
Clonorchis and Opisthorchi Liver Flukes: A Survey of Parasitic Infections and Epidemiological Modeling

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Abstract

Clonorchis sinensis and *Opisthorchis viverrini*, significant public health threats in East and Southeast Asia, cause severe hepatobiliary diseases, including liver fibrosis and cholangiocarcinoma. This survey examines the epidemiological modeling of these liver fluke infections, emphasizing their transmission dynamics, prevalence, and public health impact. The study highlights the socio-economic and environmental factors contributing to these infections, such as raw fish consumption and inadequate sanitation. Epidemiological models, including statistical and mathematical techniques, offer insights into disease progression and intervention effectiveness. Innovative approaches, like Bayesian spatial-temporal modeling and multi-omics integration, enhance understanding of host-parasite interactions and inform targeted interventions. Challenges in modeling include data integration and the complexity of transmission dynamics, necessitating multidisciplinary research and community engagement to optimize public health strategies. Future directions focus on refining diagnostic tools and therapeutic innovations, emphasizing the importance of sustainable control measures and regional cooperation to mitigate the burden of these parasitic infections. By addressing these multifaceted challenges, the survey underscores the potential for improved health outcomes through comprehensive public health strategies and advanced epidemiological modeling.

1 Introduction

1.1 Significance of Clonorchis and Opisthorchi Infections

Clonorchis sinensis and *Opisthorchis viverrini* pose significant public health challenges due to their widespread prevalence and detrimental effects on human health, particularly in East and Southeast Asia. Clonorchiasis, attributed to *Clonorchis sinensis*, affects over 15 million people globally, predominantly in East Asia [1]. These liver flukes are associated with severe hepatobiliary diseases, including liver fibrosis, cirrhosis, and cholangiocarcinoma, which contribute to increased morbidity and mortality rates. The chronicity of these infections and their capacity to cause substantial liver damage necessitate effective public health interventions [2].

The epidemiological implications extend beyond direct health effects, as demonstrated by the identification of *Opisthorchis viverrini* in rural Myanmar, revealing an underexplored public health issue [3]. Comparative studies of liver flukes, including *Opisthorchis felinus*, *O. viverrini*, and *Clonorchis sinensis*, provide critical insights into their transmission dynamics and control measures [4].

Socio-economic and environmental factors significantly contribute to the propagation of these infections. The consumption of raw or undercooked fish, a primary transmission route, is a notable risk factor, especially in regions where fish constitutes a staple protein source [5]. Additionally, environmental contamination with parasite eggs, as shown in Northern Kazakhstan, underscores the global relevance and potential health risks associated with these parasitic infections.

To effectively mitigate the burden of *Clonorchis* and *Opisthorchi* infections, a comprehensive approach is essential, encompassing epidemiological modeling, targeted public health strategies, and

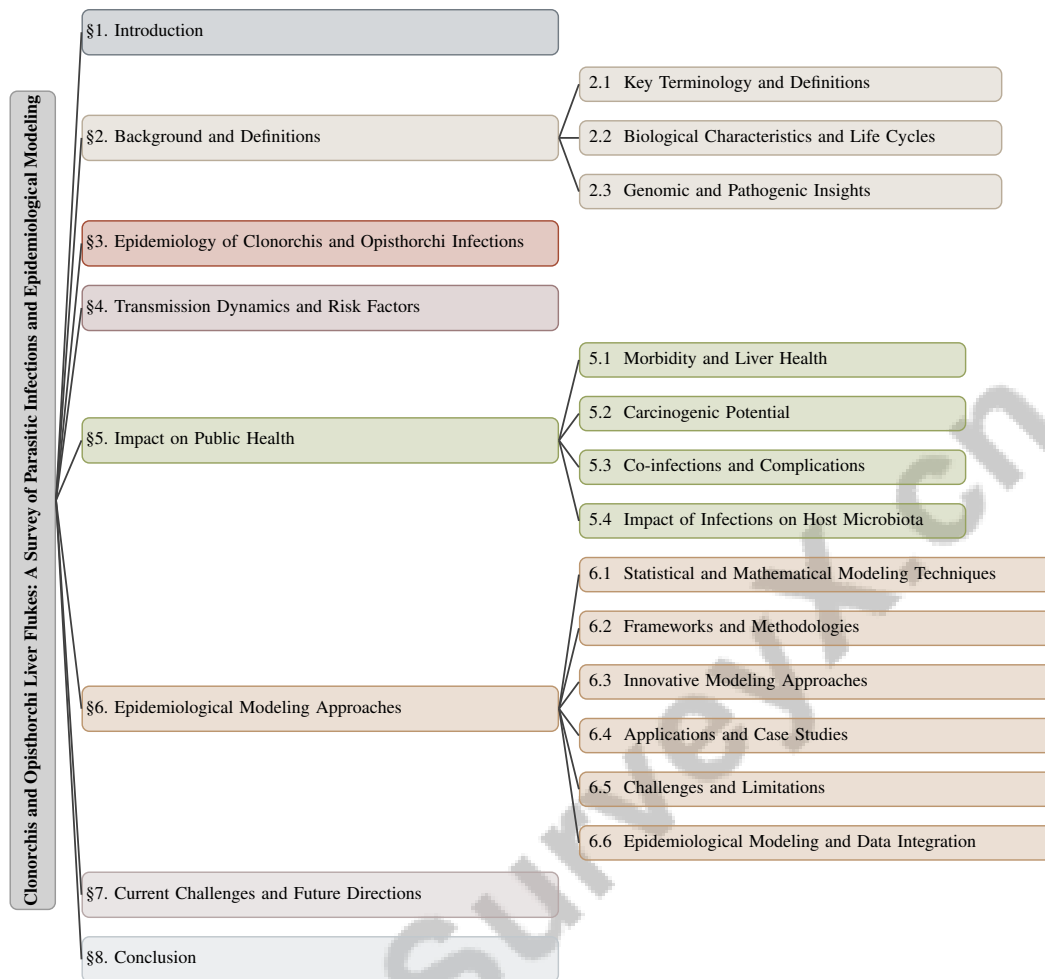


Figure 1: chapter structure

community engagement. Investigating potential therapeutic applications, particularly concerning inflammatory bowel disease, may yield innovative strategies for managing these infections while reducing tissue damage [6].

1.2 Importance of Epidemiological Modeling

Epidemiological modeling is vital for studying and controlling *Clonorchis* and *Opisthorchi* infections, offering a framework for understanding transmission dynamics and guiding public health interventions. These models simulate disease progression and evaluate intervention strategies, providing valuable insights into their effectiveness in endemic regions. Integrating epidemiological modeling with molecular approaches is crucial, especially given the scarcity of data on infections like *Opisthorchis viverrini*, which necessitates enhanced understanding and control efforts [3].

Furthermore, these models explore complex host-parasite interactions, such as the role of interleukin-1 beta (IL-1) as an inflammatory marker in liver infections, particularly with *Opisthorchis felinus* [7]. The potential of epidemiological modeling to reveal socio-ecological determinants of parasite transmission, including findings related to *Bufo marinus* feces, emphasizes its significance in proposing integrative control strategies aligned with sustainable health development [8].

