y. pestis*, as evidenced by its dominant role for *Y. pestis* maintenance in Madagascar to date (Andrianaivoarimanana et al. 2013a). In addition to the role of fleas, the human body louse, *Pediculus humanus*, is a vector that can transmit *Y. pestis* (Ayyadurai et al. 2010). This ectoparasite also lives on humans or clothes and is characterized by daily blood feeding (Schaub and Mehlhorn 2016b). Just like postulated for the human flea *P. irritans*, the body louse can transmit *Y. pestis* through infectious feces (Barbieri et al. 2021). The dynamics of the spread through Europe and increasing evidence for lice as competent vectors induced suggestions that lice were involved in transmissions to humans (Drancourt and Raoult 2016; Barbieri et al. 2021). Even improvements of hygiene and quarantine did not prevent plague from returning. Taking France as an example, annually recurring epidemics again spread along main trade routes (Duncan and Scott 2005). Centuries after its first appearance, European metropoles such as London, Vienna, and Moscow were afflicted by the disease in the seventeenth and eighteenth centuries, with death tolls similar to the outbreak in Venice at the beginning of the Black Death (Glatter and Finkelman 2021). These late outbreaks or epidemics of the second pandemic presumably spread much faster within the human population than at the beginning of this pandemic (Earn et al. 2020). The spread was not completely limited to trade as also military operations and movements of troops contributed as suggested for the last huge outbreak of the second pandemic in Europe that occurred in Russia in the eighteenth century (Morozova et al. 2020).

An important scientific question is where the Black Death originated before it reached the regions surrounding the Black Sea. Apparently, the exact origin and the events leading up to human infections are hard to decipher. At least, the strains causing the Black Death were not descendants from the Justinian plague as both belong to different genetic clades (Wagner et al. 2014). China was long believed to be the origin of the Black Death. This claim goes far back to a time even before the causative agent *Y. pestis* was identified and is based on the book "The Black Death of 1348 and 1349," written by Francis Gasquet (Slavin 2019). Consistent with this assumption, isolate sequencing and phylogenetical analyses suggest the origin of all biovars associated with human pandemics to have originated in Central Asia (Li et al. 2009). China also has a long history of plague which even today is endemic in some regions where it persists in some foci in enzootic cycles between wildlife rodents and their fleas (Ben-Ari et al. 2012). In line with this, the analysis of 300 isolates of *Y. pestis* also indicated an origin in or near China (Morelli et al. 2010). The genetic diversity displayed at the time of the Black Death resulted in the emergence of new branches. Based on the high genetic diversity found in over 100 *Y. pestis* strains from China and East Asia, China was also considered to be a likely origin (Cui et al. 2013).

Contrarily to the China origin theory, no Chinese written records exist, which can be attributed to an infectious disease matching the clinical signs of plague (Sussman 2011). The earliest time at which plague appeared in China or was mentioned is documented around 1350 in the Hebei province, years after the start of the devastating Black Death that erased a huge portion of the European population (Ben-Ari et al. 2012; Benedictow 2013). However, the lack of historical records is no proof against it since they could have been lost due to wars or fires or existing but not attributed to plague. In this regard, there are indications for outbreaks in China around 1320–1350, which might have been caused by plague at a time or preceding the Black Death in Europe. In addition, the Mongols first expanded to the east and occupied Kaifeng, where an outbreak appeared. Later, they expanded their Empire to Eastern Europe, which preceded the European appearance of plague (Kausrud et al. 2010). The Mongols also occupied the Jin state in China, where mass mortality occurred among Mongolian soldiers, but it remains unknown if these events were actually caused by plague (Slavin 2019).

Nowadays, the Black Death is believed to have its origin either in the Asian steppes, China, or India (Cohn 2008; Kausrud et al. 2010), while the Asian steppes are currently favored (Fijn and Terbish 2021). Regarding India, no historic Indian records include references to an epidemic matching the description of the Black Death (Sussman 2011). It needs to be awaited if future archaeological findings combined with molecular techniques in this region will give further insights into the presence of plague in India. The Central Asia theory assumes that the Black Death emerged at lake Issyk-Kul, one of the biggest mountain-associated lakes in Kyrgyzstan. Ancient records mentioned many deaths showing symptoms that are similar to those of the Black Death (Kausrud et al. 2010). In comparison to other years, unusually high percentages of tombstones from 1338 and 1339 possess encryptions, some of them further indicating "died of pestilence" (Slavin 2019). After 1338, plague seems to have first spread westwards by land to the Middle East, reaching the Volga river in 1347 (Cassel 2006). However, the interpretation of historical writings is controversial and questioned as imperfect (Benedictow 2013). In this regard, many theories based on the interpretation of historical descriptions are questioned since data on the molecular evolution of *Y. pestis* suggest a much earlier presence and circulation even in Europe. Actually, these new findings induced historians to reanalyze the outbreaks, resulting in support for earlier outbreaks in Asia found in historical sources (Drancourt and Raoult 2016; Barker and Chen 2022). There are also descriptions of plague outbreaks on the Russian territory located far east of the Black Sea area, including the towns Astrakhan and Sarai, in the mid-1340s (Spyrou et al. 2019).

As far as known from the molecular evolution data, the strains later causing the Black Death presumably emerged roughly in the mid-1200s (Cui et al. 2013; Spyrou et al. 2018). The impact of these new data is unclear, but there is still the possibility that Mongolian troops carried the disease together with grain stocks already in the thirteenth century through their Empire to newly conquered regions, and that the known start of the Black Death in Europe was a resurgence rather than due to a new introduction (Green 2020b). However, an earlier low-level circulation or geographically confined spots would not be surprising since it has also been recognized for the third pandemic in which *Y. pestis* circulated for decades until being perceived worldwide during its outbreak in Hong Kong in 1894. Even if there was a low-level circulation before, the comparison of *Y. pestis* genome samples across Europe also favors the introduction through Eastern Europe (Spyrou et al. 2019), but this might have been an intermediate point from a spread initiated further east. In this regard, it is interesting to see the geographical proximity of lake Issyk-Kul to the Xinjiang province, in which the historic major hub Kashi was presumably implicated in the spread of many infectious diseases via the Silk Road. Plague is still endemic in the region surrounding lake Issyk-Kul. *Y. pestis* similar to the Antique biovar was found over several years, mainly in gray marmots and their fleas (Sariyeva et al. 2019). This is also consistent with the before-mentioned molecular characterization of ancestral *Y. pestis* strains collected in the Tien Shan mountains (Eroshenko et al. 2017). Of particular interest, the before-mentioned cemeteries from Issyk-Kul containing tombstones with inscriptions presumably referring to plague lie geographically between two of the plague foci of the Tien-Shan region (Slavin 2019). This even leaves the possibility open that both pandemics originated in a region close to lake Issyk-Kul.

Other sources point to an origin in the Himalaya in the early 1330s from which it spread westwards via major trade routes (Zietz and Dunkelberg 2004). The Qinghai-Tibet Plateau, located in the Himalayas, is still the most active plague focus in China, associated with *Y. pestis* in marmots and frequent human outbreaks (He et al. 2021). In addition, some localize the origin in the Mongolian steppes around 1331, where it was acquired by European merchants who traveled westwards to explore new territories. According to this theory, plague was first brought to the Yunnan province in China by these travelers and then spread back westwards to the Mediterranean region (Redish 2013). Independent of the exact region where the Black Death might have arisen in Asia, it is likely that traders with goods traveling along the Silk Road contributed to the spread since plague reservoirs did not expand their territories in the same way. Considering the length of the Silk Road and the fact that caravans traveled in between the different nodes, it might explain why the further spread was a slow process, and it took the Black Death roughly 10 years from the presumed outbreak at lake Issyk-Kul or nearby to reach the Mediterranean region.

The emergence of the Black Death seems to have been triggered or facilitated by favoring environmental conditions (Stenseth et al. 2008). Climate factors were also associated with recent plague endemicity and emergence in other geographical areas such as Madagascar (Alderson et al. 2020). Similarly, in British Columbia, outbreaks between the late nineteenth to mid-twentieth century generally correlated with an increase in humidity (Tennant et al. 2020). Conclusive with this, a climate change of the Central Asian steppes was suggested inducing a decline of the rodent populations, including gerbils and marmots. Such climate changes are likely to have occurred several times, causing multiple waves of plague from Asia to the West (Schmid et al. 2015). The region surrounding lake Issyk-Kul was preferred by the Mongols as pastureland for their livestock, including horses, cattle, and sheep. This region experienced profound weather changes preceding the outbreak of 1338/1339 at lake Issyk-Kul, including a devastating 3-year drought (Slavin 2019). The declining vegetation might have either induced rodents to approach human settlements or fleas to search for new hosts, including humans. Of those climate factors that impact the ecosystem, the temperature is considered to be an important one affecting both current and historic plague outbreaks (Krauer et al. 2021). In addition, relative humidity was identified to play a key role in outbreaks (Tennant et al. 2020). This assumption is also consistent with observations made during the third pandemic in China, where specific ecological factors and weather conditions facilitated outbreaks (Xu et al. 2014).

Another question is whether *Y. pestis* has been introduced once or multiple times into Europe during the second pandemic. While there are still compelling arguments for the single introduction theory (Spyrou et al. 2016), a repeated introduction into Western Europe is currently favored by others, presumably from a reservoir in the East (Bramanti et al. 2021). For example, the analysis of about 300 *Y. pestis* isolates pointed to an origin in or near China, with successive epidemic waves going westwards by various routes. Besides the Silk Road discussed as a distribution path, Chinese marine voyages were also considered (Morelli et al. 2010). The assumption of multiple waves driving plague from Asia to Europe is also supported by geological data and the analysis of several thousands of historical plague outbreaks, which indicate that periodic climate changes might have caused these successive waves (Schmid et al. 2015) with temperature likely to be the dominant factor for plague occurrence (Krauer et al. 2021). In line with the latter theory, two different *Y. pestis* clades were identified by analyses of single nucleotide polymorphisms and gene deletions in human remains from different Black Death-associated mass graves across Europe (Haensch et al. 2010). The level of genetic diversity during the Black Death is also a topic of controversial discussion. For example, *Y. pestis* is ascribed to a remarkable genetic diversity around the time of the Black Death, with four lineages that diverged (Cui et al. 2013). Contrarily, in a more recent comprehensive analysis *of Y. pestis* genomes acquired from human remains from ten archaeological sites across Europe, there was no genetic diversity when the Black Death swept rapidly through Europe (Spyrou et al. 2019).

Focusing again on the question whether *Y. pestis* was introduced once or multiple times, the multiple introduction hypothesis was also suggested by phylogenetical analysis of five *Y. pestis* genome samples across Europe from the second half of the fourteenth century. These data support multiple introductions, presumably through the fur trade, a branch of the trade from Asia via the Black sea ports, which gained greater importance at that time (Namouchi et al. 2018). However, the continued resurgence of outbreaks within each pandemic did not necessarily rely completely on new introductions. Since the strains causing one of the last European outbreaks in Marseille were genetically closely related to strains from the beginning of the Black Death in the fourteenth century, *Y. pestis* presumably persisted in some geographical regions in reservoirs, followed by multiple noticeable spillovers to humans (Bos et al. 2016). This assumption is also consistent with other evaluations suggesting a long-term persistence of the initial strains over the centuries but not today (Seifert et al. 2016; Spyrou et al. 2016). One of the biological reasons for such a decline might be an increasing immunity across wildlife animals which makes them resistant to plague. The pathogen can still survive in these animals but does not develop high bacteremias. For example, the resistance of the black rat is currently believed to favor the persistence of plague foci in Madagascar (Andrianaivoarimanana et al. 2013b, 2018). However, it is difficult to establish a causal relationship since paleogenetic analyses require the availability of preserved material and the strains that caused the late outbreaks, e.g., in London, are 99.99% genetically similar to the relevant genome of modern strains (Earn et al. 2020).

Generally, a broad spectrum of susceptible hosts creates more opportunities for *Y. pestis* to persist in the wild, and a broad spectrum of wildlife rodent species turned out to be positively correlated to human plague in the present (Sun et al. 2019). Conclusive with this, the analysis of post-Black Death genomes has revealed local diversification of an extinct *Y. pestis* lineage that may have broadened the reservoir range in which the bacterium may have resided (Spyrou et al. 2019). In addition to the traditional view of black rats and their fleas, there is increasing evidence that the human flea, *P. irritans*, was the main vector during the second pandemic (Dean et al. 2018). Although *P. irritans* has only a low efficiency in transmitting *Y. pestis*, its vector competence is increased by host factors and host choice. Furthermore, it is highly prevalent in many plague-endemic areas even today (Miarinjara et al. 2021). Even lice are increasingly getting into the focus of research as drivers of the Black Death as mentioned before (Drancourt and Raoult 2016; Barbieri et al. 2021). These newly followed approaches are promising to improve the understanding of the epidemiology of the Black Death, especially since black rats were absent in some areas which experienced epidemics such as rural England (Duncan and Scott 2005).

According to traditional views, in many outbreak settings, a massive rat dying preceded the first human infections. Rats are social animals that gather in bigger communities. Close contact within a rat colony facilitates the fast spread of *Y. pestis*-infected fleas. At the peak, the rat population is massively reduced. If new suitable hosts are available, fleas tend to make an inter-species jump to other mammals, including humans, followed by human infections with *Y. pestis*. The development of a plague outbreak is therefore divided into three phases (Cesana et al. 2017). The time interval from *Y. pestis* introduction into the rat population until noticeable human epidemics roughly ranges between 5 and 35 weeks (Barker 2021). This epidemiological pattern is also noticeable with other rodents and mammals involved in epizootics, like in the USA in the 1980s, where population densities of prairie dogs and other rodents declined, coinciding with increased levels of human plague (Perry and Fetherston 1997) or in the Yunnan province in China where a plague focus has been identified after an outbreak in the mid-2000s and subsequent investigations discovered an ongoing epidemic among wildlife rodents (Wang et al. 2018). However, there is no clear historical evidence for these events (Cohn 2008; Benedictow 2013), albeit the lack of obvious descriptions might be that heavily sick rats will hide rather than expose themselves (Benedictow 2013). In contrast, there are Chinese historic writings dating back to the eighteenth century, describing rats spitting out blood and massive rat dying followed by human infections, while it is unclear if the outbreaks were precursors of the third pandemic that started in China or connected to the second pandemic (Sussman 2011). The exact circumstances and causative factors why the second pandemic declined on average until the eighteenth century are uncertain, but one reason might have been the continuous crowding out of the black rat by the brown rat *Rattus norvegicus*, which is more habituated to sylvatic areas and tends to avoid human settlements (McCormick 2003; Rakin 2003). The brown rat was absent from the Mediterranean until the sixteenth century but became the dominant species afterward (Barker 2021). In addition, improved housing and personal hygiene, combined with combating local rat populations might have helped to reduce possible interspecies jumps of rat fleas in the case of dying hosts.

After some periods of declined trade, the Silk Road experienced a revival in the thirteenth and fourteenth centuries after being controlled by the Mongols. Thus, at the time the Black Death emerged, the Silk Road was flourishing. From the beginning of the thirteenth century to the mid to late fourteenth century, the Mongols kept the largest Empire in human history, from China to Persia (Green 2020a). The warlike nation brought stability to the conquered territories and the Mongols encouraged cultural exchange and trade (Safavi-Abbasi et al. 2007). Mongolia is nowadays known to have many active plague foci covering around one-third of total Mongolia where *Y. pestis* is frequently found in marmots and their fleas (Galdan et al. 2010). Due to the habit of raw meat processing and consuming raw meat of wild rodents such as marmots, human plague cases still occur in our modern time (Kehrmann et al. 2020). In addition, hunting marmots is strongly associated with Mongolian culture and the association between plague and marmots was known to Mongolians long before any scientific evidence. In addition, the trade of over a million marmots pelts per year by Mongolians at the end of the eighteenth century, brought to Russia and China, highlights the importance of marmots for the culture (Fijn and Terbish 2021). The cultural practice of many Mongolians to consume marmots can also be found in historical records from various sources at the time of the Black Death (Slavin 2019). Consequently, the Mongols are also believed to have spread the Black Death through their massive military movements and the demand for nutrition, transporting sacks of grains or millets that could have attracted and harbored rodents (Green 2020a). Interestingly, the association of the Black Death with the trade of *Y. pestis*-contaminated grain was also postulated for other regions, including Pisa in Italy. Pisa was a major hub for grain trade in 1347 and plague outbreaks spread from there through Tuscany in a fashion that is most likely explained by an involvement of rat fleas and distribution through trade (Cesana et al. 2017). Besides other common places that attract rats such as garbage dumps, rats prefer to live in and around grain storage facilities as well as on ships transporting grain (Barker 2021). However, it is unlikely that the spillover took place in Mongolia as the ancestral strains of *Y. pestis* were not found in numerous Mongolian isolates (Riehm et al. 2012).

In Europe, the role of rats in the transmission of the Black Death has long been accepted (Rakin 2003), albeit increasingly questioned as Europe's climate is fastidious for rat fleas (Barbieri et al. 2020). However, an open question remains if rats or other rodents were also the main drivers of the spread via the Silk Road. As mentioned before, the Mongols controlled huge parts of the Silk Road at that time. Mongols traveled in large caravans including horses and other animals and garbage left by these caravans behind might have attracted rats along the Silk Road (Cassel 2006). This is a tempting theory. The caravans consisted of multiple groups, each containing more than a dozen camels with a camel driver in front. The camels were loaded with up to 150 kg of goods, but also tents, dishes, clothes, and food (Benedictow 2013). In addition, massive movements of the Mongol army happened at that time. Therefore, the Silk Road, with hundreds and thousands of caravans and moving troops, must have been a huge trash can. This surely attracted omnivores. The pure proximity could have led to human infections, but also the infection of local rodents by feeding on dead human corpses left behind on the long road could have resulted in stable infections of rat populations near local nodes or villages. Taken together, rats and other rodents are strongly believed to have propagated the spread along the Silk Road (Cassel 2006). Another possible cause could have been trade with marmot pelts contaminated with flea eggs, especially in long-distance transports. This theory is not unlikely considering the dependence of Mongolians on marmot pelt trade, which can be estimated for the late eighteenth century (Fijn and Terbish 2021), but certainly reaches back many centuries before that. The increasing importance of the fur trade to Europe started in the mid-fourteenth century and is assumed to have been a potential source of *Y. pestis* spread (Namouchi et al. 2018).

There is also growing evidence that *Y. pestis* strains, which dominated at the beginning of the Black Death in Europe, swept back presumably several times to Asia while the second pandemic declined in Europe over the centuries (Spyrou et al. 2016; Drancourt and Raoult 2016; Guellil et al. 2020). Even when the heyday of the

Silk Road started to decline in that period, it was still used for trading goods and by travelers. In the fourteenth century, huge sections of the Silk Road were controlled by Mongols who welcomed travelers from other countries (see Sect. 7.6.1). In line, genetical comparisons of current Mongolian isolates suggest a re-population of Mongolian rodents by *Y. pestis* strains from other territories (Riehm et al. 2012). This again highlights the significance of a mixture of cultures and trade for the spread of infectious diseases.

7.6.5 The Third Pandemic

By the time the third pandemic stroke the world, the Silk Road had already lost its glance. The maritime trade, increasingly practiced since the thirteenth century, accelerated and facilitated the trade of goods between the continents and hence resulted in a continuous decline of the importance of the Silk Road. The third pandemic originated in China and spread to many parts of the world (Bramanti et al. 2019a). This pandemic required a long launching period with a circulation of *Y. pestis* and human outbreaks in some Chinese provinces. The epidemiology of the third pandemic deviates in many aspects from the first two pandemics (Cohn 2008). The earliest description dates back to 1772 in the town Dali located at the Yuan river in the Yunnan province (Ben-Ari et al. 2012; Bramanti et al. 2019a). However, the outbreaks were not limited to this region since historical documents describe a wider scale affecting both, North and South China, presumably by different strains because the clinical signs were predominantly pneumonic or bulbonic plague. The new *Y. pestis* biovar Orientalis, which was later identified during the first huge outbreak in the metropole Hong Kong in 1894, must have emerged through genetic evolution in about 1855 (Demeure et al. 2019). It is possible that the precursors of these strains, in turn, originated in Western Europe during the second pandemic (Spyrou et al. 2016; Namouchi et al. 2018). Again, just like described for the Black Death, it is believed to have been transmitted by rodents to humans (Rakin 2003). The exact route of how it reached Hong Kong is unknown, but newer insights suggest that periods of increased moisture and transport have facilitated the spread in China (Xu et al. 2014).

The outbreak in Hong Kong attracted massive attention around the world. This was not surprising considering the long history of devastating pandemics and the unimaginable misery they have caused. It was the time when the Swiss physician Alexandre Yersin identified a nonmotile bacterium to be the cause of the disease (Zietz and Dunkelberg 2004). In contrast to previous pandemics, the third pandemic was mainly spread by steamships. It also reached new areas like North America and Australia through seaports. In America, the impact was relatively low, and in Australia, plague disease did not become endemic, probably due to missing rodent hosts or vectors (Rakin 2003). Nevertheless, the fear of plague triggered immense preventive measures. In many ports, the installation of rat shields became mandatory to prevent the local introduction (Sonne 2016). Although outbreaks occurred in all major ports, the measure strongly reduced the number of deaths in Europe. No pattern of plague dispersal through land routes was observed in this third pandemic, which was already mitigated through improved hygiene, housing, underground sewerage, and centralized garbage disposal and ended in Europe in the 1940s (Bramanti et al. 2019a). Previously, many so far unknown aspects of the disease were unraveled, including the transmission via rat fleas. Although this pandemic had the least consequences of all known pandemics, it still killed around 15 million people around the world, with most deaths occurring in India (Frith 2012).

7.7 Conclusions

Plague has been a terrifying disease in the past. Three recorded pandemics are known, the first two each spanning more than a century. Newer evidence indicates *Y. pestis* infected humans in Eurasia long before the known pandemics and might have caused unrecorded outbreaks or just occasional human infections. The ancient strains were likely less transmissible and virulent and went extinct. However, *Y. pestis* kept evolving and acquired characteristics that facilitated its spread. All known pandemics presumably originated in the Asian region. While it is likely that the Silk Road was implicated in the spread of the first two pandemics, facilitating the dispersal by vast amounts of humans, animals, goods such as grains, and soldiers passing the network of routes in both directions, the third pandemic was mainly spread by ships. However, even nowadays, single cases of plague disease occur in Asia, Africa, and North America.

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Dengue along the Silk Road

8

Xiaoying Zheng

Abstract

Dengue is a mosquito-borne viral disease that has rapidly spread in all regions of the world in recent years, including the BRI countries. Dengue virus (DENV) is a mosquito-borne virus belonging to the Flaviviridae family. There are DENV-1, DENV-2, DEN-3 and DENV-4 four antigenically different serotypes DENV. Aedes mosquitoes act as vector of DENVs. Dengue is found in tropical and sub-tropical climates worldwide, 70% of the actual burden is in Asia, high number of cases were reported in Bangladesh, Malaysia, Philippines, Vietnam etc. Dengue poses a significant health and economic burden in the BRI Asia Region. DENV is frequently transported from one place to another by infected travelers. Mosquito vector spread is also important risk factor. Imported dengue cases are thought to be an important source for transmission in China. DENV infection results in a wide spectrum of clinical symptoms, including dengue hemorrhagic fever (DHF). Dengue infection diagnosis include clinical and laboratory diagnosis. Dengue control measures includes patient treatment and mosquito control. Therefor, it is important to to cooperate in in dengue control among the BRI counties.

Keywords

Dengue fever · Dengue virus · Aedes · The Silk Road

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_8

8.1 Dengue Virus, Vectors, and Epidemiology

Dengue virus circulates in many parts of the world, impacting most tropical and subtropical countries. Millions of people are affected each year and global dengue incidence has dramatically increased in recent decades.

First proposed in 2013 and hailed by Xi Jinping as the "project of the century," China's Belt and Road Initiative (BRI) promises a win–win partnership with China offering loans and investment and host countries supplying new markets in the process of "inclusive globalization" (Liu et al. 2016; Zhang et al. 2018). Among 146 BRI countries, dengue is endemic or reported in more than 86 BRI countries, some of which have severe dengue epidemics.

8.1.1 Dengue Virus

Dengue is a mosquito-borne viral disease that has rapidly spread in all regions of WHO in recent years. The incidence of dengue has grown dramatically worldwide in recent decades. The virus is transmitted by female mosquitoes mainly of the species *Ae. aegypti* and, to a lesser extent, *Ae. albopictus*.

Dengue virus (DENV) is a mosquito-borne virus belonging to the Flaviviridae family. DENV is a 50-nm virus particle surrounded by a lipid membrane. The genomic RNA of about 11.000 nucleotides of length contains a single open reading frame which encodes a large polyprotein that is co- and post-translationally processed into three structural proteins (capsid (C), precursor membrane (prM), and envelope (E)) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). There are four DENV serotypes, four phylogenetically and antigenically distinct dengue virus (DENV1–4) (Messina et al. 2014). Although infection with one type confers long-term immunity, it is to that type only and not to the other three type. While many DENV infections produce only mild illness, DENV can cause an acute flu-like illness. Occasionally, this develops into a potentially lethal complication, called severe dengue. Severe dengue is a leading cause of serious illness and death in some Asian and Latin American countries. It requires management by medical professionals.

8.1.2 Dengue Vectors

Aedes mosquitoes act as a vector of DENVs. *Aedes aegypti* is considered the major vector of DENV in most of the BRT countries. It could breed in both natural containers and man-made containers. Natural contains involve such as tree holes and bromeliads, and man-made containers include discarded containers, buckets, pots, and used tires. Nowadays, in urban areas, artificial containers are the main breeding grounds for *Ae. aegypti*. *Ae. aegypti* take blood meal during daytime. There are a peak biting periods in the early morning and in the evening before sunset, respectively. Female *Ae. aegypti* may take blood meal several times between each egg-laying period, thus leading to multiple infected individuals. *Aedes* mosquito eggs can remain viable for several months after being laid under dry conditions, and they will hatch when they come into contact with water.

Aedes albopictus is the secondary dengue vector in most dengue epidemic countries. *Ae. albopictus* also take blood meal during daytime, and it is considered the primary vector of DENV in the areas with a limited number of outbreaks, where *Ae. aegypti* is either not present or present in low numbers; for example, it is the main vector in most areas of mainland China.

Ae. albopictus is native to Asia and the South Pacific and has recently been introduced into North and South America and European Region, mainly due to the international trade in used tires (*Aedes* mosquito breeding habitat) and others (lucky bamboo, etc.). The favorable breeding sites of *Ae. albopictus* seem close to dense vegetation, including plantations that is linked to increased risk of exposure for rural workers such as those in palm oil and rubber plantation; in urban areas, abundant breeding sites also have been found.

8.1.3 Dengue Epidemiology

8.1.3.1 Dengue Distribution

Dengue is found in tropical and subtropical climates worldwide, mostly in urban and semi-urban areas. Since the 1960s, the dengue virus has spread from less than 10 known countries where the disease was endemic and a few thousand cases reported each year to 128 endemic countries, an estimated 400 million infections and 100 million symptomatic cases annually. The number of dengue cases reported to WHO increased more than eightfold over the past two decades, and dengue is the only communicable disease that has increased exponentially with rapid urbanization and environmental changes. The vast majority of cases are asymptomatic or mild and self-managed; hence, the actual numbers of dengue cases are under-reported. Currently, around 100 countries and territories in WHO's Americas, South-east Asia, and Western Pacific regions report dengue cases regularly. Despite a risk of infection existing in 129 countries, 70% of the actual burden is in Asia. A high number of cases were reported in Bangladesh (101,000), Malaysia (131,000), the Philippines (420,000), and Vietnam (320,000) in Asia.

In Asia, BRI countries including Singapore, Timor-Leste, Malaysia, Myanmar, Cambodia, Viet Nam, Pakistan, Sri Lanka, Bangladesh, Nepal, Maldives, Saudi Arabia, Afghanistan, Thailand, Indonesia, the Philippines, Yemen, Lao, and China have dengue epidemic or dengue case reports. There have been no dengue reports by the National Disease Surveillance and Response System (NDSR) in Afghanistan before 2019. For the first time, locally acquired DENV cases have been detected in Afghanistan by the national surveillance and response system, mostly in provinces bordering Pakistan in 2019 (Sahak 2020). As a dengue nonendemic country, China has experienced several dengue outbreaks in recent years.

Among the 49 BRI countries in Africa, dengue has been reported, including dengue reported only in travelers, and the presence of *Ae. aegypti* mosquitoes in

31 countries. Dengue has not been reported in 9 countries (Sierra Leone, Guinea, Mauritania, Chad, Congo, Zimbabwe, Congo, Botswana, and Central Africa) but where *Ae. aegypti* mosquitoes are present (Were 2012). Before 2013, there had been no records of the dengue virus in Ethiopia (Mohan et al. 2021), but the virus has since spread to multiple regions. Dengue outbreaks were recorded in Ethiopia in 2017, 2019, and 2021, according to epidemiological evidence. Dengue fever can be transmitted all year; however, the danger is greatest during and immediately after the rainy season, which runs from June to August.

Dengue epidemics or cases have been reported in all BRI countries in North (12 BRI countries) and South America (9 BRI countries). In Europe, 4 BRI countries have reported dengue cases, including only imported cases. In the Oceania area, dengue epidemics or cases have been reported in BRI countries other than New Zealand. The threat of a possible outbreak of dengue now exists in Europe; local transmission was reported for the first time in the BRI country Croatia in 2010. Although there have been no case reports in Turkey due to DF, there is sero-epidemiological evidence indicating the presence of dengue virus (DENV) in Turkey (Uyar et al. 2013).

8.1.3.2 Dengue Transmission

Dengue is caused by a virus of the Flaviviridae family, and there are four distinct, but closely related, serotypes of the virus (DENV-1, DENV-2, DENV-3, and DENV-4) that cause dengue. DENVs are spread mainly through mosquito bites and in some cases through maternal transmission or other means.

8.1.3.2.1 Transmission through the Bite Mosquito of *Aedes* Mosquito

DENV is transmitted from human to humans through the bites of DENV-infected female *Aedes* mosquitoes, mainly the *Ae. aegypti* mosquito. Other species such as *Ae. albopictus* can also act as secondary vectors.

When mosquitoes bite on people who are viremic with DENV, they can become infected. This can be someone who has a asymptomatic, pre-symptomatic, and symptomatic dengue infection. Human-to-mosquito transmission can occur up to 2 days before the patient develops symptoms and up to 2 days after the fever subsides.

After taking an DENV-infected blood meal, the virus replicates first in the mosquito midgut and finally disseminates to the salivary glands. The extrinsic incubation period (EIP) is the time from ingesting the virus to actual transmission to a new host. When the ambient temperature is 25–28 °C, the EIP need takes about 8–12 days. The variation of external latency is not only affected by ambient temperature and also by a number of factors such as the initial viral concentration, the virus genotype, the symbiotic bacteria, and range of daily temperature fluctuations. Once infectious, the *Aedes* mosquito is capable of transmitting the virus for the rest of its life.

The risk of mosquito infection is positively associated with high viremia and high fever in the patient; conversely, high levels of DENV-specific antibodies are associated with a decreased risk of mosquito infection.

8.1.3.2.2 Maternal Transmission

The primary mode of transmission of DENV between humans involves mosquito vectors. There is the possibility of maternal transmission (from a pregnant mother to her baby). Vertical transmission rates appear low, with the risk of vertical transmission seemingly linked to the timing of the dengue infection during the pregnancy. When a mother does have a DENV infection when she is pregnant, babies may suffer from pre-term birth, low birthweight, and fetal distress.

8.1.3.2.3 Other Transmission Modes of Dengue

Rare cases of transmission via blood products, transfusions, and organ donation have been recorded. Similarly, transovarial transmission of the virus within mosquitoes has also been recorded.

8.2 Dengue Disease Burden

Dengue virus is a mosquito-borne infection that has become a health threat globally. It has been estimated to cause a substantial health and economic burden in epidemic countries. Within the Global Burden of Disease study 2013, it was estimated that dengue was responsible for 1.14 million disability-adjusted life years (DALYs) globally, and it is estimated that it is responsible for 39,884 disability-adjusted life years (DALYs) annually, representing an economic burden of US$94.87 million per year (in 2016 price) (Hung et al. 2018).

Dengue poses a significant health and economic burden in the BRI Asia Region. In Thailand, Dengue illness often leads to school and work absenteeism, medical and nonmedical expenditures, and foregone income. A research about household costs of hospitalized dengue illness in semi-rural Thailand demonstrated that hospitalized dengue illness costs approximately 19–23% of the monthly household income, although 74% of the households reported that the patient received free medical care (Tozan et al. 2017). Dengue also contributes significantly to socioeconomic burden in Nepal, and the risk of dengue infection and outbreak in Nepal is increasing year by year at different spatial scales.

In 2020, dengue affected several countries, with reports of increases in the numbers of cases in Bangladesh, Brazil, Cook Islands, Ecuador, India, Indonesia, Maldives, Mauritania, Mayotte (Fr), Nepal, Singapore, Sri Lanka, Sudan, Thailand, Timor-Leste, and Yemen. Dengue continues to affect Brazil, India, Vietnam, the Philippines, the Cook Islands, Colombia, Fiji, Kenya, Paraguay, Peru, and the Reunion islands in 2021.

Imported dengue cases are thought to be important sources for transmission of autochthonous dengue in Europe (Ahmed et al. 2020). A number of cases were imported to Norway, Sweden, Finland, Russia, Turkey, Israel, Romania, Poland, Spain, Portugal, Italy, Switzerland, Czech Republic, Denmark, the United Kingdom, the Netherlands, Belgium, Germany, and France.

8.3 Influence Factors of Dengue Epidemic

Dengue is widespread throughout the tropics, and local spatial variation in dengue virus transmission is strongly influenced by rainfall, temperature, urbanization, and distribution of the principal mosquito vector *Aedes aegypti*. The spread of secondary vector *Ae. albopictus* also contributes to the dengue epidemic.

8.3.1 Risk Due to Climate Changing

Climatic changes, landscape management, and massive human, animal, and commodity transportation represent important factors that contribute to the spread of dengue.

8.3.2 Risk Due to Travel

DENV is frequently transported from one place to another by infected travelers; when susceptible vectors are present in these new areas, there is the potential for local transmission to be established. Travel-acquired dengue cases have been increasing as the overall global dengue burden has expanded. Globalization has led to an increased incidence of the virus both in foreign travelers returning home and local outbreaks in traditionally nonendemic areas, such as southern Europe. The rise in global travel and trade has posed Europe with an increased risk of introduction and expansion of exotic arthropod vectors and autochthonous transmission of arboviruses, like dengue and chikungunya viruses, following new introductions from endemic areas. Europe is already partially colonized by another DENV vector, *Ae. albopictus.*

In Korea, imported dengue cases have been reported since 2000 when it first became a notifiable disease.