The absence of accurate diagnostic tests in resource-limited areas further highlights the necessity of epidemiological modeling to inform effective treatment and control measures for *Clonorchis sinensis* infections [1]. Additionally, understanding the pathogenicity and carcinogenic potential of liver fluke species, including the molecular characteristics and implications of factors like Cs GRN

in cholangiocarcinoma and hepatocellular carcinoma metastasis, is crucial for developing targeted interventions.

Epidemiological modeling connects empirical data with theoretical frameworks, underscoring the need for regional cooperation and comprehensive public health strategies to combat liver fluke infections [9]. This approach is essential for the strategic planning and implementation of interventions aimed at alleviating the public health burden posed by these parasitic infections.

1.3 Structure of the Survey

This survey is systematically organized to provide an in-depth examination of *Clonorchis* and *Opisthorchi* liver flukes, emphasizing their epidemiological modeling and public health implications. The introduction highlights the significance of these parasitic infections and the role of epidemiological modeling in understanding and controlling their spread. Following this, the survey offers a comprehensive overview of liver flukes—specifically *Clonorchis sinensis*, *Opisthorchis* spp., and *Metorchis* spp.—detailing their biological characteristics, life cycles, and essential terminology, which are critical for grasping their epidemiology and associated health risks, including their classification as carcinogens and their involvement in diseases such as cholangiocarcinoma [10, 4, 11].

Subsequent sections address the epidemiology of *Clonorchis* and *Opisthorchi* infections, focusing on their global distribution, particularly in Southeast Asia and China, and the environmental conditions influencing their prevalence. The survey also explores transmission dynamics and risk factors, considering socio-economic, environmental, dietary, behavioral, and demographic aspects that contribute to infection risks.

The analysis of public health impacts includes a thorough evaluation of various factors, such as the morbidity associated with liver fluke infections, the carcinogenic potential of *Opisthorchis viverrini* as classified by the International Agency for Research on Cancer, the exacerbating role of co-infections—especially with *Helicobacter pylori*—in hepatobiliary diseases, and the alterations in host microbiota resulting from these infections, which may lead to cholangiocarcinoma in endemic regions [12, 13, 11]. The survey further reviews epidemiological modeling approaches, discussing statistical and mathematical techniques, frameworks, methodologies, and innovative modeling strategies, complemented by applications and case studies. Challenges and limitations in modeling efforts are also addressed, alongside the importance of data integration.

Significant challenges and future research directions in tackling cholangiocarcinoma associated with *Opisthorchis viverrini* infection are highlighted, emphasizing the need for effective public health strategies, community engagement, and ongoing investigations into the molecular and immunological mechanisms underlying the disease, particularly concerning co-infection with *Helicobacter pylori* [3, 10, 11]. The survey concludes with a discussion on future innovations in diagnostics and therapeutics, underscoring the necessity for integrated public health strategies to mitigate the impact of these parasitic infections. The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Key Terminology and Definitions

A thorough understanding of the terminology associated with *Clonorchis* and *Opisthorchis* infections is crucial for comprehending their epidemiological and public health significance. These liver flukes, *Clonorchis sinensis* and *Opisthorchis viverrini*, inhabit bile ducts and are linked to severe health conditions such as cholangiocarcinoma, falling under helminthiasis, which includes infections by parasitic worms like trematodes [6]. Clonorchiasis, caused by *Clonorchis sinensis*, and opisthorchiasis, resulting from *Opisthorchis* species, are primarily transmitted through the ingestion of raw or undercooked fish containing metacercariae, highlighting socio-cultural influences on infection dynamics [14]. Metorchosis, within the *Opisthorchiidae* family, further illustrates the variety of infections these parasites cause [14].

Epidemiological modeling employs mathematical and statistical methods to simulate disease dynamics and assess intervention strategies, offering insights into social and environmental factors affecting infection rates and potential co-infections [6]. Understanding these terms is vital for addressing public health challenges, particularly in regions where environmental contamination increases the

risk of foodborne diseases like cholangiocarcinoma [10, 4, 11]. These definitions form the foundation for exploring the epidemiological and public health impact of liver fluke infections and devising effective control measures.

2.2 Biological Characteristics and Life Cycles

The biological traits and life cycles of *Clonorchis sinensis* and *Opisthorchis* species are pivotal for understanding their transmission and public health implications. These flukes undergo complex life cycles involving freshwater snails, fish, and mammals, with humans as definitive hosts [10]. The cycle starts with egg excretion in feces, leading to miracidia infecting snails, where they develop into sporocysts, rediae, and cercariae, which are then released into water [10]. Cercariae penetrate fish, encysting as metacercariae, and humans become infected by consuming undercooked fish [15]. Metacercariae excyst in the duodenum, migrating to the bile ducts to mature into adult flukes [16]. These life cycle stages, notably in regions like the Amur River basin, are crucial for understanding human health impacts [17].

Host-parasite interactions involve intricate immunological responses, with *Clonorchis sinensis* inducing Th2/Treg-dominated responses essential for long-term parasitism [6]. This immune modulation is crucial for understanding the pathogenesis of liver fluke infections and their link to diseases like cholangiocarcinoma [2]. The role of Cs GRN in epithelial-mesenchymal transition (EMT) connects these infections to severe health outcomes via cancer cell migration [5]. Liver fluke infections also alter host microbiota and metabolic pathways, affecting host-parasite-microbiota interactions [18]. Species-specific responses in liver and kidney further illustrate complex host-parasite dynamics [16]. These infections alter biliary microbiota, influencing microbial diversity [19].

Understanding the life cycles and biological characteristics of *Clonorchis* and *Opisthorchi* species is vital for developing effective public health interventions. Identifying key life cycle stages and transmission factors, such as dietary habits and environmental conditions, enables targeted strategies to reduce infection rates and health risks [20]. Genomic insights into *O. felinus* enhance understanding of liver fluke biology and its implications for human health [21].

2.3 Genomic and Pathogenic Insights

Genomic and pathogenic insights into *Clonorchis sinensis* and *Opisthorchis* species enhance our understanding of their biology and pathogenic mechanisms. The draft genome assembly of *Opisthorchis felinus* provides a basis for comparative genomic studies, advancing knowledge of liver fluke biology and epidemiology [21]. This genomic information is crucial for identifying molecular targets for diagnostic and therapeutic interventions, especially in endemic areas.

Clonorchiasis pathogenesis involves complex parasite-host immune interactions. Molecular investigations into *C. sinensis* juvenile infections reveal physiological responses and pathological manifestations, critical for developing strategies to mitigate early infection stages and prevent long-term complications [20]. Biomarkers like gamma-glutamyl transferase (GGT) and d-glucuronate offer promising non-invasive diagnostic tools for clonorchiasis, enhancing early detection and management [22].

Liver fluke-host microbiome interactions significantly influence infection pathogenesis, with *C. sinensis* causing substantial biliary microbiome alterations, increasing pathogenic genera, and decreasing beneficial ones, contributing to pathogenesis [19]. Comparative analyses reveal species-specific microbiome changes due to different liver fluke infections, underscoring the importance of understanding these interactions for targeted interventions [23]. The synergistic effects of liver flukes and *Helicobacter* spp. on biliary disease pathogenesis highlight infection complexity, with implications for tissue damage and malignancy [11]. This interaction framework emphasizes integrated approaches considering microbial and parasitic factors in managing liver fluke infections.

Ongoing research into genomic and pathogenic aspects of liver flukes, alongside advancements in diagnostic and therapeutic technologies, promises improved control and treatment strategies. The development of rapid diagnostic assays, like the RPA-LFD assay for *C. sinensis* detection, exemplifies genomic insights enhancing public health responses to parasitic infections [1].

In examining the epidemiology of *Clonorchis* and *Opisthorchi* infections, it is crucial to understand the various factors that contribute to their global distribution and prevalence. Figure 2 illustrates

the hierarchical structure of these infections, emphasizing regional specifics in Southeast Asia and China. This figure not only highlights key infection rates and instances of mixed infections but also delves into the health implications and transmission dynamics associated with these parasitic diseases. Furthermore, it addresses public health concerns and environmental influences, thereby providing a comprehensive overview of the multifaceted factors that underpin the spread and impact of *Clonorchis* and *Opisthorchi* infections. Such visual representation enhances our understanding of the intricate relationships between epidemiological factors and the broader implications for public health.

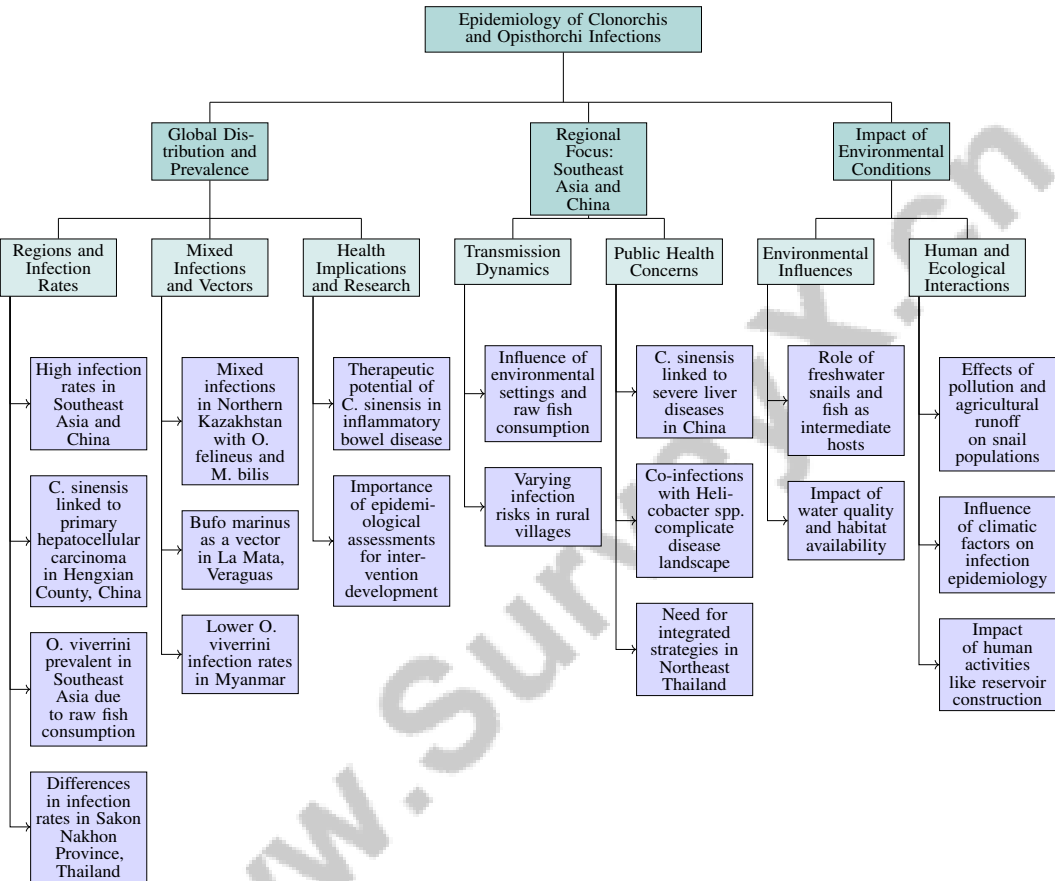


Figure 2: This figure illustrates the hierarchical structure of the epidemiology of *Clonorchis* and *Opisthorchi* infections, focusing on global distribution and prevalence, regional specifics in Southeast Asia and China, and the impact of environmental conditions. The figure highlights key infection rates, mixed infections, health implications, transmission dynamics, public health concerns, and environmental influences, providing a comprehensive overview of the factors contributing to the spread and impact of these infections.

3 Epidemiology of *Clonorchis* and *Opisthorchi* Infections

3.1 Global Distribution and Prevalence

Clonorchis sinensis and *Opisthorchis viverrini* infections are major public health concerns, particularly in Southeast Asia and China. In Hengxian County, China, *C. sinensis* is significantly associated with an increased incidence of primary hepatocellular carcinoma (HCC), with infection rates varying due to socio-economic and environmental factors [4]. *O. viverrini*, prevalent in Southeast Asia, poses health risks through the consumption of raw or undercooked fish [15]. Research in Sakon Nakhon Province, Thailand, highlights stark differences in infection rates between hotspot and non-hotspot areas, underscoring the need for targeted interventions [15]. The complexity of global distribution is further illustrated by mixed infections, such as *O. felineus* and *M. bilis* in Northern Kazakhstan [14].

This complexity is visually represented in Figure 3, which illustrates the global distribution and prevalence of liver fluke infections, highlighting regional prevalence, health implications, and research focus areas. In regions like La Mata, Veraguas, the role of *Bufo marinus* as a vector exemplifies diverse geographic spread and ecological interactions affecting prevalence. Myanmar's lower *O. viverrini* infection rates compared to neighboring countries emphasize the importance of localized epidemiological studies [3]. Understanding these infections' prevalence is crucial for public health planning. Emerging research on the therapeutic potential of *C. sinensis* in inflammatory bowel disease adds complexity to its health implications [6]. Comprehensive epidemiological assessments are vital for developing interventions to mitigate the health impacts of these infections globally.

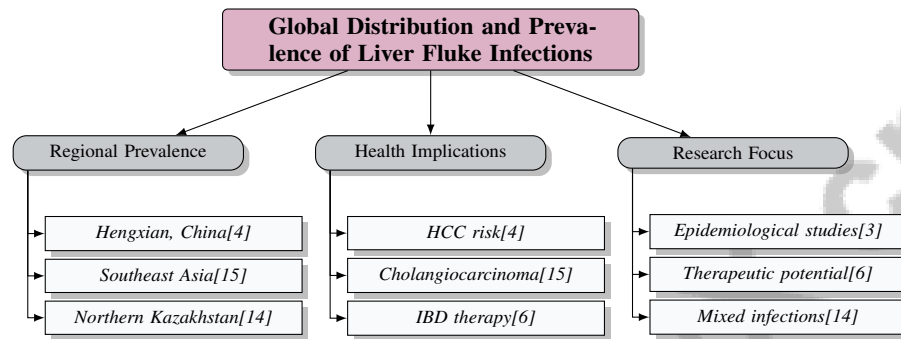


Figure 3: This figure illustrates the global distribution and prevalence of liver fluke infections, highlighting regional prevalence, health implications, and research focus areas.