Every year in South Korea, it is reported that a few hundred people are infected during travel to dengue-endemic countries. However, there have been no domestic infections reported so far. With a gradual change toward a subtropical climate owing to global warming, Korea could face a spread of domestic dengue in the near future.

8.3.3 Risk Due to Mosquito Vector Spread

Among the invasive mosquitoes registered all over the world, *Aedes* species are particularly frequent and important. *Ae. albopictus* is highly adaptive. Its geographical spread is largely due to its tolerance of colder conditions as an egg and adult. In Europe, *Ae. albopictus* first arrived in 1979 in Albania and in 1990 in Italy. Currently, the species is established in more than 20 countries, and it has been responsible for outbreaks of dengue in Croatia, France, and Italy. Public health concerns have spurred research on the suitability of the European continent to the establishment of *Ae. albopictus.*

8.3.4 Risk Due to Other Infectious Diseases

The COVID-19 pandemic is placing immense pressure on health care and management systems worldwide. Recently, as COVID-19 has spread around the globe and more adults have been exposed to it, there have been more reports of coinfections with other infectious diseases. WHO has emphasized the importance of sustaining efforts to prevent, detect, and treat vector-borne diseases during this pandemic such as dengue and other arboviral diseases, as case numbers increase in several countries and place urban populations at the highest risk for both diseases. The combined impact of the COVID-19 and dengue epidemics could have devastating consequences on the populations at risk.

In August 2020, during the coronavirus disease (COVID-19) pandemic, five locally acquired cases of dengue virus type 1 were detected in a family cluster in Vicenza Province, North-East Italy, where *Aedes albopictus* mosquitoes are endemic. The primary case was an importation from West Sumatra, Indonesia. This is the first outbreak of autochthonous dengue reported in Italy. During the COVID-19 pandemic, screening of febrile travelers from endemic countries is crucial in areas where competent vectors are present.

In Bangladesh, an alarming situation is a devastating dengue outbreak amid the COVID-19 pandemic. As the COVID-19 outbreak wreaks havoc, the following rise in dengue illnesses has been a source of considerable concern. As health care has been stretched thin in these dangerous times, the vulnerable population has been left at the mercy of these two viral infections.

In Africa BRI countries, for example, Ethiopia has been facing a serious public health problem regarding the dengue outbreak amid the COVID-19 pandemic.

Under the current pandemic, when health officials are mainly focused on containing the virus, every other infectious disease outbreak could obstruct COVID-19-fighting efforts and pose diagnostic challenges for medical personnel.

8.4 Disease Characteristics (Signs and Symptoms)

DENV infection results in a wide spectrum of clinical symptoms, ranging from mild fever to dengue hemorrhagic fever (DHF), the latter of which can progress to dengue shock syndrome (DSS) and death. There are around 90 million symptomatic cases of dengue each year, with severe disease in around 1% of cases, including life-threatening hemorrhage or shock syndrome.

Symptoms of DENV infection typically appear 3–14 days after inoculation by the *Aedes* mosquito and most commonly manifests as a self-limiting febrile illness. However, in severe dengue, plasma leakage may be profound and result in hemorrhage, disseminated intravascular coagulation, and circulatory collapse. The dengue virus may also cause organ dysfunction. Cases of myocarditis, myocardial dysfunction, and arrhythmias, including atrioventricular block, have been reported. The World Health Organization classifies dengue into two major categories: dengue (with/without warning signs) and severe dengue.

8.4.1 Dengue Fever

Most DENV infections are asymptomatic or present a mild illness. It can manifest as a severe, flu-like illness that affects infants, young children, and adults but seldom causes death. Symptoms usually last for 2–7 days, after an incubation period of 4–10 days after the bite from an infected mosquito. These symptoms are known as dengue fever (DF), which is an acute, self-limited, febrile illness. Symptoms usually last for 2–7 days, after an incubation period of 4–10 days after the bite from an infected mosquito.

Recovery from infection is believed to provide lifelong immunity against that serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections (secondary infection) by other serotypes increase the risk of developing severe dengue.

8.4.2 Severe Dengue

Severe dengue is a severe form of dengue fever with clinical manifestations of severe bleeding, shock, and severe organ damage. It was first recognized in the Philippines and Thailand in the 1950s during dengue epidemics. Nowadays, severe dengue has become a leading cause of hospitalization and death among children and adults in most Asian and Latin American regions. Severe dengue fever is a potentially fatal complication caused by severe bleeding, plasma leaking, respiratory distress, fluid accumulation, and organ impairment.

Some dengue patients develop dengue hemorrhagic fever (DHF), which is a severe syndrome, and patients may present hematomas with marked thrombocytopenia or extremely low platelet counts. DHF symptoms include increased vascular fragility, raised plasma leakage/heme concentration coagulation abnormalities, and loss of fluid. DHF appeared in Singapore in the 1960s and quickly became a major cause of childhood death (Ooi et al. 2006). DHF is probably caused by viral antigens and host immune responses, virus-specific antibodies, or other factors. If dengue patients develop dengue shock syndrome (DSS), more severe clinical symptoms occur. Symptoms of DSS are similar to DHF, and it may develop into hypovolemic shock and have the risk of multiple organ failure.

Genetic differences among DENV genotypes are associated with differential viral virulence that may contribute to the development of the severe diseases, such as DHF and DSS.

8.5 Diagnostics

Dengue infection diagnosis includes clinical and laboratory diagnosis. Dengue infection has a wide clinical spectrum that includes both severe and mild manifestations.

In the 2009 WHO guidelines, dengue is defined as fever plus two or more of the following: nausea/vomiting, rash, aches and pains, positive tourniquet test, leukopenia, or any warning sign (outlined in the guidelines).

In China's 2018 guidelines for case surveillance of dengue fever, the diagnosis of dengue fever is based on the epidemiological history, clinical manifestations, and laboratory results.

Several laboratory methods can be used for the diagnosis of DENV infection. Depending on the time of patient presentation, the application of different diagnostic methods may be more or less appropriate. Patient samples collected during the first week of illness should be tested by laboratory methods.

8.5.1 Virus Isolation Methods

The virus may be isolated from the blood during the first few days of infection. Isolation of dengue virus from the serum, cerebrospinal fluid, blood cells, or tissues of patients in the acute phase can confirm the diagnosis.

8.5.2 RT-PCR or Real-Time Fluorescence Quantitative PCR Technique

The gene sequence of the dengue virus was detected by RT-PCR or real-time fluorescence quantitative PCR can help confirm the diagnosis. Various reverse transcriptase–polymerase chain reaction (RT-PCR) methods are available and are considered the gold standard. However, they require specialized equipment and training for staff to perform these tests.

8.5.3 Serological Methods

8.5.3.1 Detection of Dengue Virus NS1 Antigen

The virus may also be detected by testing for a virus-produced protein, NS1. In China, a clinically diagnosed case with a positive result of dengue virus NS1 antigen detection can be confirmed. There are commercially produced rapid diagnostic tests available for this, and it takes only ~20 mins to determine the result, and the test does not require specialized laboratory techniques or equipment.

8.5.3.2 Detection of Anti-Dengue Virus Antibodies

Enzyme-linked immunosorbent assays (ELISA) is one of the commonly used antibody detection methods. The detection of anti-dengue antibodies may confirm the presence of a recent or past infection. IgM antibodies are detectable ~1 week after infection and remain detectable for about 3 months. The presence of IgM is indicative of a recent DENV infection. IgG antibody levels take longer to develop and remain in the body for years. The presence of IgG is indicative of a past infection. A clinically diagnosed case with the titer of serum specific antibody in the convalescent period increased more than four times than that in the acute period should be laboratory confirmed. A number of preventive strategies have been proposed particularly on reduction of the mosquito vector by using mechanical, chemical, and biological approaches.

8.6 Prevention and Control

Dengue virus is a mosquito-borne infection that has become a health threat globally. A large number of dengue cases are reported during monsoon seasons due to the high prevalence of vectors each year, and many of the dengue cases are not reported or classified. Dengue control measures include isolation and treatment of existing patients and medical observation of close contacts, active epidemic surveillance, mosquito control, community engagement, and vaccine prevention. Given an optimal temperature for vector breeding and a lack of a safe, effective dengue vaccine and urban transmission cycle of dengue virus (human-mosquito-human), dengue preventive measures are emphasized in endemic areas such as Southeast Asia.

8.6.1 Dengue Patient Treatment

There is no specific treatment for dengue fever. Currently, treatments for dengue infection are only symptomatic, as no antiviral agents nor vaccines are available to combat this virus. Patients should rest, stay hydrated, and seek medical advice. Depending on the clinical manifestations and other circumstances, patients may be sent home, be referred for in-hospital management, or require emergency treatment and urgent referral.

Supportive care such as fever reducers and painkillers can be taken to control the symptoms of muscle aches and pains and fever. The best options to treat these symptoms are acetaminophen or paracetamol.

NSAIDs (non-steroidal anti-inflammatory drugs), such as ibuprofen and aspirin, should be avoided. These anti-inflammatory drugs act by thinning the blood, and in a disease with a risk of hemorrhage, blood thinners may exacerbate the prognosis.

For severe dengue, medical care by physicians and nurses experienced with the effects and progression of the disease can save lives, decreasing mortality rates to less than 1% in the majority of the countries.

Dengue patients in China displayed distinct clinical characteristics compared to patients in endemic countries. To standardize the diagnosis and treatment of dengue fever, the experts of the Society of Infectious Diseases, the Society of Tropical Medicine and Parasitology of Chinese Medical Association, the Chinese Society of Emergency Medicine, and the Association of Chinese Medicine have reached this guideline based on guidelines for diagnosis, treatment, prevention, and control of dengue; guidelines for diagnosis and treatment of dengue; health industry standard of the People's Republic of China "diagnosis for dengue fever (WS216–2018)"; and systemic reports on dengue. The guideline includes eight aspects: introduction, terminology, epidemiology and prevention, etiology and pathogenesis, clinical features, diagnosis, treatment, and problems to be solved.

The dengue virus may circulate in the blood during the first week of illness. So if people have been infected with dengue, he/she should avoid getting further mosquito bites during the time; if not, the infected person may transmit the virus to new uninfected mosquitoes, who may in turn infect other people.

8.6.2 Vaccination against Dengue

Vaccines are a principal preventive approach for combating infectious diseases. Vaccination in the human population is one of the key strategies to prevent the risk of dengue virus transmission from a human host to a mosquito vector (Bos et al. 2018).

Because DENV has four different serotypes, a practical dengue vaccine should provide long-term protection for infections of homotypic and heterotypic serotypes. Multiple strategies have been exploited for vaccine development. There are live attenuated dengue vaccines, live chimeric dengue vaccines, inactivated dengue vaccines, and recombinant protein, DNA, and subunit dengue vaccines.

Live attenuated vaccines, which contain attenuated pathogenic microorganisms, are capable of producing a broad range of immune responses. The scientists of Mahidol University in Thailand developed a tetravalent attenuated dengue vaccine (LAV), which was generated by serial passaging of four DENV serotypes in a cell culture. Three dengue serotype viruses (DENV1, 2, and 4) were attenuated in primary dog kidney cells, whereas DENV3 was serially passaged to reduce its virulence in primary African green monkey kidney cells. The candidate vaccine was used in phase I and II clinical trials in Thai adults and children. Not all of the volunteers developed antibodies for all four dengue serotypes, and some experienced unacceptable reactogenicity and further clinical testing was terminated.

The first dengue vaccine, Dengvaxia® (CYD-TDV) developed by Sanofi Pasteur, was licensed in December 2015 and has now been approved by regulatory authorities in ~20 countries. The Dengvaxia vaccine is a tetravalent chimeric vaccine. For each of the four dengue serotypes, the prM and E genes from virulent DENV strains are substituted into the backbone of the yellow fever virus 17D vaccine strain.

Except the licensed Dengvaxia vaccine, several dengue vaccine candidates are in clinical trials or under preclinical evaluation, and multiple strategies have been exploited for vaccine development.

Although many vaccines that target either the DENV virions or the viral structural proteins have been licensed or under clinical trials, significant safety concerns remain unresolved (Liu et al. 2016).

Vaccination should be considered as part of an integrated dengue prevention and control strategy. There is an ongoing need to adhere to other disease preventive measures such as well-executed and sustained vector control. Individuals, whether vaccinated or not, should seek prompt medical care if dengue-like symptoms occur.

8.6.3 *Aedes* Mosquito Vector Control

The rise of dengue cases can be prevented by controlling vector spread. Due to the lack of an effective vaccine and drug to cure these diseases, mosquito control is the only method available to reduce disease risk. At present, the main method to control or prevent the transmission of dengue virus is to combat the mosquito vectors.

Reduction of the mosquito vector is achieved using environmental management and chemical, mechanical, and biological approaches. The integration of vector management approaches is encouraged by WHO to achieve sustainable, effective, locally adapted vector control interventions.

8.6.3.1 Environmental Management

The proximity of mosquito vector breeding sites to human habitation is a significant risk factor for dengue, preventing mosquitoes from accessing egg-laying habitats by environmental management and modification;

Prevention of mosquito breeding is performed by disposing of solid waste properly and removing artificial man-made habitats that can hold water; covering, emptying, and cleaning of domestic water storage containers on a weekly basis; reducing the breeding sites for *Aedes* mosquitoes that transmit vector-borne dengue by enhancing access to piped water, constructing houses with built-in screens to block mosquito entry; clearing waste; and improving drainage and keeping the environment clean.

8.6.3.2 Mechanical Approaches

Mechanical approaches such as mosquito traps, electric mosquito swatters, and mosquito nets are used.

8.6.3.3 Chemical Control

Insecticides are among the most effective ways to control mosquito populations, but the majority of them have negative impacts on health and environment and some are no longer effective due to the emergence of insecticide-resistant mosquitoes. Most of the available preventive and control measures involve an application of chemical-based products. The inappropriate use of chemicals causes insecticide resistance and environmental contamination.

8.6.3.4 Biological Control

As there are few effective sustainable tools available to combat *Aedes*-borne diseases, all new tools that demonstrate public health value against dengue and similar viruses will be a welcome addition to the vector control arsenal. A number of novel approaches have been employed to control mosquito populations. Biological control using bacterial infections such as *Wolbachia* results in the reduction of vector. Over the past two decades, various innovative strategies to reduce the transmission of dengue have been developed. Some strategies aim to reduce mosquito populations, which are known as population suppression; the strategies that aim to make wild mosquitoes unable to transmit infectious diseases by spreading genetic modifications or bacterial infections through natural populations are known as population replacement. Both population suppression and population replacement have developed in some BRT countries, like China, Singapore, Malaysia, Indonesia, and Thailand.

8.6.3.4.1 Population Replacement

Wolbachia are intercellular natural symbiotic bacteria in insects that are known to reduce the capacity of *Ae. aegypti* and *Ae. albopictus* to transmit dengue virus and related viruses under laboratory conditions. However, epidemiological evidence has been awaited to demonstrate the large-scale deployment of *Wolbachia*-infected *Ae. aegypti* in reducing the overall frequency of the transmission of the dengue virus within a population; the results of the study from Indonesia are therefore of great interest.

A three-year trial in Indonesia has produced encouraging results that show a significant reduction in the number of dengue cases. The trial conducted by the World Mosquito Program in close collaboration with the Tahija Foundation and the Gadjah Mada University in Indonesia tested *Ae. aegypti* mosquitoes carrying *Wolbachia* for their capacity to inhibit the transmission of the dengue virus.

It involved the release *Wolbachia*-infected *Ae. aegypti* mosquitoes in and around the dengue-endemic city of Yogyakarta.

The study found that in the city and surrounding areas where the infected mosquitoes were released the number of cases of dengue decreased significantly compared with parts of the city where they were not. *Ae. aegypti* mosquitoes infected with the wMel strain of *Wolbachia pipientis* are less susceptible than wild-type *Ae. aegypti* to dengue virus infection. Introgression of wMel into *Ae. aegypti* populations was effective in reducing the incidence of symptomatic dengue and resulted in fewer hospitalizations for dengue among the participants (Utarini et al. 2019).

In Malaysia, releases of *Ae. aegypti* mosquitoes carrying wAlbB were carried out in six diverse sites in greater Kuala Lumpur, with high endemic dengue transmission (Nazni et al. 2019). The strain was successfully established and maintained at very high population frequency at some sites or persisted with additional releases following fluctuations at other sites. In the release sites, reduced human dengue incidence was observed when compared to control sites based on passive case monitoring. *Wolbachia* provides a promising option as a tool for dengue control.

8.6.3.4.2 Population Suppression

Population suppression strategies currently being developed in BRT countries include sterile insect technique (SIT), incompatible insect technique (IIT), and combination of IIT with SIT (IIT-SIT). All these strategies reduce mosquito density by continuously releasing sterilized males.

In SIT, artificially-reared radiation-sterilized males are released into the field to mate with wild females. SIT has been used with great success against other insect pests; for example, the New World screwworm, *Cochliomyia hominivorax*, has been eradicated from Northern and Central America; the tsetse fly, *Glossina austeni*, from Unguja Island, Zanzibar, since 1997; and the Mediterranean fruit fly, *Ceratitis capitata*, from Mexico. The program is still ongoing to contain its reinvasion from Guatemala, and the codling moth, *Cydia pomonella*, has been suppressed using SIT in British Columbia, Canada, for more than 25 years.

SIT is an innovative nuclear technique that sterilizes mosquitoes to be tested in countries to control dengue, Zika, and chikungunya. It is an environmentally friendly control method. The SIT against mosquitoes is still under development in BRT countries. SIT is not a stand-alone technique, but rather meant to complement existing vector control measures within area-wide integrated control strategies for mosquito control.