3.2 Regional Focus: Southeast Asia and China

Southeast Asia and China are central to studying *Clonorchis* and *Opisthorchi* infections due to their high prevalence and public health impact. Environmental settings and behaviors, especially raw fish consumption, significantly influence transmission dynamics. Studies reveal varying infection risks tied to environmental contexts in rural villages, highlighting the need for tailored interventions [24]. The spatial-temporal distribution of *O. viverrini* in Southeast Asia remains unclear, complicating public health initiatives [25]. In Thailand, high *O. viverrini* prevalence is linked to dietary and environmental factors.

In China, *C. sinensis* poses significant public health concerns, particularly in areas with high raw fish consumption, and is associated with severe liver diseases, including cholangiocarcinoma [11]. Co-infections with *Helicobacter* spp. complicate the disease landscape, contributing to biliary disease pathogenesis [11]. Control efforts must consider environmental, behavioral, and microbial interdependencies. By integrating epidemiological modeling with local ecosystem and cultural insights, strategies can be tailored to reduce parasitic infections and improve health outcomes in regions like Northeast Thailand [25, 24].

3.3 Impact of Environmental Conditions

Environmental conditions play a crucial role in the transmission and prevalence of *Clonorchis* and *Opisthorchi* infections, influencing both the parasites' life cycles and host behaviors. The abundance of intermediate hosts, such as freshwater snails and fish, depends on environmental factors like water quality and habitat availability, affecting parasite survival and transmission [10]. Aquatic ecological interactions are vital for liver flukes' persistence. Water quality changes from pollution and agricultural runoff can alter snail populations, impacting transmission potential. Organic matter contamination can increase snail populations, enhancing parasite life cycle completion [15]. Climatic factors, including temperature and rainfall, influence snail and fish breeding cycles, affecting infection epidemiology [25].

Human activities, such as reservoir construction and irrigation, create new habitats for intermediate hosts, facilitating liver fluke spread. Modifying landscapes for agriculture increases human contact with infected fish, raising transmission risk [24]. Environmental degradation and deforestation can disrupt ecological balance, potentially leading to parasitic disease emergence or re-emergence [11]. The interplay between environmental and socio-economic conditions is significant. In regions

where fish is a primary protein source, economic constraints may limit safe food preparation access, increasing raw or undercooked fish consumption risk. Understanding environmental determinants is crucial for developing effective public health interventions. These must consider ecological factors, such as freshwater ecosystem health and agricultural practices, alongside socio-economic influences, including dietary habits and community networks. In regions like Northeast Thailand and Northern Vietnam, high infection rates are linked to traditional raw fish consumption and contaminated freshwater reliance, necessitating a multifaceted disease prevention approach aligned with sustainable health development goals [10, 26, 24].

4 Transmission Dynamics and Risk Factors

The transmission of *Clonorchis* and *Opisthorchi* infections is influenced by an intricate combination of socio-cultural, ecological, and biological factors. Identifying these dynamics and risk factors is essential for devising effective public health interventions.

4.1 Risk Factors and Contributing Factors

Cultural practices, such as the consumption of raw or undercooked fish in Vietnam, significantly elevate *C. sinensis* infection rates [26]. This tradition, compounded by low educational levels and awareness, poses challenges for disease control [26]. Agricultural intensification increases human exposure to infected fish, necessitating integrated approaches that consider both environmental and socio-cultural dimensions [24, 27]. Urbanization and wildlife interactions, like those involving *Bufo marinus*, further illustrate ecological contributions to transmission [27].

Demographic factors also affect infection rates, with males and individuals of Zhuang ethnicity showing higher susceptibility to *C. sinensis*, highlighting the need for targeted interventions [28]. The complex transmission cycle involving snails, fish, and mammals complicates intervention strategies [29]. The presence of *Bithynia* snails, exacerbated by fecal contamination, and the morphological similarity of *O. viverrini* eggs to other trematodes complicate diagnosis and control efforts [15, 3]. In areas like Kuzbass, ecological and public health inadequacies contribute to helminthiasis spread [30].

Interactions between liver flukes and host microbiota are crucial yet complex, complicating the understanding of infections' impacts on health [23]. Therapeutic interventions, such as r Cs CP and Cs CA, show promise in alleviating inflammatory bowel disease symptoms, underscoring the multifaceted nature of these infections and their health implications [6]. Addressing these risk factors through interdisciplinary research and community-based interventions is vital for mitigating the burden of *Clonorchis* and *Opisthorchi* infections [9].

Figure 4 illustrates the key risk and contributing factors for *Clonorchis* and *Opisthorchi* infections, categorized into cultural and socioeconomic factors, ecological and demographic factors, and microbiota and health impacts. This figure highlights the complexity of transmission and the need for targeted interventions, reinforcing the discussion of the multifaceted nature of these infections and their broad implications for public health.

4.2 Raw Fish Consumption and Dietary Habits

Dietary habits, particularly raw or undercooked fish consumption, are central to *Clonorchis* and *Opisthorchi* transmission dynamics. This cultural practice, prevalent in regions like Northeast Thailand, significantly increases liver fluke infection risks [24]. The metacercariae, the infective larval stage, are commonly found in freshwater fish consumed by humans.

Research underscores the impact of these dietary habits on infection rates, necessitating public health strategies that address cultural practices to mitigate risks [31]. In rural areas, socio-economic factors limiting access to safe food preparation exacerbate raw fish consumption reliance. Environmental factors, such as fecal contamination in aquatic environments, further heighten infection risks, with *Bithynia* snails serving as intermediate hosts for *O. viverrini* [15].

To mitigate health risks, comprehensive strategies including public health education, community engagement, and the promotion of alternative dietary practices are essential. By increasing awareness of the dangers of raw fish and encouraging safer food preparation techniques, it is possible to reduce *Clonorchis* and *Opisthorchi* infections [11, 10, 26, 24].

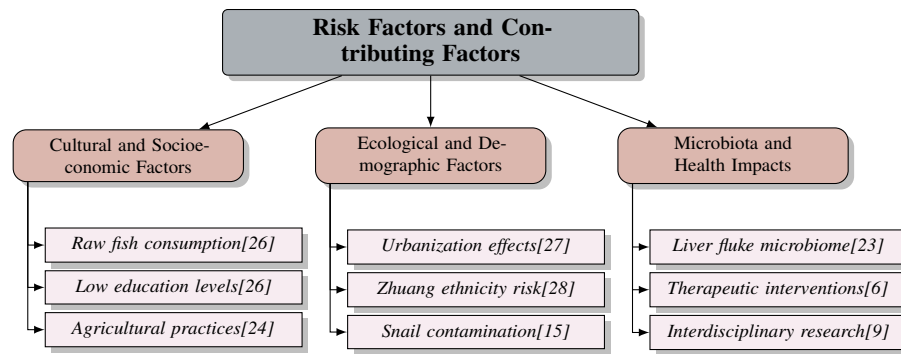


Figure 4: This figure illustrates the key risk and contributing factors for Clonorchis and Opisthorchi infections, categorized into cultural and socioeconomic factors, ecological and demographic factors, and microbiota and health impacts. It highlights the complexity of transmission and the need for targeted interventions.

4.3 Socio-Economic and Environmental Factors

Socio-economic and environmental factors influencing Clonorchis and Opisthorchi infection rates reflect the complex interplay between human activities, ecological conditions, and public health infrastructure. Non-compliance with sanitary standards and inadequate public health resources significantly contribute to infection spread, particularly in rural and economically disadvantaged areas with limited access to clean water and sanitation [30].

Economic constraints restrict healthcare and education access, resulting in low awareness of liver fluke risks and hindering control measures. In regions where fish is a primary protein source, economic pressures increase raw fish consumption, elevating parasite exposure. Studies in rural Northeast Thailand and northern Vietnam illustrate how cultural practices, social networks, and environmental conditions contribute to this trend [26, 24]. Environmental degradation from deforestation, agriculture, and urbanization alters intermediate host habitats, facilitating liver fluke transmission [15, 30, 10, 11, 24].

Addressing these factors requires comprehensive public health strategies integrating community education, improved sanitation, and sustainable environmental management. By addressing socio-economic, environmental, and cultural practices influencing parasitic infections, targeted interventions can reduce risks and enhance health outcomes [32, 24].

4.4 Behavioral and Demographic Risk Factors

Behavioral and demographic factors significantly influence Clonorchis and Opisthorchi infection dynamics. Practices like consuming raw or undercooked fish are ingrained in cultural traditions of many endemic communities, particularly in Southeast Asia. These habits drive infection as metacercariae are commonly found in freshwater fish consumed by humans [24]. The persistence of these practices, despite known health risks, emphasizes the need for culturally sensitive public health interventions advocating for safer food preparation while respecting local traditions.

Demographic factors, including age, gender, and ethnicity, determine infection risk. Groups like males and specific ethnic populations, such as the Zhuang, show higher susceptibility to *C. sinensis*, underscoring the importance of targeted strategies [28]. Higher infection prevalence may stem from differences in dietary habits, occupational exposures, or genetic predispositions, warranting further research.

Socio-economic status also plays a crucial role in infection risk. Economic constraints limit healthcare and education access, resulting in low awareness of liver fluke risks and hindering control measures. In regions where fish is a primary protein source, economic pressures increase raw fish consumption, elevating parasite exposure. Studies in rural Northeast Thailand and northern Vietnam highlight cultural practices, social networks, and environmental conditions contributing to this trend [26, 24]. Migration and urbanization facilitate liver fluke spread by enabling infected individuals' movement and introducing parasitic diseases into new areas. Urban expansion increases human interaction

with freshwater ecosystems, elevating transmission risks, especially in culturally prevalent raw fish consumption regions [26, 24]. Understanding these factors is essential for developing comprehensive public health strategies aimed at reducing *Clonorchis* and *Opisthorchi* infections.

5 Impact on Public Health

Liver fluke infections, particularly those caused by *Clonorchis sinensis* and *Opisthorchis* species, present significant public health challenges due to their associations with morbidity and liver health issues. *Clonorchis sinensis* is notably prevalent in Asia, correlating with severe hepatobiliary morbidity, highlighting the urgent need for public health interventions [2, 10, 33]. In rural northern Vietnam, a high prevalence rate of 40.4

5.1 Morbidity and Liver Health

The morbidity associated with *Clonorchis sinensis* and *Opisthorchis* infections significantly impacts liver health, leading to hepatobiliary diseases such as liver fibrosis, cirrhosis, and cholangiocarcinoma. The severity of these conditions is closely linked to infection intensity [2]. Understanding the mechanisms, including parasite-induced immunological changes, is crucial for addressing liver damage [2]. *Opisthorchis viverrini* infections contribute similarly to liver morbidity, necessitating further research [3]. Mixed infections with other parasites complicate the epidemiological landscape, enhancing our understanding of disease morbidity [14]. Environmental interactions, such as those involving amphibian feces, further affect liver health [27].

Therapeutic interventions, such as combining praziquantel and curcumin, show promise in reducing parasitic load and inflammatory markers, suggesting improved treatment strategies [7]. Additionally, therapies derived from *Clonorchis sinensis* for inflammatory bowel disease offer novel avenues for liver health improvement [6]. Advances in diagnostics, like the RPA-LFD assay, enhance monitoring and management of clonorchiasis [1]. The relationship between liver fluke infections and host microbiota alterations complicates morbidity, as changes in gut microbiota may exacerbate inflammation and carcinogenesis [8].

5.2 Carcinogenic Potential

Clonorchis sinensis and *Opisthorchi* species are significant carcinogens linked to cholangiocarcinoma (CCA) and other liver malignancies. These parasites induce chronic inflammation and direct tissue damage, with overexpression of progranulin (PGRN) further highlighting their oncogenic potential [5]. *C. sinensis* infection is associated with severe liver diseases, including CCA, through immune-mediated pathways [22]. Comparative studies show *O. viverrini* is linked to greater biliary neoplastic changes, while *O. felinus* and *C. sinensis* lead to more fibrotic responses [16]. Both *O. viverrini* and *C. sinensis* are classified as major carcinogens, with *O. felinus* potentially warranting reclassification [4, 34]. The use of anti-cancer drugs like mebendazole illustrates the complex interplay between therapy and carcinogenic potential [35]. Understanding these mechanisms is crucial for interventions aimed at reducing cancer risk [9].

5.3 Co-infections and Complications

Co-infections with *Clonorchis sinensis* and *Opisthorchi* species complicate health management due to interactions with other pathogens, such as *Helicobacter pylori*, which increase cholangiocarcinoma (CCA) risk [11]. The interplay between co-infections and liver fluke infections affects disease severity and management [13]. Drug resistance in parasites like hookworms poses significant treatment challenges, highlighting the need for novel therapeutic strategies [35]. Variability in diagnostics and preventive measures against CCA complicates accurate diagnosis and management [12]. The potential link between *O. felinus* infection and CCA underscores the complexities of co-infections [34]. Understanding these interactions is crucial for developing comprehensive public health strategies.

5.4 Impact of Infections on Host Microbiota

Clonorchis sinensis and *Opisthorchi* infections profoundly affect host microbiota, influencing overall health. Dysbiosis from *C. sinensis* infection correlates with infection intensity and exacerbates liver disease progression [18]. Alterations in gut microbiota affect metabolic and immune pathways, impacting susceptibility to other infections [18]. Changes in biliary microbiota associated with *C. sinensis* infection contribute to hepatobiliary disease development [19]. Co-infections further complicate microbiota dynamics, affecting disease outcomes and treatment [13]. Incorporating microbiota research into public health strategies can enhance interventions for liver fluke infections, especially in endemic regions where raw fish consumption is prevalent [12, 10, 23, 11, 24].