The development of SIT against mosquitoes has progressed rapidly in recent years with significant advances made with the development of genetic sexing strains, mass-rearing, sex separation, handling, radiation, quality control, and release technologies.

Recent progress in the development of the SIT package against mosquitoes allows envisaging its larger-scale deployment. Four phases are presented, that is, from preparatory activities to operational deployment, with some milestones highlighted that include go/no-go criteria.

Phase 0 is a pre-intervention phase in which stakeholder commitment is secured; eight BRT countries are at phase 0: Brunei Darussalam, Myanmar, Pakistan, Cambodia, Fiji, Lao P.D.R., Nepal, and Viet Nam.

Phase I includes the collection of all relevant baseline data that are required to develop an appropriate intervention strategy against target mosquito populations. The Philippines and Bangladesh are at phase 1.

Phase II includes all necessary activities for a successful small-scale field trial; China, Indonesia, Malaysia, Sri Lanka, and Thailand are at phase 2.

Phase III includes the necessary activities to upscale the intervention; only Singapore is at phase 3.

Phase IV corresponds to the area-wide deployment of the intervention (including the release of sterile mosquitoes) that is guided by an adaptive management approach and the evaluation of the SIT program. No BRI countries are at this phase.

IIT and IIT-SIT.

Incompatible insect technique (IIT) uses cytoplasmic incompatibility (CI) caused by the maternally inherited endosymbiotic bacteria *Wolbachia* to sterilize field females when they mate with released males infected with a different *Wolbachia* strain. *Wolbachia*-based sterilization used by IIT has little or no impact on male fitness and mating competitiveness. The successful field trial in Guangzhou, China, demonstrates the feasibility of the area-wide application of IIT/SIT for mosquito vector control. Combined IIT/SIT nearly eliminated two field populations of *A. albopictus* over a two-year period (Zhang et al. 2018).

In Singapore, a three-year trial demonstrated that *Wolbachia*-based IIT dramatically reduces both wild-type *Ae. aegypti* populations [reductions of 92.7% (95% CI: 84.7%–95.8%) and 98.3% (97.7%–99.8%)] and dengue incidence [reductions of 71% (43%–87%) to 88% (57%–99%)] in ten targeted areas. Releases of male *Wolbachia*-infected *Ae. aegypti* suppress dengue mosquitoes and reduce dengue incidence in high-rise urban areas in Singapore (Liew et al. 2021).

In Thailand (Kittayapong et al. 2019), the first proof of-concept to suppress *Aedes aegypti* vector populations by using IIT-SIT in semi-rural settings was conducted. Whether open field release of sterile males, produced from combining the sterile insect technique using radiation with the insect incompatible technique through *Wolbachia*-induced incompatibility (SIT/IIT), could suppress natural populations of *Ae. aegypti* in semi-rural village settings was explored. The pilot trial involved the release of 100–200 sterile males per household in a treated area over a 6-month period. High efficacy of this approach was evidenced by a significant reduction in the numbers of wild *Ae. aegypti* females and an increase in sterility by reduction in the egg hatch rate of wild *Ae. aegypti* females in the treated area.

However, IIT may be undermined by the accidental release of females infected with the same *Wolbachia* strain as released males. Accidental release of fertile females might cause population replacement, whereby individuals infected with the same *Wolbachia* strain as released males replace the wild-type field population, preventing population suppression (as mating between released males and field females are no longer incompatible). While combining IIT and SIT, low-dose irradiation sterilizes residual females not removed from released males without affecting the latter's fitness or mating performance. Irradiation provides protection against accidental female release, especially compared to manual checking, as wPip-positive larvae did not increase despite more (>ten-fold) mosquitoes being released. In addition, irradiated HC males also induce HC female sterility and further reduce the risk of population replacement.

8.6.4 Personal Protection to Avoid Mosquito Bites

Some personal household protection measures can be used for avoiding mosquito biting, such as repellents, coils, vaporizers, window screens, etc. Because the *Aedes* mosquito vectors bite throughout the day, these measures must be observed during the day both inside and outside of the home or at work/school. When going outside, it is recommended to wear clothing that minimizes skin contact with mosquitoes.

8.6.5 Community Engagement

Some unsuccessful mosquito control strategies have often been associated with the lack of local community involvement and the inability to scale-up local, small-scale success to mega-cities and large geographical areas.

The following approaches have been implemented to achieve mosquito control: educating the community on the risks of mosquito-borne diseases; engaging with the community to improve participation and mobilization for sustained vector control; and mosquito vector control programs working jointly with city planners, environmentalists, engineers, and sectors that manage water and sanitation.

8.6.6 Active Mosquito Monitoring

Vector abundance and species composition should be actively monitored to determine the effectiveness of control measures.

Monitoring the prevalence of the virus in the *Aedes* mosquito population was performed by an active screening of sentinel mosquito collections prospectively. The monitoring of mosquito vectors can also be combined with environment and clinical surveillance. In addition, many international collaboration groups conduct research to find new tools and innovative strategies that can contribute to global efforts to interrupt dengue transmission. In Singapore, types of urban housing influence indoor breeding and dengue cases. The strategic plan of Urban Redevelopment Authority of Singapore focuses on affording public housing in high-rise buildings as a solution for the growing population.

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Intestinal Parasites at the Xuanquanzhi Relay Station on the Silk Road 2000 Years Ago

9

Piers D. Mitchell and Hui-Yuan Yeh

Abstract

The Silk Road has been presumed to have acted as a conduit for the spread of infectious diseases as people have traveled along it for the last 2000 years. However, until recently, there was no firm archaeological evidence to demonstrate the movement of people with such infections in the past. Here, we explore the evidence implicating the Silk Road in disease spread, the potential for using parasites to track migrations in past populations, and the sources of evidence for these parasites. We then consider the archaeological and textual evidence for intestinal parasites in ancient China before interpreting the significance of the findings from the latrines at the Silk Road relay station at Xuanquanzhi in the Hexi corridor. The discovery of evidence for Chinese liver fluke in this arid region of China, 1500 km away from regions where it could be endemic, provides the first firm archaeological evidence for the long-distance travel of people with infectious diseases along the Silk Road.

Keywords

Chinese liver fluke · Latrines · Parasites · Relay station · Roundworm · Silk Road · Taenia tapeworm · Whipworm · Xuanquanzhi

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_9

9.1 Introduction

The Silk Road was a network of routes that connected East Asia with the cities of the Near East and eastern Mediterranean. Clearly, trade across Asia took place for millennia, well before any formalized route such as the Silk Road. The concept of particular routes, with the construction of stations along the way where travelers and their pack animals could rest and recuperate, is thought to have originated in Han dynasty China (202 BCE–CE 220) (Boulnois and Mayhew 2005; Liu 2010; Hansen 2012). As there was not one Silk Road, but a network of routes that split and rejoined, this allowed travelers to choose a range of options depending on the time of year, the climate, the nature of their journey, and where they might wish to trade on the way.

9.2 Disease and the Silk Road

There are a number of ways that disease has been associated with the Silk Road. Some conditions have been noted to be more common in the various populations that live along the Silk Road network. Behçet's disease is a multisystem vasculitis associated with mucosal and genital ulceration as well as ocular inflammation. It is strongly associated with the major histocompatibility complex (MHC) antigen HLA-B51. It is thought that the gene for this condition may have been spread among the peoples living along the Silk Road by travelers and merchants who settled and had families, resulting in the unexpectedly high occurrence of the condition (Sazzini et al. 2015). Due to its geographic distribution, it is often referred to as the Silk Road Disease (James 1986; Verity et al. 1999).

The Silk Road has been proposed as a likely conduit for the spread of infectious diseases as well. Some of these were in the form of epidemics or pandemics, and others as chronic, endemic infections. Bubonic plague is a bacterial infection caused by *Yersinia pestis* and has been responsible for three worldwide pandemics in the last 1500 years, as well as numerous more localized epidemics. Plague DNA has been recovered from Neolithic and Bronze Age human burials in central Asia and Europe, showing the great antiquity of its presence in the region (Rasmussen et al. 2015; Valtuena et al. 2017). By the time the Silk Road had developed 2000 years ago, plague seemed to have become endemic in the burrowing mammals of central Asia. It is thought that outbreaks where *Y. pestis* jumped from these wild animals to the human population led to repeated epidemics, and when those people and their pack animals happened to be traveling along the Silk Road network, there was potential for transfer of plague between communities. Since the first plague pandemic of the sixth century CE and the second plague pandemic of the fourteenth century CE, both seem to have originated in central Asia and then spread west to the Mediterranean and Europe; the most direct route for this would be the Silk Road network (Morelli et al. 2010; Schmid et al. 2015). However, we should bear in mind that in the absence of any studies analyzing ancient burials at sites along the Silk Road network for the DNA of plague, this hypothesis remains a theoretical one.

Leprosy is a dermatological and neurological disease caused by infection with *Mycobacterium leprae*. Following genetic analysis of modern strains, it was proposed that the Silk Road was the likely route for its spread between western, central, and eastern Asia around 2000 years ago (Monot et al. 2009). More recent analysis of 154 modern genomes of leprosy from patients in 25 countries shows the oldest strains of leprosy in the world appear to come from China, Japan, and Korea (Benjak et al. 2018). This would suggest that leprosy likely originated in east Asia. For the disease to have spread west across Asia and into Europe and Africa, the Silk Road network seems a plausible method by which such travel may have taken place.

Anthrax is a bacterial infection of animals and humans caused by *Bacillus anthracis*. A study of worldwide strains shows 12 sub-lineages and sub-groups, and three of these were only found in the western province of Xinjiang in China. Together with the geographic distribution of other sub-groups, it was proposed that it was the past movement of people and animals along the Silk Road network as it passed through Xinjiang that led to the spread of strains and contributed to the geographic variation seen today (Simonson et al. 2009).

Brucellosis is a bacterial infection of livestock animals and humans that is caused by *Brucella melitensis*, *B. abortus*, and *B. suis*. Analysis of modern strains across Europe and Asia suggests the past and continuing exchange of strains between countries along the Silk Road (Liu et al. 2021).

However, one thing in common for all these studies is that the association with the Silk Road has been made based on modern disease distribution. There have been no archaeological cases of ancient leprosy, plague, anthrax, or brucellosis excavated at sites along the Silk Road. If we are to better understand the potential for the Silk Road to act as a conduit for infectious diseases in the past, then such an archaeological approach is needed. Here, we describe how intestinal parasites from past populations can be used for such an investigation.

9.3 Sources of Evidence for Parasites in Past Populations

The eggs of intestinal parasitic worms (helminths) are robust in order to resist digestion in the intestines. This also means that they may survive many centuries in archaeological contexts. Human fecal material can be recovered from a number of different sources. Latrines and cesspits contain the fecal material of multiple individuals that have accumulated over a period of time, often many years (Graff et al. 2020; Matsui et al. 2003). Sediment from the pelvic area of human burials contains the decomposed remains of the intestines and their contents, which includes the eggs of any parasites present (Le Bailly et al. 2006; Mitchell 2017a). Pieces of preserved feces, known as coprolites, can be recovered from rubbish pits or middens (Briant and Dean 2006; Shillito et al. 2020; Yang et al. 2022). Sediment layers dating from when a settlement was in use may contain the mixed feces of both humans and animals (Kim et al. 2016; Ledger et al. 2019). When environmental conditions allow the preservation of soft tissues, mummies can allow more complete survival of parasites (Lynnerup 2007; Seo et al. 2017). Once societies have developed writing, then textual evidence can provide descriptions of disease such as parasites, and give an understanding of what people thought caused them (Anastasiou et al. 2018; Mitchell 2017b).

9.4 How Parasites Can Provide Evidence for Migration with Disease

While some species of parasite are found wherever humans are found, others are restricted to particular geographical areas. This generally results from the life cycle of that parasite, where it must pass through one or more local intermediate hosts, or be spread by insect vectors that can only survive in the environmental conditions provided in one region (Mitchell 2013). If we then find evidence for those parasites in a region where the climate or environment could not possibly allow it to be endemic, then this would indicate that people had become infected by that parasite elsewhere before traveling to this new region.

It has been noted that the earliest settlers of the Americas who migrated from northeast Asia 20–15,000 years ago do not seem to have been infected by those species of intestinal parasite that require a period of maturation in warm, moist conditions on the ground, such as hookworm and whipworm. However, these species then appear in the Americas several thousand years later (Montenegro et al. 2006). It has been argued that the early settlers who migrated slowly across the cold Bering land bridge between Russia and North America lost these species as they could not re-infect the population and the original worms died of old age. However, later migrants using the faster sea route could have reached parts of North America where the climate was warmer before their worms died of old age, so allowing the spread of these parasites across the continent (Araújo et al. 2008).

The eggs of two species of schistosomes (*S. haematobium* and *S. mansoni*) have been identified in the sediment from a latrine dating from 1450 to 1550 CE in Montbéliard in France (Bouchet and Paicheler 1995; Bouchet et al. 2002). Schistosomiasis could not have been endemic in the region at that time since the freshwater snails required as its intermediate host do not survive in cold winters. For this reason, the endemic areas today are in tropical and subtropical regions, such as Africa, Asia, and South America. Finding the eggs in the medieval latrine in France indicates either that a person from Africa or the Middle East traveled to France and used the facilities or that a French person traveled to an endemic region, contracted the parasite, and returned home shedding the eggs when the used this toilet.

A latrine from the Christian quarter of Jerusalem, not far from the Church of the Holy Sepulchre, was dated to the fifteenth century CE. It was found to contain fragments of pottery from northern Italy, suggesting it may have been a guest house for Italian merchants or pilgrims. While eggs of some of the species of parasites in the cesspit sediment were commonly found in the region, the fish tapeworm eggs and cysts of *Entamoeba histolytica* were parasites much more commonly found in Europe rather than the Near East (Yeh et al. 2015). Indeed, the previous evidence for both these species in the region was from crusader period latrines of the knights of the Order of St. John from thirteenth century CE Acre (Israel), again where Europeans had traveled to the Holy Land (Mitchell et al. 2011). Both these examples would be most compatible with Europeans traveling to the Levant with intestinal parasites typical of their native countries.

During the late 1800s, a significant number of Chinese people migrated to North America to take on work as manual laborers. Latrines from a Chinese compound in San Bernardino, California, dating from 1880 to 1930 contained the eggs of not only those parasites already endemic in the region but also those of Chinese liver fluke (*Clonorchis sinensis*) (Reinhard et al. 2008). This species can only complete its life cycle in east Asia where the water snails that act as intermediate hosts are endemic. This finding highlights how migrant workers from China must have become infected with liver flukes before they crossed the Pacific, resulting in these parasite eggs being found in the latrines they used in North America.

9.5 Archaeological and Textual Evidence for Parasites in China

If we are to detect the spread of parasites along the Silk Road by travelers, we need to understand where different species of parasites were endemic in the region in the past (Seo and Shin 2015). The eggs of seven species of helminth have been recovered from excavations in China, dating from the Spring and Autumn period (770/771 BCE-476/403 BCE) to the Qing dynasty (ended 1911/1912) (Yeh and Mitchell 2016). The sources of evidence were 1 latrine, 13 mummies, and the pelvic sediment from 20 burials. The species most commonly found were whipworm (*Trichuris trichiura*), roundworm (*Ascaris lumbricoides*), and Chinese liver fluke (*Clonorchis sinensis*). Other species identified less commonly were *Taenia* tapeworm, oriental schistosome (*Schistosoma japonicum*), the intestinal fluke (*Fasciolopsis buski*), and pinworm (*Enterobius vermicularis*) (Yeh and Mitchell 2016).

Texts from ancient China describing intestinal worms have been analyzed and interpreted in the light of the species found at archaeological sites. The medical text Su Wen, Huangdi Neijing is thought to have been written at the time between the Warring States period (45–221 BCE) and the Han Dynasty (206 BCE–CE 220). In it was recorded that “severe coughing would lead to vomiting long worms out.” This description is highly suggestive of roundworm infection as they migrate from the lungs via the throat and then down into the intestines (Yeh et al. 2019). Long, flat worms that were white in color were also described in early texts. The work Jin Gui Yao Lue was written in the Eastern Han dynasty by Zhang Zhongjing around CE 217. These worms were described as similar in shape to an iris leaf, which would be highly suggestive of tapeworms such as *Taenia asiatica* or *T. solium* (Yeh et al. 2019).

The significant majority of evidence comes from excavations in eastern and southern China, with little or no results published from northeast, north, or western China, except for one relay station on the Silk Road at Xuanquanzhi. We will now compare this relay station with the results obtained from eastern and southern China.

9.6 The Latrines at Xuanquanzhi Relay Station

During the Han dynasty (202 BCE–CE 220) a considerable number of relay stations were built along the Silk Road. Their purpose was to supply fresh horses for the postal service, and so act as a reliable and swift method of communication between local governments and the imperial court (Lien 2015). They also hosted visitors on their travels. Xuanquanzhi relay station near the town of Dunhuang in Gansu province. This was located in the Hexi corridor of the Silk Road, a thousand-kilometer band of territory that connected the Yellow River region in the east to the Tarim Basin and Taklamakan Desert in the west. The corridor is bounded by the Qilian Mountains, the Beishan Mountains, and the Gobi Desert to the north. It is an arid region with low rainfall. The relay station was built in 111 BCE and continued in use until CE 109. During the Six Dynasties period (CE 220/222–589), it was used as a beacon tower (He 2000; Lien 2015).