6 Epidemiological Modeling Approaches

Category	Feature	Method
Statistical and Mathematical Modeling Techniques	Epidemiological Modeling	SInf[36]
Frameworks and Methodologies	Metabolic Profiling Techniques	NTA[22]
Innovative Modeling Approaches	Data Integration Techniques	MOA[20]
Challenges and Limitations	Network Modeling Limitations	MWD[37]
Epidemiological Modeling and Data Integration	Statistical Modeling	BSTJM[25]

Table 1: This table summarizes various methods and techniques used in epidemiological modeling, focusing on *Clonorchis* and *Opisthorchi* infections. It categorizes the methods into statistical and mathematical modeling techniques, frameworks and methodologies, innovative modeling approaches, challenges and limitations, and epidemiological modeling and data integration, each with their respective features and references.

Epidemiological modeling employs statistical and mathematical methodologies to illuminate the dynamics of infectious diseases, particularly focusing on transmission patterns and control measures concerning *Clonorchis* and *Opisthorchi* infections. These models analyze complex interactions and inform public health strategies to mitigate the impact of these parasitic diseases. Table 1 provides a comprehensive overview of the diverse methods and techniques employed in the epidemiological modeling of *Clonorchis* and *Opisthorchi* infections, highlighting their applications and the challenges faced in this field. Additionally, Table 4 provides a detailed comparison of the different methods and techniques utilized in the epidemiological modeling of *Clonorchis* and *Opisthorchi* infections, illustrating their applications and challenges in the field. The following subsections discuss specific modeling techniques and their applications.

6.1 Statistical and Mathematical Modeling Techniques

Method Name	Modeling Techniques	Data Integration	Application Scenarios
SInf[36]	Gillespie Algorithm	Demographic Data	Livestock Populations
BSTJM[25]	Bayesian Geostatistical Framework	Diverse Data Sources	Public Health Interventions
MWD[37]	Sir Simulations	Degree Distribution	Epidemic Dynamics
NTA[22]	Statistical Analysis	Biochemical Indices	Early Diagnosis

Table 2: Overview of various modeling techniques applied to study *Clonorchis* and *Opisthorchi* infections, detailing their methodological frameworks, data integration approaches, and specific application scenarios. This table highlights the diversity in modeling strategies, ranging from stochastic simulations to Bayesian frameworks, employed to enhance our understanding of infection dynamics and inform public health interventions.

The integration of statistical and mathematical modeling techniques is essential for understanding *Clonorchis* and *Opisthorchi* infections' transmission dynamics and control mechanisms. Table 2 presents an overview of the statistical and mathematical modeling techniques utilized in the study of *Clonorchis* and *Opisthorchi* infections, illustrating their methodological diversity and application in public health contexts. Advanced Bayesian spatial-temporal models analyze interactions among host populations, infections, and environmental factors, especially in Southeast Asia, generating high-resolution disease risk maps critical for targeted public health interventions [13, 10, 25, 32, 24]. Logistic regression models explore associations between risk factors and infection rates, evaluating socio-demographic and environmental influences on *Clonorchis sinensis* infection [36].

Mathematical models, including deterministic ordinary differential equations (ODEs) and stochastic individual-based models, simulate liver fluke infections' transmission dynamics. These models use a compartmental approach, categorizing individuals as susceptible, infected, or recovered, and integrate complex dynamics like subpopulation interactions with data-driven parameters. The Gillespie stochastic simulation method enhances infection dynamics modeling [38, 36]. Differential equations provide a theoretical basis for understanding intervention impacts and assessing disease eradication potential.

Innovative approaches, such as Bayesian Spatial-Temporal Joint Modeling (BSTJM), integrate point-referenced and area-aggregated disease data with influencing factors, estimating spatial-temporal distribution patterns of *Opisthorchis viverrini* infections [25]. The Weibull distribution's application in parameterizing heterogeneity offers flexibility in epidemiological data modeling [37]. Coupling epidemic processes over extended intervals provides a framework for predicting infection spread and evaluating control measures [39]. Non-targeted metabolomics offers a comprehensive strategy to investigate metabolic profiles and identify potential biomarkers, refining diagnostic and therapeutic interventions [22]. Recombinant cysteine protease (r Cs CP) exemplifies the integration of bioinformatics and functional assays in understanding infection dynamics [6].

Integrating diverse modeling techniques enhances understanding of liver fluke infections by examining relationships between environmental factors, human behaviors, and parasitic transmission, forming a foundation for evidence-based public health strategies aimed at reducing prevalence and impact, particularly in regions like Northeast Thailand [10, 24].

6.2 Frameworks and Methodologies

Epidemiological modeling frameworks and methodologies are crucial for understanding transmission dynamics and control strategies for *Clonorchis* and *Opisthorchis* infections, especially in Southeast Asia. Bayesian spatial-temporal models generate high-resolution disease risk maps, revealing significant prevalence and informing targeted interventions [25, 29]. These frameworks integrate various data sources, modeling complex interactions between host, parasite, and environment, facilitating effective public health interventions.

Compartmental models, dividing populations into categories like susceptible, infected, and recovered, are foundational in modeling infection spread and assessing intervention impacts [40]. These models, often implemented through ODEs, allow scenario simulations and control measure evaluations like mass drug administration and health education campaigns.

Agent-based models (ABMs) simulate interactions among individuals, considering heterogeneity in behavior and demographics, useful for capturing behavioral factors like raw fish consumption on liver fluke infection spread [29]. Bayesian modeling techniques, including BSTJM, integrate spatial and temporal data with influencing factors, estimating infection distribution patterns and identifying hotspots [25].

The integration of statistical and mathematical methodologies is illustrated through logistic regression models for identifying risk factors and continuous-time Markov chains for simulating infection dynamics. Frameworks like SimInf employ the Gillespie stochastic simulation algorithm to model disease spread in subpopulations, incorporating real-world data such as births, deaths, and movements [39, 40, 32, 36, 38]. These models provide insights into socio-demographic and environmental determinants of infection, guiding public health strategies.

Non-targeted metabolomics offers a novel framework to investigate metabolic profiles and identify potential biomarkers for liver fluke infections [22]. This approach enhances understanding of host-parasite interactions and informs diagnostic and therapeutic interventions.

The diversity of frameworks and methodologies in epidemiological modeling enhances prediction of infection trends, evaluation of intervention strategies, and reduction of *Clonorchis* and *Opisthorchi* infections' burden. Combining data-driven models with empirical observations tailors and enhances public health policies to tackle parasitic diseases' complex challenges, such as opisthorchiasis, a significant public health concern in Southeast Asia [40, 32, 25, 38, 24].

Method Name	Data Integration	Analytical Techniques	Therapeutic Strategies
BSTJM[25]	Diverse Data Sources	Bayesian Geostatistical Framework	-
MOA[20]	Multi-omics Techniques	Multi-omics Techniques	Early Intervention Therapy

Table 3: Summary of innovative modeling approaches for Clonorchis and Opisthorchi infections, highlighting the integration of diverse data sources and analytical techniques. The table details methods such as the Bayesian geostatistical framework and multi-omics techniques, along with their respective data integration and therapeutic strategies.