When the relay station was excavated, there was surprisingly good preservation of organic material, including bamboo, silk, linen fabrics, and paper (He 2000). The latrines contained a number of wooden latrine sticks with cloth wrapped around one end (Fig. 9.1). It is thought that they were used for wiping after using the toilet. Dried feces preserved adherent to the cloth on these sticks was sampled and analyzed for parasite eggs. Using a process of disaggregation and passing through micro-sieves prior to microscopy (Anastasiou and Mitchell 2013), the eggs of whipworm, roundworm, *Taenia* tapeworm, and Chinese liver fluke (Fig. 9.2) were identified (Yeh et al. 2016).

Whipworm and roundworm are parasites spread by poor sanitation, so it would not be unexpected for travelers who would not be able to wash their hands after going to the toilet. *Taenia* tapeworm is contracted by eating undercooked pork or beef, and it would not be surprising if it was endemic in the region. However, Chinese liver fluke is endemic only in well-watered and marshy regions of southern and eastern China and Korea, where the local water snails and fish complete the parasite's life cycle. The closest area to Dunhuang, where it is endemic today, is 1500 km away. The climate at Xuanquanzhi appears to have been just as arid when the relay station was in use as it is today. This means that Chinese liver fluke could not have been endemic in the region back then. The fluke could only have been deposited in the relay station latrine if a traveler from the east contracted the parasite

Fig. 9.1 Latrine sticks recovered from the excavation at Xuanquanzhi relay station on the Silk Road. Image: Hui-Yuan Yeh

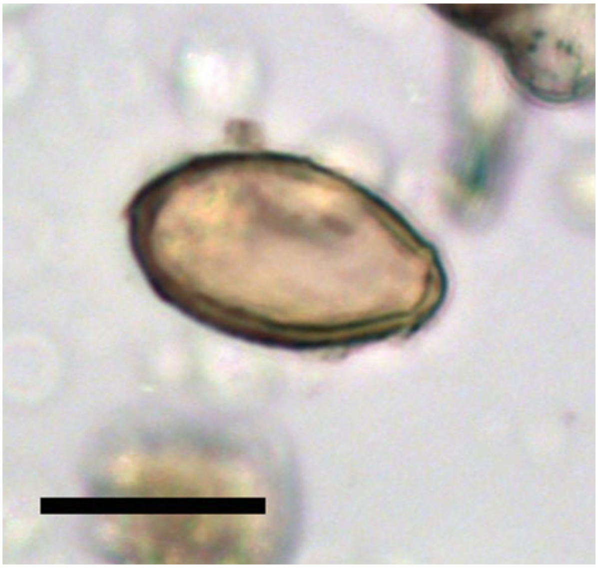

Fig. 9.2 Egg of Chinese liver fluke from the latrine at Xuanquanzhi relay station. Egg dimensions, 29 × 16 μm. The black scale bar represents 20 μm. Image reproduced with permission of Elsevier publishing, from Yeh et al. 2016

there, traveled west along the Silk Road, and used the latrines at Xuanquanzhi (Yeh et al. 2016). As such, this is the first reliable evidence for the movement of people with infectious diseases along the Silk Road.

9.7 Conclusion

Here we show how parasites with a restricted geographic distribution can be used to identify the movement of people with infectious diseases as they undertake long-distance migrations or trade. The evidence from Xuanquanzhi relay station provides direct evidence for the spread, supporting previous work comparing modern strains of different infectious diseases present along various sections of the Silk Road. If a concerted effort is made to excavate and study multiple relay stations along the Silk Road, it is likely that plenty more evidence of this kind may come to light.

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Dicrocoelium in Iran: From Bronze Age to the Twenty-First Century

10

Alireza Sazmand, Alireza Nourian, and Masoud Nezamabadi

Abstract

Members of the genus *Dicrocoelium* are cosmopolitan hermaphroditic trematodes, which commonly occur in the biliary system of ruminants, especially cattle and sheep. There are two intermediate hosts (land snails and ants) involved in the parasite life cycle, and the final host becomes infected after ingestion of the larvae containing ant. Light infections are generally symptomless; therefore, the disease is often get underestimated by practitioners and researchers. In humans, *Dicrocoelium* causes a rare food-borne zoonotic disease of the biliary tract. In this chapter, we summarize the current knowledge on different aspects of *Dicrocoelium* and dicrocoeliosis/dicrocoeliasis, including biology, clinical presentations, pathogenesis, and diagnosis with special emphasis on the current and ancient epidemiology of this fascinating worm in Iran, covering 15 human cases from the Bronze Age to very 2022.

Keywords

Archaeology · *Dicrocoelium* · Dicrocoeliosis · Dicrocoeliasis · Iran · Paleoparasitology

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_10

10.1 Introduction

10.1.1 What Is Dicrocoelium?

The members of genus *Dicrocoelium* Dujardin, 1845 (Greek *dicroos* = double, *koilia* = body cavity) are hermaphroditic trematodes normally found in the biliary system of ruminants, mainly cattle and sheep. *Dicrocoelium* species (e.g., *D. dendriticum*, *D. hospes*, and *D. chinensis*) are known as "small liver fluke, lancet fluke, and lanceolate fluke" and have low host specificity; thus, many other mammals such as camels, equids, rabbits and hares, dogs, and non-human primates can become infected. Humans are inadvertent definitive hosts (Otranto and Traversa 2003).

Five species, i.e., *D. dendriticum* Rudolphi 1819, *D. hospes* Looss, 1907, *D. chinensis* Tang and Tang, 1978, *D. orientale* Sudarikov & Ryjikov, 1951, and *D. petrowi* Kassimov, 1952, have been referred as valid (GBIF 2022). However, the most well-known one is *D. dendriticum* (Latin: *dendriticus* = furcated), with a global distribution in herbivorous mammals, mainly ruminants, of the Holarctic region. It is found in almost every country in the European continent and neighboring islands as well as the northern coast of Africa. In Asia, *D. dendriticum* is reported from Russia, Turkey, Syria, Iran, India, China, the Philippines, and Japan. In the Americas, the parasite is found in the USA, Canada, Cuba, Colombia, and Brazil. The second species, *D. hospes*, is endemic to sub-Saharan West Africa. The third well-known species, *D. chinensis*, has been mostly found in various ruminants from East Asia and in sika deer (*Cervus nippon*) from different regions of Europe, which is thought to probably be imported from Asian countries (Otranto et al. 2007).

10.1.2 Life Cycle

The life cycle of *Dicrocoelium* is a rather fascinating example of biological adaptation of a parasite to its host (Fig. 10.1). First intermediate hosts are various air-breathing land snails, such as species of the genera *Cochlicopa* (=*Cionella*), *Helix*, *Xerolenta* (=*Helicella*), and *Zebrina*. Over 90 species of land snails have been found to be competent vectors of *D. dendriticum*, several of which, particularly, *Cochlicopa lubrica*, have worldwide distribution. *Helicella obvia* is found in Germany, *Helicella corderoi* in Spain, *Zebrina hohenackeri* in the Caucasia, and *Cernuella virgata* in Italy. The cercariae are squeezed out from snails as "slime balls," which are clusters of many hundreds covered by a mucilaginous substance and are ingested by several species of ants, especially the members of genus *Formica*, e.g., *F. fusca*, *F. pratensis*, and *F. rufibarbis*, as the second intermediate host. The definitive mammalian host is infected accidentally via ingestion of an infected ant while feeding on vegetables, fruits, and water (Otranto and Traversa 2002; Toledo and Fried 2019).

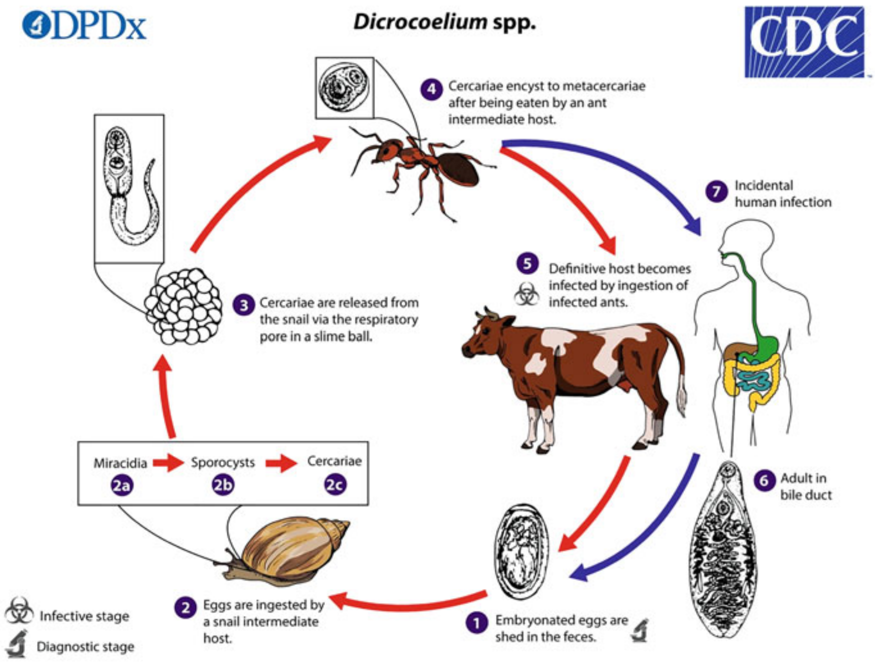

Fig. 10.1 Life cycle of *Dicrocoelium* spp. Dark brown embryonated eggs containing miracidia are shed in definitive hosts' (typically ruminants) feces (1). The operculated eggs, which are oval and unilaterally flattened and contain a miracidium, are then ingested by the snail as the first intermediate host (2). Upon hatching, the emerged miracidia (2a) penetrate the intestinal epithelium, migrate to the hepatopancreas and stay in the neighboring vascular connective tissue, and become mother sporocysts (2b). The sporocysts then migrate to the digestive glands where they produce several daughter sporocysts, each of which gives rise to numerous cercariae (2c). The cercariae migrate to the snail respiratory chambers, where they are shed from the host in masses of 3000–5000 cercariae, namely slime balls of 10 mm in diameter, which are enveloped in a mucilaginous substance (3). Upon ingestion of slime ball by the second intermediate host (ant), the cercariae encyst in the gaster becoming infective metacercariae. However, one (or rarely two) non-encysted cercaria invades and occupies the subesophageal ganglion (brain-worm), which can cause a cataleptic spasm at the ambient temperature of about 15–20 °C or lower (e.g., early in the morning). These spasms can "paralyze" the ant on the tips of pasturage and grass, where grazing ruminants can readily swallow it (4). When the infected ant is ingested by a proper definitive host (5), the metacercariae emerge from the cyst in the duodenum. The larvae migrate to the small and then larger bile ducts and finally to the gall bladder via the ductus choledochus, where they mature into egg-producing flukes (6). Humans can serve as definitive hosts if the infected ants are ingested (7). After approximately two months prepatent period during which reproduction by hermaphroditism or cross-fertilization takes place, the eggs are released into the environment via the host feces (Otranto and Traversa 2003; Toledo and Fried 2019). Image is reproduced from DPDx CDC https://www.cdc.gov/dpdx/dicrocoeliasis/index.html

10.1.3 Epidemiology in Livestock

The environment and presence of intermediate and definitive hosts play an important role in the epidemiology of *Dicrocoelium*. The presence of *D. dendriticum* depends upon dry and alkaline or calcareous soils, which provide ecologically favorable environments for its intermediate hosts. The parasite eggs are highly resistant in such an environment, as they can spend the winter and remain infectious for even 20 months on pasture. In countries of the Mediterranean region, the excretion of eggs in sheep feces is seasonal, with a winter peak of about 323.4 ± 18.5 eggs per gram (EPG). In addition, the epidemiology of dicrocoeliosis is influenced by: (1) host species, the susceptibility of sheep is higher than goats; (2) age of the animal, the prevalence of infection in cattle older than 6 years is higher than of calves younger than 18 months; (3) physiological condition, hosts stressed by confinement and transportation have higher levels of fecal egg excretion; and (4) sex, female animals show higher prevalences of dicrocoeliosis than males at necropsy. Differences in the dicrocoeliosis prevalence are also thought to depend on the snail species and the season; for instance, in Spain, a higher prevalence of infection was reported in September in *H. itala* and in February in *H. corderoi* than other months (Otranto and Traversa 2003; Manga-González et al. 2001).

10.1.4 Clinical Presentation in Livestock

Light infections remain largely symptomless; thus, the disease is often underestimated by practitioners and researchers because dicrocoeliosis is cloaked by the pathological effects of other parasitic infections. However, developmental delay may occur as a result of reduced liver activity. Heavy infections may lead to liver cirrhosis following cholangitis, granulomatous reaction, and abscess formation. Animals suffering from *Dicrocoelium* infection may show anemia, dropsy, and cachexia. Major hepatic lesions are detectable by examination of the organ during necropsy, through which superficial scars and disruption of bile ducts resulted from the buccal stylets of liver flukes are apparent. Most of the time, the infected liver is not consumable by humans and is condemned, thus imposing considerable economic losses to the livestock industry (Otranto and Traversa 2003).

10.1.5 Human Dicrocoeliasis

Both *D. dendriticum* and *D. hospes* cause rare food-borne zoonotic diseases in the human biliary system. Infection happens via the ingestion of metacercariae-containing ants, while pseudo-infections (presence of parasite eggs in feces in the absence of adult flukes) occur after the consumption of parasitized animal liver. Up until 1982, approximately 300 cases were documented in the literature based on the recovery of eggs in human feces; however, the epidemiology of human dicrocoeliasis is not known, especially when there are both true and pseudo-infections (Jeandron et al. 2011; Moure et al. 2017; Lavilla-Salgado et al. 2021). *Dicrocoelium dendriticum* is known to be present in definitive hosts throughout Europe, North Africa, and Asia and can be found infrequently in North America. The known clinical cases have mostly occurred in North Africa and the Middle East. On the other hand, *D. hospes* is endemic in sub-Saharan West Africa; several animal cases have been reported in Senegal, Ghana, Sierra Leone, and Mali. Most infections involve low numbers of worms and are not associated with observable symptoms. In severe infections, there may be symptoms of generalized gastrointestinal/abdominal distress associated with cholecystitis and liver abscesses. In addition, the existence of flukes in subcutaneous masses has been sporadically reported (https://www.cdc.gov/dpdx/dicrocoeliasis/index.html).

10.1.6 Diagnosis

In livestock, considering the subclinical nature of the disease, dicrocoeliosis is mostly diagnosed during necropsy of the liver, microscopic examination of duodenal fluid, and by coproscopy for the detection of parasite eggs. Adult *Dicrocoelium* is flattened, with both the anterior and posterior ends tapered. The paired testes are located behind the ventral sucker (acetabulum). The tiny ovary lies just behind the testes (Fig. 10.2a). The operculated thick-shelled dark brown eggs of *D. dendriticum* measure 35–45 μm × 20–30 μm and are fully embryonated when shed in feces (Fig. 10.2b).

In human patients, the adult flukes are hardly recovered, and eggs may be found in stool following consumption of the infected liver; therefore, additional samples should be collected to recognize this type of passage (aka, pseudo-parasitosis) from a true infection. Misdiagnosis can be avoided through stool examination following a liver-free diet for at least 3 days. Other differences between the true- and pseudo-infections are clinical manifestations, eosinophilia, elevation of IgE, liver and pancreas malfunction, existence of parasites eggs after a several days of

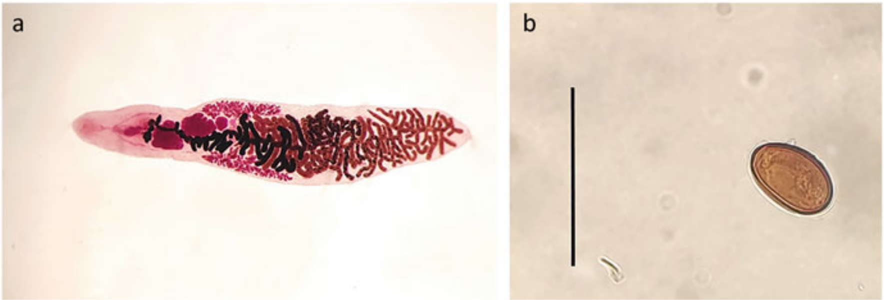

Fig. 10.2 (**a**) Adult *D. dendriticum*, stained with carmine. (**b**) Egg of *D. dendriticum* extracted from a mature trematode. Image courtesy of Sina Mohtasebi (University of Calgary, Canada), scale bar = 80 μm

consumption of liver free diet, and observation of embryonated eggs (Lavilla-Salgado et al. 2021). The most common laboratory finding is “eggs in transit” with a variable color shell of yellow, orange, or light brown, containing an indistinct dark yellow oval mass, often with 1–4 shiny globules. Embryonated eggs, instead, exhibit a uniformly dark brown shell, containing a ciliated embryo (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5303036/figure/fig1/) (Engbaek et al. 2003).

10.2 Ancient Dicrocoeliosis/Dicrocoeliasis

10.2.1 What Do We Know?

The existence of ancient dicrocoeliosis/dicrocoeliasis is confirmed based on the discovery of eggs preserved in ancient human and animal coprolites or in archaeological samples from occupation layers, which are then commonly extracted using micrometrical sieving techniques. The most ancient *Dicrocoelium* eggs belong to earlier than 550,000 years BP (Pleistocene period) and were recovered by analysis of a coprolite sample from “Caune de l’Arago,” a cave near Tautavel, France (Jouy-Avantin et al. 1999), indicating the long time presence of dicrocoeliosis/dicrocoeliasis in the Old World. Studying the paleoparasitological records, Le Bailly and Bouchet (2010) chrono-geographically classified the occurrence, distribution, and migration evidence of ancient dicrocoeliosis/dicrocoeliasis. They discussed relationships between ancient human/animal migrations and the presence of *Dicrocoelium* in the archaeological areas of the Old World and New World. In addition, they noted that the *Dicrocoelium* findings could represent herding and breeding and probably dietary habits of ancient humans over the world (Le Bailly and Bouchet 2010). Available paleoparasitological findings in neighboring regions of the Middle East indicate that the trematode eggs found in the archaeological sites of the European continent are largely overtopped by the members of class Trematoda: *Fasciola* and *Dicrocoelium* (Bouchet et al. 2003; Dittmar and Teegen 2003). Moreover, there is only one report of a single ancient fluke egg (*Dicrocoelium* sp.) from South Africa (Dittmar and Steyn 2004).

The paleoparasitological recovery of several *Dicrocoelium* sp. eggs in Kerma, Sudan, could provide the first bit of information on ancient dicrocoeliasis in the Middle East (Harter 2003). In another survey, Zias and colleagues found *Dicrocoelium* sp. eggs in a soil sample from an ancient animal stable, northwest of the Qumran archaeological site in the Middle East (Zias et al. 2006).

A review by Savinetsky and Khrustalev presents findings of parasites through examination of ancient animal dung layers and coprolites in northern neighboring regions of the Middle East, Russia, North Caucasus, and middle Asia (South Turkmenistan). The authors found *Dicrocoelium* eggs in deposits of sheep dung (*Ovis aries*) and East Caucasian turs (*Capra caucasica cylindricornis*) (Savinetsky and Khrustalev 2013).

10.2.2 Challenges in Ancient Egg Identification

The use of light microscopy in paleoparasitological research is problematic, when applied for egg identification, since many parasites from the same genus have eggs with very similar shapes and sizes. This similarity sometimes occurs in eggs of the same family and even the same order. Identification of eggs is more precise when the biological origin of the studied material is known. However, many analyses are performed on sediment samples collected from latrines or cesspits; thus, the biological origin of the fecal material from such structures may have single or multiple origins (Le Bailly and Bouchet 2010). In such cases, identifications are less precise and are the subject of debate (Sazmand 2021).

It has been stated that "*the identification of the eggs* as D. dendriticum *for the majority of all the European paleoparasitological results is almost certain since all other species have a different current geographical distribution and/or a different egg size*" (Le Bailly and Bouchet 2010). Based on this assumption, *Dicrocoelium* spp. eggs detected in coprolites in Iran were reported as *D. dendriticum* (Makki et al. 2017; Bizhani et al. 2017; Mowlavi et al. 2015). However, given the present dearth of information on the archaeomalacology and lack of molecular studies, other present or extinct *Dicrocoeliidae* species, e.g., *D. chinensis* or *D. hospes*, cannot be ruled out. In this instance, the role of climate changes in geographic distributions of snail-borne trematodes would need to be considered in the differential diagnosis of the recovered eggs (Stensgaard et al. 2019). Thus, it becomes evident that further study of mollusks in the archaeological sites is required for recognition of possible sources of trematode infection in the given area (Insoll and Hutchins 2005).

10.3 Dicrocoeliosis and Dicrocoeliasis in Iran

10.3.1 Current Epidemiology

In livestock, *D. dendriticum* dicrocoeliosis is widespread all over the country (Nazarbeigy et al. 2021). Adult worms and/or eggs have been found in sheep, goats, cattle, buffaloes (Borji et al. 2012; Rafyi et al. 1971), camels (Sazmand et al. 2019; Sazmand and Joachim 2017), horses, and donkeys (Sazmand et al. 2020). Previous epidemiological studies showed infection rates of up to 85% in sheep, 66% in cattle, and 23.25% in goats (Ahmadi et al. 2010). Based on a systematic review of articles published between 2000–2015, 3.1% (2.2–4.2%) of sheep, 1.3% (0.9–1.9%) of goats, and 2.1% (1.1–3.5%) of cattle were infected with *D. dendriticum* in Iran (Bari et al. 2016). According to a more recent article, abattoir data were collected from 413 abattoirs representing all 31 Iran provinces (Kiani et al. 2021). In total, 3.08% (95% CI: 3.07–3.09%) of slaughtered cattle and 4.63% (95% CI: 4.62–4.63%) of slaughtered sheep and goats were infected with *Dicrocoelium* spp. from 2015 to 2019. Annual prevalence of cattle dicrocoeliosis ranged from 2.7% in 2019 to 3.0% in 2015, while in sheep and goats it ranged from 3.7% in 2015 to 4.8% in 2019. The majority of dicrocoeliosis cases were found in northern Iran, which has a Mediterranean climate. Considering the average price of US$8.20 per cattle liver and US$15.24 per sheep/goat liver, condemnation of 186,009 cattle and 2,701,274 sheep and goat livers has resulted in economic losses of US$1,668,986 and US$41,771,377, respectively (Kiani et al. 2021).

In wild mammals, there are also a few reports of dicrocoeliosis. The infection of *Ovis ammon orientalis* (wild sheep), *Gazella subgutturosa* (Goitered gazelle), and *Sus scrofa* (wild boar) has been documented (Eslami and Farsad-Hamdi 1992; Eslami et al. 1980).

In humans, 14 confirmed cases of dicrocoeliasis have so far been reported from Iran, all of which except three were from the Northern provinces of Mazandaran, Gilan, and Golestan. In these areas, the local population generally consumes large quantities of raw vegetables, both as appetizers and as part of their main meals. The first two patients were diagnosed with the infection in 1967 following an examination of 1065 individuals in Mazandaran (Sohrabi 1973). The next patient was a 15-year-old boy from Isfahan, central Iran, and was detected during coprological examination of 718 individuals (Farid 1971). Arfa and his colleagues in 1977 reported seven patients during the examination of 1240 individuals in Golestan province (Arfaa et al. 1977). There were no reported human cases for decades until 2010, when two patients were diagnosed in Gilan province (Ashrafi 2010). In the same year, one patient suffering from chronic diarrhea was diagnosed to be infected with *Dicrocoelium* in Esfahan (Mahmoodi et al. 2010). In another occasion, one individual from Qazvin was found positive for *Dicrocoelium* egg in the fecal specimen (Sadeghi and Borji 2015), but the authors did not follow up on the case to find out if he/she was a true-infected case. Very recently in 2022, another patient, again in Gilan, has been diagnosed with the infection (personal communication with Professor Keyhan Ashrafi).

10.3.2 Archaeoparasitological and Paleoparasitological Findings

Since 2013, a number of paleoparasitological reports have been published from archaeological sites in Iran, among which are the records of fluke ova, including *Dicrocoelium* sp. eggs in samples belonged to ancient Iran from the Bronze Age to Sassanid archaeological strata (Askari et al. 2018; Bizhani et al. 2017; Makki et al. 2017; Mowlavi et al. 2015; Nezamabadi 2014; Nezamabadi et al. 2013). All these findings are based on egg recovery using a trisodium phosphate solution for rehydration of soil sediments and observation of samples by light microscopy.

The first case of ancient *Dicrocoelium* egg in Iran was reported by Nezamabadi et al. (2013) following an examination of fecal polluted soil sediment without definite dating, but recovered from the archaeological layers of Chahrabad salt mine in North Western Iran. Therefore, this record should not be considered reliable paleoparasitological data due to incomplete description and inaccurate dating of the main sediment sample. In particular, the structure of the salt mine under archaeological excavation raises the possibility of contamination of deeper/older layers by more superficial ones belonging to more recent periods. The only *Dicrocoelium* egg recovered in 2017 from the Kiasar archaeological site, dated back to 247 BC–224 AD (Bizhani et al. 2017), also seriously lacks the essential criteria for being identified as a parasite egg. The image provided in this article is not clear enough, potentiating the risk of confusing pollen grain with *Dicrocoelium* egg (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5558072/figure/F3/). Another single *Dicrocoelium* egg reported in 2017 was collected from the Shahr-e Sukhteh site, located in southeastern Iran and dated back to 3200–1800 BC (Makki et al. 2017). Similarly, this report suffers from the same shortcomings, raising doubts about the correctness of *Dicrocoelium* egg identification (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5450963/figure/f3-kjp-55-2-197/). However, up until now, it seems that the presence of two *Dicrocoelium* eggs extracted from a burial sample in a Bronze Age cemetery, dated 2600–2200 BC in Yasuj, southwestern Iran (Mowlavi et al. 2015), is the only reliable record of the presence of *Dicrocoelium* in ancient Iran.

10.4 Conclusion

This chapter introduced the current knowledge on different aspects of *Dicrocoelium* and dicrocoeliosis/dicrocoeliasis, including biology, clinical presentations, pathogenesis, and diagnosis, with special emphasis on the current and ancient epidemiology of this fascinating worm in Iran. Since Iran rests along the Silk Road, a network of trade routes that connected the East and West, it was central to the economic, cultural, political, and religious interactions among these regions from the second century BC to the eighteenth century AD. Furthermore, the present ruins of Persepolis, the ancient ceremonial capital of the Achaemenid Empire (dated from around 515 BC), show that conquered peoples of different nations, including Ethiopians, Arabs, Thracians, Indians, Parthians, Cappadocians, Elamites, and Medians, brought gifts and animals from different nations for the king (Fig. 10.3). Hence, until now, we cannot determine the origin of *Dicrocoelium* in Iran. Advancement of ancient DNA analysis employing molecular phylogenetic techniques might shed light on the infection dynamics throughout history.

Fig. 10.3 The panels at the southern end of the Apadana Staircase in Persepolis show 23 delegations bringing their tributes, such as animals, to the Achaemenid king. Among them, Ethiopians, Arabs, Thracians, Indians, Parthians, Cappadocians, Elamites, and Medians have been recognized. Human and animal movements could have impacts on the transfer of pathogens such as *Dicrocoelium*. Pictures are reproduced from Wikimedia Commons files licensed under the Creative Commons Attribution 2.0 Generic license

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11 Development of Vaccine to Stop Endemic of Hydatid Disease and Promote Connectivity of the Belt and Road Initiative

Yilin Zhang and Jie Liu

Abstract

The long-term commitment of the Belt and Road Initiative (BRI) is not only to enhance economic connectivity to promote interconnected development but also to build a healthy Belt and Silk Road corridor for mutual prosperity. Sustainable prosperity and health are not just interest to China or a few countries, they are of global interest since the transmission of communicable diseases has no border limt. The outbreak of COVID-19 has highlighted the importance of a safe, clean, and sustainable environment in reducing systemic health risks, and has promoted the priority of One Health conception. The successful experiences of Argentina, China, and Uruguay in reducing the incidence of *Echinococcus* infections and controlling of the spread of the parasite will be valuable references to share with BRI countries. Advances in vaccine research and development will be offered and benefited to all BRI countries to achieve a mutual benefit of health. Collaboration and academic communication among BRI members will facilitate the success of vaccine development. In addition, the development of new technologies to stop the spread of parasites, to eliminate pathogens in an environmentally friendly way, and to diagnose and treat the disease will also play a key role in improving global health.

Keywords

Vaccine · Echinococcosis · Cystic echinococcosis · Hydatid cyst · *Echinococcus granulosus* · Alveolar echinococcosis · *Echinococcus multilocularis* · Belt and road initiative

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1_11

11.1 Introduction

The Belt and Road Initiative (BRI) is a strategy launched by China as a leading member to promote economic cooperation among member countries. The initiative has been proposed to facilitate the free flow of capital, goods, services, and personnel to establish an integrated market and regional economic framework for common prosperity. Globalization, along with accelerated migration of population, has facilitated the spread of many infectious agents and communicable diseases to every corner of the world in history. There will be serious consequences of infectious disease transmission to naïve areas, people, and animals if proper cautions are not taken and communication of health science and advanced technology among partners is not strengtheded.

Echinococcosis is a zoonotic parasitic disease distributed in most rural areas of the world and causes health and economic burdens to people in countries and regions. Many of them are developing countries and under-represented populations. The infectious agent of this disease is a tapeworm called *Echinococcus* that lives within their mammal host and completes their life cycle parasitically. Both wild and domestic animals can be hosts of the parasite. Although the host varies depending on the parasite species, domestic and wild carnivores, such as dogs and foxes, are the most common and popular definitive hosts, while livestock and rodents are the most common and popular intermediate hosts. Free flow of goods and services and personnel traveling potentially carry and spread the parasite to naïve or low endemic areas or to establish new endemic centers. The control measures cover a variety of aspects in the disease transmission, spreading, prevention, diagnosis, and treatment, which have reduced the endemic of echinococcosis and offered the opportunity to eradicate the parasite in some countries and regions. The outcome is significant, but the eradication is not complete due to limitations in the efficiency of technology, geographic nature, culture, and religious beliefs. For complete eradication of the parasite and to block the transmission of echinococcosis, we need to explore new technology and to develop effective programs to control the pathways of infection and transmission. Vaccine has been proven to be the most potent and cost-effective approach to control infectious diseases. Vaccination could stand alone or be complementary to other control programs in preventing infection and reducing the burden of public health in humans and of economy in livestock industry. The initial success of sheep vaccination has shown promising aspects for the prevention of cystic echinococcosis. To facilitate effective and safe vaccine development, we review the pathogenesis, epidemiology, and life cycle of the parasite to identify vulnerable checkpoints for intervention; we analyzed the success and challenge of current control programs to share lessons learned during the practice. We list a couple of promising vaccine candidates to encourage intensive research and test for future vaccine development. We believe that effective collaboration of all BRI partners and relevant sectors will significantly reduce the prevalence of echinococcosis and will potentially eradicate the parasite and improve public health, thus pursuing a common prosperity among the BRI members.

11.2 Pathogenesis and Epidemiology

Human echinococcosis (hydatidosis, or hydatid disease) is a zoonotic parasitic disease caused by tapeworms of the genus *Echinococcus*. There are mainly two types of tapeworms inducing human echinococcosis: *Echinococcus granulosus* (*E. granulosus*) and *Echinococcus multilocularis* (*E. multilocularis*, Fig. 11.1), which induce cystic echinococcosis (also known as hydatid cyst) and alveolar echinococcosis, respectively (Deplazes et al. 2017). Both humans and animals suffer

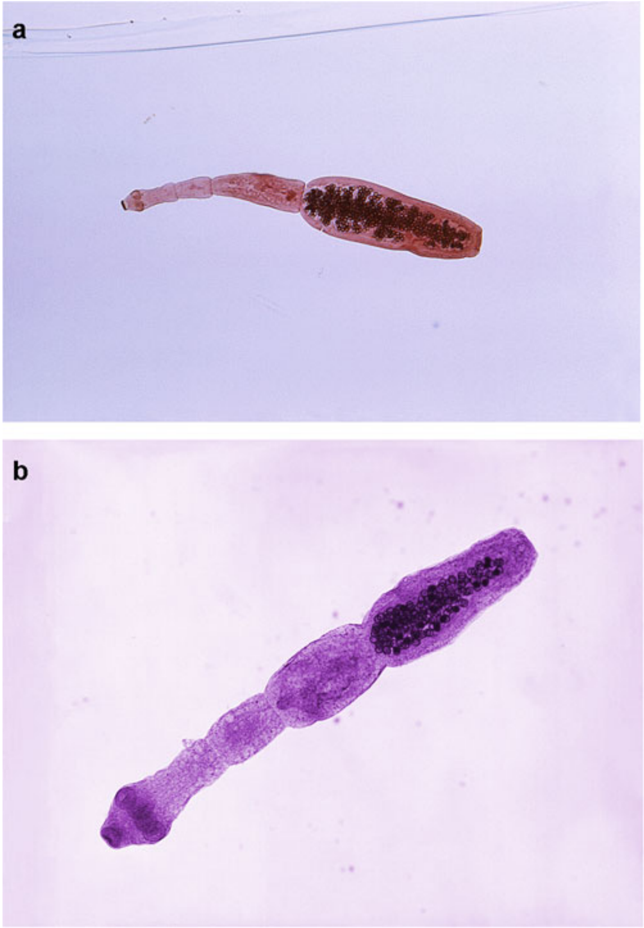

Fig. 11.1 Adult worms of *Echinococcus*. (**a**) *Echinococcus granulosus* can grow 2–7 mm in length, comprising a scolex, neck, and 3–4 proglottids, with the final one gravid. The scolex has four suckers and a rostellum with two rows of 30–36 hooks. The uterus of the gravid proglottid has irregular branches and lateral sacs. (**b**) *Echinococcus multilocularis* is very similar to *E. granulosus* but is slightly smaller, with 1.2–4.5 mm long and 4–5 proglottids. The uterus of gravid proglottid without lateral sacs (from CDC Public Health Image Library)

from those tapeworms. Humans are accidental intermediate hosts for both tapeworm species and are infected by ingesting *Echinococcus* eggs in contaminated food and water. The larvae hatch inside the host's intestine. Then oncospheres are released, which penetrate the intestinal mucosal barrier, and invade finally targeted organs via circulation (Thompson and Jenkins 2014).