6.3 Innovative Modeling Approaches

Table 3 provides an overview of the innovative modeling approaches used in the study of Clonorchis and Opisthorchi infections, emphasizing the integration of diverse data sources and advanced analytical techniques. Innovative modeling approaches in studying Clonorchis and Opisthorchi infections have advanced understanding of these parasitic diseases by integrating diverse data sources and employing sophisticated analytical techniques. The Bayesian geostatistical framework generates high-resolution risk maps, providing spatial representations of infection risk across endemic regions, combining epidemiological data with environmental and socio-demographic factors to identify infection hotspots and guide targeted public health interventions [25].

Multi-omics techniques represent another breakthrough in modeling liver fluke infections. By integrating genomic, transcriptomic, and proteomic data, researchers gain a comprehensive understanding of molecular changes during early infection stages, identifying key molecular pathways in host-parasite interactions, offering potential therapeutic targets [20].

Therapeutic modeling has advanced through combining praziquantel with disodium glycyrrhizinate and curcumin, targeting the parasite while modulating the host's inflammatory response, enhancing treatment efficacy and reducing liver damage [7].

Genomic insights enrich understanding of liver fluke biology, exemplified by the first draft genome assembly for Opisthorchis felinus, revealing unique genetic features like trans-splicing in RNA processing, contributing to the parasite's adaptability and pathogenicity. These findings provide a foundation for comparative genomic studies and novel diagnostic and therapeutic strategies [21].

Innovative modeling approaches emphasize integrating advanced technologies and interdisciplinary methodologies to deepen understanding of Clonorchis sinensis and Opisthorchis spp. infections. These studies highlight the importance of genomic data and spatial-temporal mapping in identifying genetic diversity, disease prevalence, and potential parasite-host interaction pathways, informing prevention and control strategies for these public health threats in Southeast Asia and beyond [25, 29, 21].

6.4 Applications and Case Studies

Epidemiological modeling has been instrumental in applying theoretical insights to practical scenarios, particularly in understanding and managing Clonorchis and Opisthorchi infections' transmission dynamics. These models provide robust frameworks for simulating disease transmission dynamics and assessing intervention efficacy, demonstrating practical applications across public health and ecological management sectors. For instance, the R package SimInf facilitates large-scale epidemiological modeling by integrating real-world data on population dynamics, while advanced Bayesian spatial-temporal models create high-resolution risk maps for diseases like opisthorchiasis in Southeast Asia, aiding targeted public health interventions [40, 25, 32, 36, 38].

Structured versus decorated cospans have been applied to fields like electrical circuits and Petri nets, as well as epidemiological modeling [41]. This approach integrates complex systems into cohesive models, allowing detailed analyses of transmission pathways and intervention impacts. Researchers can simulate various scenarios and optimize control measures to reduce infection rates.

A systems-thinking perspective views Opisthorchis viverrini (Ov) transmission as an ecological problem rather than purely biomedical [42]. This approach emphasizes interconnected environmental, social, and biological factors shaping disease dynamics. By considering ecosystem services and disservices, this perspective provides a framework for understanding how environmental changes and

human activities influence liver fluke infections' spread, crucial for developing sustainable public health strategies addressing transmission's root causes.

Mathematical models evaluate intervention effectiveness through sensitivity analysis and basic reproduction number calculations [29]. These analyses provide insights into key parameters influencing disease spread and control measures' potential impact. Simulations assess mass drug administration, health education, and environmental modifications' effects on reducing infection prevalence, guiding policymakers in resource allocation and strategy implementation maximizing public health benefits.

Case studies from endemic regions demonstrate these models' practical applications in informing policy decisions and guiding public health interventions. By combining epidemiological data with localized ecological factors and cultural practices, these models provide customized interventions effectively tackling specific health challenges faced by communities, particularly in regions like Northeast Thailand, where factors like raw fish consumption and environmental conditions significantly influence parasitic infections' risk. This approach enhances public health strategies' relevance and strengthens community engagement in addressing endemic diseases like opisthorchiasis [38, 25, 40, 24]. Consequently, these models play a critical role in mitigating Clonorchis and Opisthorchi infections' burden and improving health outcomes in diverse settings.

6.5 Challenges and Limitations

Modeling Clonorchis and Opisthorchi infections presents challenges and limitations hindering comprehensive and accurate epidemiological models' development. A primary challenge is liver fluke transmission dynamics' complexity, influenced by socio-economic, environmental, and biological factors. The lack of comparative studies under controlled conditions complicates understanding liver fluke pathogenicity and developing effective control measures [4].

A significant limitation is insufficient attention to liver flukes in health policies and inadequate exploration of transmission dynamics and control measures [9]. This gap underscores the need for targeted research to inform public health strategies and enhance intervention effectiveness. Additionally, differentiating between metorchiasis and opisthorchiasis complicates diagnosis and epidemiological surveillance [14].

Relying solely on degree distribution may not fully capture the global topological features necessary for accurate network-based infection dynamics modeling [37]. This limitation highlights the need for sophisticated modeling approaches considering intricate interactions within host-parasite networks.

In software engineering for epidemiological modeling, high transparency, explainability, and reproducibility levels present a significant challenge [38]. Neglecting these factors can lead to models lacking robustness and credibility. Adhering to software engineering standards is crucial for enhancing epidemiological models' reliability and utility.

Limited comprehensive genetic studies constrain understanding genetic factors influencing liver fluke infections [14]. This limitation affects targeted intervention development and identifying potential genetic markers for disease susceptibility and resistance.

Addressing these challenges and limitations is essential for advancing epidemiological modeling and improving public health interventions aimed at controlling Clonorchis and Opisthorchi infections. Integrating multidisciplinary research efforts and utilizing advanced modeling techniques can create comprehensive models capturing liver flukes' intricate transmission dynamics, such as Clonorchis sinensis and Opisthorchis spp., associated with significant health risks, including cholangiocarcinoma due to co-infections with pathogens like Helicobacter pylori [10, 11].

6.6 Epidemiological Modeling and Data Integration

Epidemiological modeling and data integration are crucial for understanding and managing Clonorchis and Opisthorchi infections, particularly in Southeast Asia, where high-resolution disease risk maps and Bayesian spatial-temporal joint models identify prevalence hotspots and inform targeted public health interventions. These models leverage georeferenced disease data and influencing factors to enhance knowledge of transmission dynamics and risk factors, aiding effective control of these neglected tropical diseases [21, 10, 25, 26, 33]. Effective modeling requires synthesizing diverse data sources, including epidemiological, environmental, and socio-demographic information, to

capture these infections’ complex dynamics. Integrating data from various disciplines enhances model accuracy and predictive power, facilitating targeted public health interventions’ development.

Key aspects of data integration include incorporating ecological dynamics into epidemiological models. Understanding fish procurement’s ecological dynamics is essential for assessing infection risk and informing control strategies [24]. This approach examines interactions between human activities, environmental conditions, and intermediate hosts’ life cycles, such as snails and fish, crucial for liver fluke transmission.

Community engagement in health education is another vital data integration component. Future research should enhance community involvement to improve awareness and understanding of liver fluke infections and their transmission dynamics [24]. By incorporating community insights and feedback into epidemiological models, researchers can develop culturally sensitive and effective public health strategies.