Both cystic and alveolar shapes of echinococcosis have a similar long incubation period that may last years, induce a serious morbidity and mortality, and induce a substantial health and economic burden to human society. In cystic echinococcosis, pathological cysts develop mostly in the liver and lung due to the invasion and residency of *E. granulosus* larvae, and less frequently in kidneys, spleen, and other organs. Gastral-intestinal and respiratory symptoms, such as nausea, vomiting, cough, and short breath, occur when the organ function is reduced by cysts. In alveolar echinococcosis, tumor-like lesions locate mostly in the liver. Less frequently, they locate in other organs. Symptoms like abnormal liver functions, weight loss, tiredness, and hepatic failure occur when lesions are big enough to impact the liver function and when the functional failure cannot be compensated. Alveolar echinococcosis is more progressive than cystic echinococcosis and thus is fatal if left untreated. There are more than one million humans living with these diseases (Butt and Khan 2019). Many of them suffer from severe symptoms of illness that are life-threatening or at least challenging, with a strongly compromised life quality. The WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) reported nearly 20 thousand deaths and about 871 thousand disability-adjusted life-years (DALYs) that are suffering from echinococcosis each year worldwide (WHO 2015). It costs more than $3 billion globally per year for diagnosis and treatment of human cases (Yu et al. 2018). Early diagnosis and quick treatment significantly decrease the morbidity rate, need of hospitalization, and improvement of the prognosis (McManus et al. 2012). But the early detection of an *Echinococcus* infection is still a challenge, especially in remote areas where the medical infrastructure and public health services are scarce. Then, often, most of the cases are present, and the patients with a suspicious infection need a costly and time-consuming travel to referral hospitals for the diagnosis and treatment. The diagnosis of echinococcosis mostly needs ultrasonic imaging, complemented or validated by more expensive and sophisticated computed tomography (CT) and/or the magnetic resonance imaging (MRI) scan. Specific diagnostic tools are optional due to their moderate specificity and sensitivity. Serology is applied to detect specific antibodies; test kits to detect specific identities, such as nucleic acid specific to the parasite and extracellular vesicles carrying specific biomarkers, are under ongoing development. More specific and sensitive tools are needed to improve the accuracy of early diagnosis; they should be portable and convenient. Further accessible diagnostic tools are needed for onsite application in remote areas. Albendazole, a drug of the anthelmintics class, has been applied as the first choice for the treatment of echinococcosis, but the treatment is not very specific and could be prolonged and complicated by serious adverse effects (Grüner et al. 2017; Liu et al. 2015), thus requiring early diagnosis and intervention. Drugs have little effect on large cysts and lesions that alternate or impair organ function and need to be removed by surgery. Unfortunately, many

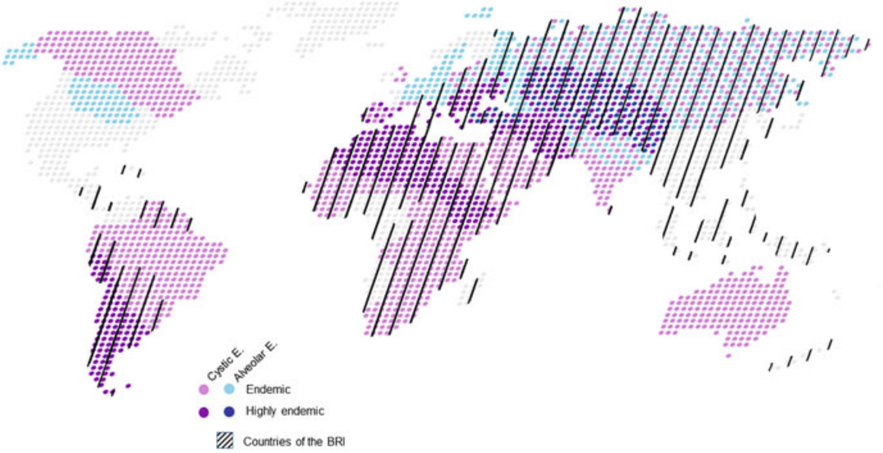

Fig. 11.2 Echinococcosis distribution and countries of the BRI. The dots cover area with echinococcosis endemic, purple and blue representing cystic and alveolar echinococcosis, respectively (data from WHO, 2019). The darkness of color indicates highly endemic. The shield lines cover countries of BRI (data from Belt and Road Portal, 2022)

patients are often diagnosed at an advanced stage of the disease due to the lack of reliable and sensitive detection tools and are often asymptomatic at an early stage of the disease. Albendazole will not be effective in preventing recurrence or eliminating residual echinococcosis if the surgical removal of the lesion is not complete. Relapse often happens in such cases. Echinococcosis is not only a huge challenge to public health but also an enormous burden to human society and economy. In addition, cystic echinococcosis is also an important challenge to the livestock industry. The annual expenditure due to the treatment and loss is about $ 2.19 billion per year (Qian et al. 2017). Establishment of BRI can facilitate health cooperation, expand medical service, and improve public health service in China and in other alliance countries.

Echinococcosis is a worldwide health challenge, and almost all populations in the BRI area encounter the threat of echinococcosis (Fig. 11.2). Among the two major types, cystic echinococcosis is globally distributed and is found on all continents except for Antarctica. In contrast, the spread of alveolar echinococcosis is relatively limited to the northern hemisphere and occurs mostly in China, Russia, and some European countries although there are overlaps with the distribution of cases of cystic echinococcosis. Differential distribution is partially dependent on specificity of the hosts (Figs. 11.3a and 11.2b). Cystic echinococcosis is transmitted primarily by domestic dogs as the main definitive hosts and sheep as the main intermediate hosts. The life cycle depends on human social and economic activities (Craig and Larrieu 2006). In contrast, alveolar echinococcosis is primarily transmitted by wild foxes and dogs as the main definitive hosts and rodents as the main intermediate host (Wang et al. 2006), which has relatively limited access to human society. Human cases are mostly in China, Central Asia, Argentina, Brazil, Chile, Uruguay, Peru,

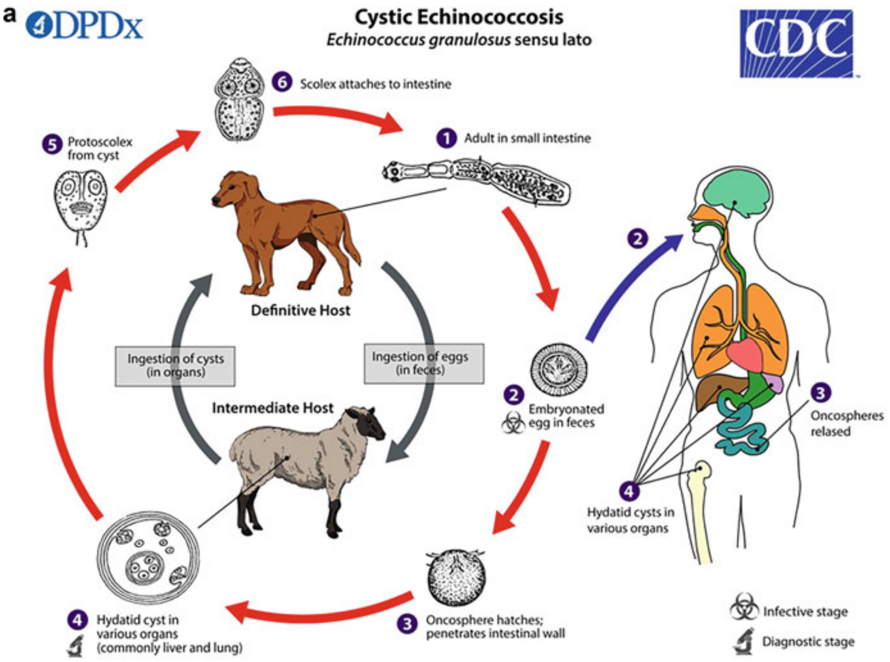

Fig. 11.3 Life cycle of *Echinococcus*. (**a**) *Echinococcus granulosus* and (**b**) *Echinococcus multilocularis*. (1) The adult worm resides in the small intestine of the definitive host (shown as dog and fox for *E. granulosus* and *E. multilocularis,* respectively) and releases infectious eggs that are passed in the feces. (2) After ingestion by a suitable intermediate host (shown as sheep and rodent for *E. granulosus* and *E. multilocularis*, respectively, as well as human as accidental intermediate host), eggs hatch in the small intestine and release six-hooked oncospheres. (3) The oncosphere penetrates the intestinal wall and migrates through the circulatory system into various organs, especially the liver and lungs. (4) In these organs, the oncosphere of *E. granulosus* develops into a thick-walled hydatid cyst that enlarges gradually, producing protoscoleces and daughter cysts that fill the cyst interior; the oncosphere of *E. multilocularis* develops into a multi-chambered, thin-walled hydatid cyst that proliferates by successive outward budding. Numerous protoscoleces develop within these cysts. The definitive host becomes infected by ingesting the cyst-containing organs of the infected intermediate host. (5) After ingestion, the protoscoleces evaginate and attach to the intestinal mucosa. (6) Development of adult stages (quoted from CDC)

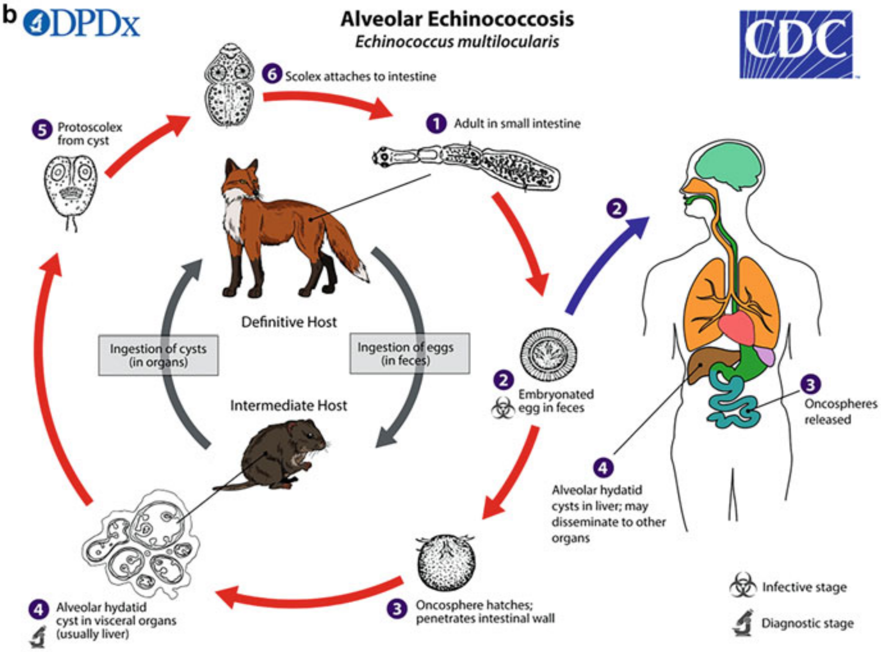

Fig. 11.3 (continued)

and East Africa, with the prevalence ranging from 5% to more than 10%. The average fatality rate in those five South American countries is about 2.9% (Pavletic et al. 2017). In those highly endemic regions, echinococcosis is a serious challenge to public health and social economy. Where the population is at risk for diseases, the number of patients ranks among the highest in the world. The endemiological characteristics are associated with the geographic nature, biological features, social behavior, religious belief, and cultural differentiation. All of these factors complicate the prevention programs. In China, endemic of echinococcosis is found mostly in the west and north pastoral and agricultural areas covering 40% of the land area of China, such as Inner Mongolia, Sichuan, Yunnan, Tibet, Shanxi, Gansu, Qinghai, Ningxia, and Xinjiang, with a total population of about 50 million in risk of contracting the parasite. Sichuan, particularly in its western area, is the hardest hit region by the *Echinococcus* worms covering both cystic and alveolar echinococcosis. The general prevalence is 0.462%. Among these cases, the cystic echinococcosis occurrence is 0.221%, and the alveolar echinococcosis occurrence is 0.244% (He et al. 2021). The highest prevalence rates can reach a height of 14.3% in some areas. Since the BRI promotes communication and connectivity of culture and business, acknowledgment of *Echinococcus* distribution and the pattern of epidemiology will provide crucial information for taking proper prevention to reduce the risk of contracting the parasite and to take necessary measures to limit the transmission of the diseases, as well as to minimize the occurrence of developing new endemic centers.

11.3 Current Control Measures and Interventions

Understanding the life cycle of *Echinococcus* species and the transmission of the disease informs the development of control measures to mitigate the contagious incidence. In order to block the transmission chain and to reduce the incidence of human infection, control measures need to consider both definitive and intermediate animal hosts as an essential portion of the One-Health approach to improve public education and hygienic service. Current control programs have shown case reduction in endemic areas, including the number of patients and infected animals. These programs may be shared among BRI countries and regions to minimize the impact of echinococcosis on economy and public health. Canines, such as dogs and foxes, are the most popular definitive hosts for the *Echinococcus* species. The definitive hosts are infected by digesting infected intermediate hosts. Sheep, goats, cattle, and camels are popular intermediate hosts for *E. granulosus* and rodents are popular intermediate hosts of *E. multilocularis*. The intermediate hosts contract the parasite by ingesting eggs created by definitive hosts. Humans are infected in the same way as other intermediate mammals but do not transmit directly the infection to other hosts, which are called accidental intermediate hosts. The echinococcus life cycle is maintained in a definitive and intermediate host loop, and the parasites are transmitted to naïve hosts that join this loop. Blocking the transmission pathway can halt the spread of parasites and reduce the incidence of infections.

There are checkpoints in the parasite life cycle vulnerable to interventions, and cystic echinococcosis is relatively more preventable than alveolar echinococcosis since *E. granulosus* is mostly transmitted and maintained in a life cycle within a definitive–intermediate loop consisting of domestic animals. Periodically deworming dogs by drugs such as praziquantel reduces the transmission of infectious shapes of *Echinococcus* to livestock and to humans. Improving hygiene and public services will mitigate the risk of contracting the infectious agent. For example, sanitary control in livestock slaughtering sites prevents the spreading of infectious agents. Removal of potentially infectious waste cuts the resources for accidental infections. Enhancing public education of pastoral communities and sanitary water supply reduces contact with infectious agents. Visiting a doctor's office for early diagnosis and treatment will improve the outcome of therapy. Investment in public interest, such as free sanitation, hygiene, reimbursement of transportation, health education, and medical services, will be beneficial to human society. This investment will be paid back by reducing health and economic burden. Development and mandatory implementation of vaccines for sheep have contributed to the livestock industry and agriculture economy and also indirectly reduced the risk of infections among humans. Vaccination with *E. granulosus* recombinant antigen EG95 has shown encouraging prospects of preventing and controlling infections. Vaccine trials in sheep showed effectiveness and safety in lambs against

E. granulosus infection (Larrieu et al. 2019c; Lightowlers et al. 1999). This vaccine has been licensed and is now commercially available in China and in Argentina. Surveillance is the key to the epidemiology of echinococcosis, to the estimation of the risk, and to the priority determination of control programs. The surveillance data are also necessary to monitor the progress of control measures and their outcome, especially in the case of alveolar echinococcosis because of the involvement of wild animals. But the surveillance of animals is a challenging task because the disease of the livestock is asymptomatic and close living wild animals are not monitored in most of the time. A combination of all those programs, such as vaccination of livestock, deworming of dogs, improvement of sanitary in slaughtering, and education of public health, can systemically strengthen prevention and help control infections of *Echinococcus* and halt the spread of echinococcosis. For example, China's program focuses on parasite source control, surveillance network, updated epidemiology, swift decision-making, diagnosis, and treatment improvement, which has achieved promising outcomes. The implementation of vaccination significantly reduces the prevalence of cystic echinococcosis and the number of cysts in vaccinated animals. Elimination of echinococcosis in humans will be accomplished, especially for cystic echinococcosis, with effective collaboration with strategic BRI partners and relevant sectors.

11.4 Achievements, Challenges, and Resolutions

The combination of multiple control programs that cover various aspects of the disease transmission, spreading, prevention, diagnosis, and treatment has reduced the endemic of echinococcosis and offered opportunities to eliminate the parasite in the near future and dose to humans. With the improvement of public education, dog deworming, and hygiene, aided with technological advancement in diagnosis and therapeutic, there are significant achievements in controlling cystic and alveolar echinococcosis, particularly in cystic echinococcosis, with the available EG95 vaccine (Barnes et al. 2012; Wen et al. 2019). The recent advances in ultrasonic and CT imaging offer diagnosis in an earlier and quicker fashion; development in treatment like albendazole and PAIR (puncture, aspiration, injection, respiration) results in better prognosis; and vaccination reduces greatly the infection of sheep and limits the source of infectious agents (Larrieu et al. 2019b). New Zealand and Tasmania are examples of the success in eradication of CE as a public health issue and even in the eradication of the parasite in dogs and sheep (Craig et al. 2017; Larrieu et al. 2019a). Continental areas, such as in Argentina, Uruguay, and China, also show some progress in control of cystic echinococcosis (Pavletic et al. 2017; van Kesteren et al. 2015). The prevalence of cystic echinococcosis in the Sichuan area of China dropped from 0.88% in 2012 surveillance to 0.31% in the 2016–2019 survey (He et al. 2021), although the prevalence of alveolar echinococcosis has a moderate increase from 0.27% to 0.35%. Consistent and sustainable control programs are needed to further reduce the health and economic burden of cystic echinococcosis and to prevent the rebound of alveolar echinococcosis in most parts of endemic and epidemic regions.

In contrast to the success of control in continentally or geographically isolated regions, continental areas show moderate gain in control of echinococcosis, where most BRI countries are located, and the impact on reducing human infections is limited (Larrieu et al. 2019a). The BRI area is huge, and the echinococcosis is broadly distributed, covering almost all land areas where the human cases continue to be a substantial cause of morbidity and mortality. A large number of wild animals harbor the parasite as definitive and intermediate hosts. The number of stray dogs makes the deworming strategy a poor outcome. Elimination of infectious parasites and diseases from wild and stray animals is challenging. Deworming of wild and stray hosts with medicated baits significantly reduced the echinococcosis but cannot sterilize the parasite and its transmission in wild and stray populations. Control of foxes and stray dogs has been demonstrated to be inefficient and encountered opposition from the humane society. From biodiversity, human, cost-effective, and sustainability points of view, these control measures are controversial. Most human cases occur in developing countries and in underrepresented populations as many other neglected diseases in the BRI area. Professionals that have been trained and experienced in advanced parasitic diseases are scarce. The investment is limited, and the priority to control echinococcosis is not fully recognized. The expense of implementing the complex control programs in a vast area is a heavy financial burden. Such an implementation is not sustainable. Early diagnosis with an advanced technology is not available in remote areas. Patients with cystic echinococcosis have shown 2.2% post-operative death rates after surgical removal and about 6.5% relapses post-medical intervention (Budke et al. 2006). Drug intervention is a long-lasting effort with significant adverse effects. Although the complex of programs was initiated in continental areas of South America in Argentina, Uruguay, Chile, and Peru as well as in China for more than 30 years, none of the endemic areas have reached a complete eradication stage. Reemergence of diseases often happens with partial or total discontinuation of control programs (Craig and Larrieu 2006; Larrieu and Zanini 2012). To reach a sustainable outcome, we need to explore novel and effective programs to control infection and transmission. Vaccines have been proven to be the most potent and cost-effective approach to control infectious diseases. Vaccination could be stand-alone or complementary to other control programs to prevent the development of infection and reduce the burden of health both in humans and in the livestock industry. Among the two major echinococcosis, the cystic echinococcosis is relatively preventable, compared with alveolar echinococcosis, since the definitive and intermediate hosts are mostly domestic. The initial success of sheep vaccination has also shown promise for cystic echinococcosis prevention. Here, we review recent advances and those candidates in development against cystic echinococcosis.

11.5 Vaccine Candidates

11.5.1 EG95

EG95 is one of the most promising candidates for vaccine development (Lightowlers et al. 1996). EG95 is an oncosphere protein encoded by the *eg95* gene family that is highly conservative in structure, with three exons separated by two introns (Chow et al. 2001). Exon 1 encodes a signal peptide, and exons 2 and 3 encode the mature and secreted proteins. The *eg95* family has at least seven members from *eg95–1* to *eg95–7* and expresses differentially at stages of the oncosphere development. Among them, *eg95*–1 and − 4 are only expressed during oncosphere development; *eg95*–5 and − 6 can be expressed during oncosphere development, as well as beyond. *eg95*–5 can also be expressed during protoscolex and adult worm development, and *eg95*–6 can also be expressed in the adult worm. *eg95*–7 is a pseudogene (Chow et al. 2001, 2004). The EG95 protein comprises 156 amino acids with a molecular mass of 16.5 kDa, consisting of a secretory signal peptide, a transmembrane domain, and a fibronectin type III (FnIII) domain. It is worth noting that the FnIII domain is also included in other taeniae vaccine candidates, such as *Taenia ovis* To16, *Taenia solium* TSOL18, and *Echinococcus multilocularis* EM95 (Gauci and Lightowlers 2003). The FnIII is highly homologous with the immunoglobulin superfamily, cell adhesion proteins, and cell surface receptors with a capacity for cell attachment (Obara et al. 2010). EG95 is detected in the cytoplasm and secretory granules of penetration gland cells of nonactivated or recently activated oncospheres but not on the surface membrane (Jabbar et al. 2011). Studies found that immune sheep serums against oncosphere or EG95 could damage the activated oncosphere (Heath et al. 1994), suggesting EG95 antigen or epitope is present on the surface of the oncosphere once activated. Expression of EG95 makes the oncosphere susceptible to immune effector molecules.

Oncospheres are a crucial stage during the development of the tapeworm. In the host intestine, cestode eggs hatch and release oncospheres, which penetrate the mucosal barrier, enter the circulation system, and migrate to the destination tissues and organs. The liver is the most common site for deposition because of enriched circulation, and often for cyst developed. The success of oncosphere penetration into mucosal tissue represents the establishment of early parasitic life of the pathogen and the development of hydatid cysts. Blocking the penetration of the oncosphere is the key to preventing the disease, and oncosphere antigens inducing host immune responses are potential targets for vaccine development. Animals immunized with EG95 have shown to reduce cyst numbers, size, and weight, and the EG95, as a vaccine candidate to prevent *E. granulosus*, has been extensively studied. Significant progress has been made in recent years (Table 11.1). Maternal antibodies induced by EG95 immunization showed prophylactic effects in calves against *E. granulosus* infection, and the efficacy correlated with the specific antibody titer (Heath and Koolaard 2012; Heath et al. 2012). The EG95-specific antibody also mediated a complement-dependent killing to eliminate invasion oncospheres at an early stage of infection (Heath et al. 1994). Vaccine based on EG95 recombinant protein

Table 11.1 Protective effect of EG95-related vaccines

Antigen(s)	Adjuvant (carrier)	Animal (antigen delivery)	Challenge	Results	Ref.
GST-EG95	Saponin \QuilA \Montanide ISA70\no adjuvant	Sheep (s.c.)	1000 Eg eggs	The protection rate against egg infection was 96–100%. The inhibition rate of cyst activity was 99.3%.	(Lightowlers et al. 1996, 1999)
	Quil A	Tammar wallaby (s.c.)	8000 Eg eggs	Specific IgG ↑. The protective rate against egg infection was 96.36–100%.	(Barnes et al. 2009)
	Saponin	Cattle, Calves (s.c.)	10,000 Eg eggs	Maternal antibody can last for at least 17 weeks, and protection was 94%. Calves can get 100% protection at the age of 16 weeks.	(Heath et al. 2012)
EG95 inclusion body	Oil-based	Sheep And Llama (s.c.)	1000 Eg eggs	Ab titer ↑, the reduction of live cysts counts was 84%, 94.7%.	(Poggio et al. 2016)
EG95NC$^-$	SeppicISA11R Quil A	Sheep (s.c.)	1000 Eg eggs	EG95 IgG ↑, and the protection was 100%.	(Jazouli et al. 2020)
BCG-EG95	BCG	Mice (s.c.) (i.n.) (i.o.) (i.m.)	50 PSCs	The cyst reduction rate was 18.20%–92.46% in BCG-EG95 groups. Serum IgG, IgG2a, IgG2b ↑ IgG1, IgG3 and IgE ↓; IL-2, IFN-γ, TNF-α ↑, IL-4 ↓ in the supernatant of immune spleen cells.	(Wen-Gui and You-Ming 2007)

(continued)

Table 11.1 (continued)

Antigen(s)	Adjuvant (carrier)	Animal (antigen delivery)	Challenge	Results	Ref.
EG95 (VV399)	(vaccinia virus)	Mice (i.n.) Sheep (s.c.) (i.m.)	2000 Eg eggs	Mice immunized once intranasally developed effective oncosphere-killing antibody by day 42 post-infection. Sheep primed with VV399 and boosted with EG95 protein produced 90% protection.	(Dutton et al. 2012)
EG95–5	Alum/CFA/IFA	Mice (s.c.)	\	IgG ↑; (IgG1, IgG2a, IgG2b, IgG3 ↑) IFN-γ, TNF-α, IL-12 ↑; IL-4, IL-10 → .	(Pirestani et al. 2014)
EG95	(*Lactococcus lactis*)	Mice (s.c.) (i.o.)	\	Heat-killed strain: IgG ↑. Live strain: sIgA ↑. Spleen lymphocytes: IFN-γ ↑, IL-4, IL-10 → .	(Ebrahimzadeh et al. 2021)

Abbreviations: *CFA* complete Freund's adjuvant; *IFA* incomplete Freund's adjuvant; *s.c* subcutaneous; *i.m* intramuscular; *i.n* intranasal; *i.o*, intraoral; *PSCs* protoscoleces of *E. granulosus*

(GST-EG95) and expressed by *E. coli* has been licensed and is on the market as a vaccine for veterinary usage. Inoculation with the EG95 vaccine showed a protective effect on sheep and cattle challenged with *E. granulosus* eggs (Heath and Koolaard 2012; Heath et al. 2012), and the effectiveness has been verified by multisite tests in several countries. Although being immunogenic and potent to induce antibody production, the detail in epitopes that induce B cell-producing protective antibodies need to be identified and characterized. Epitope mapping by using overlapping peptides showed that EG95 had four linear epitopes (Woollard et al. 1998). However, synthesized peptides expressing those four epitopes or peptides without intact FnIII structure did not induce protection against challenge infection (Woollard et al. 2000a, b), suggesting epitopes that inducing protective antibody production may be confirmational and associated with the FnIII domain. This hypothesis has been partially proven by simulating a confirmational epitope peptide E100 (with a sequence of KXNNDPXAA) with phage display technology and inducing a protective antibody production (Read et al. 2009). With the advantage of bioinformatics, those epitopes of EG95 are being predicted, their characterizations are being explored, and their functions are being proven (Wang et al. 2019).

Despite being conservative, EG95 sequences slightly vary among *E. granulosus* genotypes, suggesting that recombinant EG95 vaccines based on a single sequence may not provide full protection to all subtypes of *E. granulosus*. Genetic analysis has revealed that *E. granulosus* have 10 genotypes, G1–G10, with differences in geographical distribution and the preferences for intermediate hosts. Among them, G1 (sheep strain) and G6 (camel strain) are the most frequently detected genotypes in human echinococcosis. In these two genotypes, the sequence of EG95 differs by 5–17 amino acids (Alvarez Rojas et al. 2012; Chow et al. 2008), and the antibodies induced by these two genotypes did not cross-react, indicating that genetic variants may have an impact on EG95 vaccine efficacy (Alvarez Rojas et al. 2013). To develop an effective vaccine based on EG95, the antigenic variation has to be taken into consideration, and multivalent EG95 vaccines may provide wider and better protection to *E. granulosus* infection than single valent vaccines in a vast population and in a spectrum of endemic areas.

11.5.2 EgP-29

EgP-29 is a 29-kDa nonsecretory protein identified in *E. granulosus* and expressed on the surface of the tegument and rostellum of protoscoleces, as well as in the germinal layer of the cyst, but it is absent in hydatid cyst fluid or adult worm extracts. Study has shown that EgP-29 can be recognized specifically by serum from cyst echinococcosis patients, as well as by antibody specific to Ag5, a protein that has a different structure and is often used as a diagnostic marker of echinococcosis (Gonzalez et al. 2000). Because EgP-29 is expressed in an area that the worm interacts with the host mucosal epithelium, it may be a vaccine candidate to induce immune effector molecules blocking the worm penetrating into mucosal tissue in addition to its diagnostic value.

The efficacy of EgP-29 in preventing *E. granulosus* infection was evaluated in animal models. Recombinant EgP-29 (rEgP-29) expressed by *E. coli* construction induced high titer of specific IgG1 and IgG2b production in mice and provided 96.6% efficacy of protection upon protoscoleces challenge (Shi et al. 2009). DNA construction of EgP-29 as a vaccine (pcEgP-29) was also evaluated and showed 93% efficacy on protection against protoscoleces challenge. Mice immunized with the pcEgP-29 had fewer numbers, were smaller in size, and had less weight of the cyst developed than mice without the immunization (Gharibi et al. 2021). This result demonstrated that EgP-29 is potent at inducing protective immune responses in mice and preventing the infection of *E. granulosus* protoscoleces. The evaluation of EgP-29 as a vaccine candidate was further extended to sheep since mice are not the natural intermediate host for *E. granulosus*, and the pathogenicity and immune responses may differ from that of sheep and humans. Also, the immune response induced by protoscolex invasion and egg hatch and oncosphere penetration may differ. Upon oral challenge with *E. granulosus* eggs, rEgP-29 immunization protects sheep from developing echinococcosis. The efficacy of protection reached 94.5%, with high titers of IgG (both IgG1 and IgG2), IgE, and other elevated effector cytokines, such as IFN-γ, IL-2, and IL-4 (Wang et al. 2016). rEgP-29 could upregulate miR-374b-5p to promote CD4+ T cells producing IFN-γ, IL-2, and IL-17a expression, suppressing IL-10 expression, and inducing CD4 T cell differentiation toward Th1 and Th17 phenotypes to provide protection against pathogen invasion (Li et al. 2020). Further understanding the biological significance of EgP-29 in the life cycle of *E. granulosus* will provide more information about its induction of protective immunity and identification of potent epitopes inducing protective immunity, which will render rEgP-29 a promising vaccine candidate against *E. granulosus* infection.

11.5.3 FABPs

Fatty acid-binding proteins (FABPs) are members of the intracellular lipid-binding protein superfamily that locate in cells of vertebrates and invertebrates. Since parasites cannot synthesize fatty acids by themselves, they rely on lipids generated by the host for nutrition. The FABPs, as lipid carrier proteins, are essential for the absorption, storage, and transportation of fatty acids by parasites (Jakobsson et al. 2003). Family members of FABP, such as SM14 derived from *Schistosoma mansoni* (Mossallam et al. 2015) and Sj-FABP derived from *Schistosoma japonica* induced protective immune response and significantly reduced the number of adult worms in the host. FABPs are another promising vaccine candidate against *E. granulosus*.

Two fatty acid-binding proteins, EgFABP1 (also known as EgDf1) and EgFABP2, are present in *E. granulosus*. Both have 76% homology in amino acid sequences (Esteves et al. 2003) and are highly homologous with vertebrate cardioid fatty acid-binding proteins (H-FABP) found in vertebrates. Only EgFABP1 can be expressed in quantities on the surface of protoscolex (Alvite and Esteves 2016). EgFABP1 was found to bind to fatty acids with various chain lengths in *E. coli* and to interact with the cell membrane through direct contact with the phospholipid layer for substance exchanges (Porfido et al. 2012). This observation considers that EgFABP1 is involved in the exchange and transport of fatty acids in vivo. Since EgFABP1 presents in cystic fluid and secretions of protoscolex (Aziz et al. 2011), it may promote protoscolex growth and development.

Because of its role in *E. granulosus* growth and development, EgFABP1 is extensively studied as a potential vaccine candidate. In a mouse model, oral delivery of attenuated live *Salmonella* expressing recombinant EgFABP1 induced high titer of antibody against EgFABP1, as well as cytokine production of spleen lymphocytes, and the responses were more potent than those induced by intravenous immunization (Chabalgoity et al. 1997). In canines, oral delivery of the attenuated live *Salmonella* expressing recombinant EgFABP1 also elicited humoral and cellular immune responses. But the oral delivery might induce immune tolerance; only 1/3 of

PBMCs from immunized canines responded to the stimulation in vitro (Chabalgoity et al. 2000). This result challenges the research and development of EgFABP1 as a vaccine candidate for oral delivery against *E. granulosus* infection.

11.5.4 EgA31

EgA31 was identified from a cDNA library of *E. granulosus* cells screened with serum from an infected canine (Fu et al. 1999). *ega31* encode a protein with a molecular mass of 66 kDa expressed in the tegument, subtegumental parenchyma of the adult with a main location in the region of the sucker, and on the surface of the protoscolex. In protoscolex, the expression of EgA31 mRNA in the sucker regions is upregulated when the scolex evagination. This observation suggests that the EgA31 may interact with myosin to participate in muscle filament assembly of the muscle cells through its coiled-coil domains and proline-rich domain (Fu et al. 1999). It is worth noting that the developing worms attach mainly by grasping substantial plugs of tissue with their suckers on the scolex. When the scolex does not evaginate or cannot attach to the intestinal mucosa of the host in a short period of time after evagination, the worm will be swept out of the small intestine (Thompson 2017). Therefore, the suckers of protoscolex should be potential targets of the host immune system to prevent parasite invasion.

A study found that EgA31 can induce antibody production in canines and can be recognized by the serum of canines and humans infected with *E. granulosus* (Fu et al. 1999). Primed with EgA31 peptide, paracortical zone hyperplasia, secondary follicle formation, CD4+ T lymphocytes, B lymphocyte increase, and other indicators of active cellular immune responses can be observed in canine lymph nodes (Fu et al. 2000). Similar immune responses may also be observed in regional mucosal lymphoid tissues such as Peyer's patches. It is speculated that the EgA31 may enter the intestinal epithelial tissue via the tight junction of the suckers, be recognized by the host immune system, elicit local and systemic immune responses, and trigger the cascade of anti-*E. granulosus* insect immune responses.

As an initial vaccine candidate, preliminary data showed that recombinant EgA31 elicited both Th1 and Th2 immune responses in mice, with the Th2 being dominant (Fraize et al. 2005). Since the Th2-biased immune response was associated with inflammatory pathology of hydatid cyst and Th1-mediated responses were more efficient in killing protoscoleces, recombinant chimera protein (GST-chEgA31) with multiple T cell epitopes was designed to promote Th1 and limited Th2 immune responses (Esmaelizad et al. 2013b). The test result showed that the GST-chEgA31 immunization elicited a protective Th1 immune response in mice and protected 50–60% of mice challenged with protoscoleces. Following this rationale of design, a chimera protein (ChMEA) with five selected proteins was constructed, including EgGST, EgA31, EG95, EgTrp, and Eg14–3-3. The ChMEA immunization elicited Th1 type cytokine, for example, IFN-γ, and production of mouse spleen cells and protected 99.6% of mice from protoscoleces challenge (Esmaelizad et al. 2013a). The results demonstrated that ChMEA is a promising candidate for vaccines against an *E. granulosus* infection.

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H. Mehlhorn et al. (eds.), *Infectious Diseases along the Silk Roads*, Parasitology Research Monographs 17, https://doi.org/10.1007/978-3-031-35275-1