Advanced modeling techniques, like Bayesian spatial-temporal joint modeling, offer powerful tools for integrating diverse datasets and capturing infections’ spatial and temporal distribution patterns [25]. These models enable identifying infection hotspots and allocating resources to areas with the highest need, optimizing public health interventions’ impact.

Integrating genetic, environmental, and behavioral data is essential for understanding liver fluke infections’ multifactorial nature. Recent advancements in genomics and bioinformatics enable researchers to identify genetic markers linked to susceptibility and resistance against various infections. This knowledge is crucial for informing targeted therapeutic interventions, particularly in complex host-parasite interactions where co-infections significantly alter immune responses and influence disease outcomes. Understanding these genetic factors aids in designing more effective treatments and enhances disease diagnosis and vaccine development strategies [20, 13].

Integrating diverse data sources into epidemiological models significantly enhances understanding and management of Clonorchis and Opisthorchis infections by enabling high-resolution disease risk maps, identifying areas of varying prevalence, and informing targeted control interventions in Southeast Asia, where these infections pose a considerable public health threat [21, 25, 10]. Adopting a multidisciplinary approach combining ecological, genetic, and community-based insights can optimize public health strategies to reduce these parasitic diseases’ burden and improve health outcomes in affected populations.

Feature	Statistical and Mathematical Modeling Techniques	Frameworks and Methodologies	Innovative Modeling Approaches
Modeling Technique	Bayesian Spatial-temporal	Compartmental Models	Multi-omics Techniques
Data Integration	Host-environment Interactions	Socio-demographic Data	Genomic, Proteomic Data
Application Focus	Disease Risk Maps	Intervention Assessment	Therapeutic Targets

Table 4: This table presents a comparative analysis of various epidemiological modeling approaches used in the study of Clonorchis and Opisthorchi infections. It categorizes the modeling techniques into statistical and mathematical modeling techniques, frameworks and methodologies, and innovative modeling approaches, highlighting their specific applications and the types of data integration employed. The table serves as a comprehensive reference for understanding the diverse strategies and challenges in modeling these parasitic infections.

7 Current Challenges and Future Directions

The persistent public health challenges posed by Clonorchis sinensis and Opisthorchis infections demand comprehensive strategies that integrate community involvement with health initiatives. The following subsection explores the critical role of public health strategies and community participation, emphasizing how tailored educational programs and active engagement from affected populations can enhance intervention outcomes and reduce infection rates. Understanding cultural contexts and social dynamics is vital for creating public health responses that resonate with and empower communities to adopt preventive measures.

7.1 Public Health Strategies and Community Engagement

Mitigating Clonorchis sinensis and Opisthorchis infections requires effective public health strategies and community engagement. Addressing cultural factors, such as raw fish consumption, necessitates

targeted educational programs that highlight health risks and promote safer food preparation methods [26]. Enhancing public health education is crucial for raising awareness of liver fluke infections and their transmission dynamics, particularly in rural and underserved areas [30]. This should be complemented by precise epidemiological monitoring systems to track infection trends and evaluate interventions.

Improving sanitary standards is another critical component. Access to clean water and sanitation can significantly reduce transmission by minimizing contact with contaminated sources, necessitating infrastructure development in areas with inadequate sanitation [30]. The integration of innovative diagnostic tools and alternative treatments is vital, with future research focusing on rapid diagnostic methods and evaluating alternative therapeutic options [9].

Community involvement is essential for successful public health strategies. Engaging community members in developing and implementing interventions ensures cultural sensitivity and alignment with local needs. This involvement fosters ownership and responsibility, encouraging preventive measures and supporting public health efforts [28]. To ensure reproducibility and effectiveness, funding agencies and journals should mandate access to baseline software and documentation, enhancing transparency and disseminating best practices [38].

A multifaceted strategy, including educational initiatives, infrastructural improvements, and technological innovations, is crucial for effectively mitigating infections linked to severe hepatobiliary diseases like cholangiocarcinoma. This approach should involve proactive community engagement, particularly in regions like Northeast Thailand, where cultural practices and ecological factors contribute to high transmission rates, improving public health outcomes and promoting sustainable control measures [2, 10].

7.2 Research on Molecular and Immunological Mechanisms

Research into the molecular and immunological mechanisms of *Clonorchis sinensis* and *Opisthorchis* spp. infections is vital for understanding these parasitic diseases. Studies reveal how these parasites induce specific immune responses, such as the Th1/Th2 mixed response in *Clonorchis* infections, and highlight the dynamic polarization of hepatic macrophages. Genomic analysis of *Opisthorchis felinus* uncovers genetic pathways crucial for developing targeted diagnostic tools and interventions [3, 21, 43, 1, 20]. The modulation of host immune responses, particularly through macrophage polarization, significantly impacts pathogenesis, making the investigation of these pathways essential for identifying therapeutic targets.

Liver fluke infections' influence on host microbiota composition and function is gaining interest, with studies indicating that infections can lead to dysbiosis, exacerbating liver damage and contributing to hepatobiliary disease pathogenesis. Understanding these interactions is critical for developing microbiota-based therapeutic strategies [12, 10, 40, 32, 11]. Future research should explore recombinant proteins like r Cs CP and Cs CA for their potential in treating human inflammatory bowel disease, as they show promise in modulating immune responses [6].

Co-infection dynamics are another critical research area, as multiple pathogens can significantly alter immune responses and disease outcomes. Understanding these molecular mechanisms is essential for developing targeted therapies and effective disease management strategies. Chronic infections with pathogens like malaria and *Mycobacterium tuberculosis* can modify immune responses, affecting susceptibility to other infections and vaccine efficacy [13, 25, 20, 11, 44].

Ongoing molecular genetics research aims to improve diagnostic accuracy for *Opisthorchis viverrini* infections, a significant carcinogen linked to bile duct cancer, and to elucidate ecological factors influencing infection rates and co-infections' role in disease pathogenesis. Understanding these interactions is crucial for enhancing diagnosis and informing effective therapeutic strategies [1, 13, 11]. Developing novel biomarkers for early cholangiocarcinoma detection and exploring vaccine options against liver flukes are critical research areas promising to advance diagnostic and therapeutic strategies [3, 21].

7.3 Future Directions in Diagnostic and Therapeutic Innovations

Future diagnostic and therapeutic innovations for *Clonorchis* and *Opisthorchi* infections hold significant potential for advancing public health strategies. Refining epidemiological models to incorporate

real-time data could enhance predictive capabilities, and integrating machine learning techniques could improve models' accuracy in predicting infection trends and evaluating interventions [40]. Additionally, refining models to include realistic transmission dynamics and exploring varying parameters in different epidemic contexts could provide deeper insights into infection spread and control [39].

Innovations in diagnostic methodologies are crucial for improving detection and management. Developing simpler DNA extraction methods for tools like the RPA-LFD assay can facilitate field application and reduce costs, enhancing accessibility in resource-limited settings [1]. Exploring additional diagnostic methods to improve prevalence estimates and investigating the association between pet contact and *C. sinensis* infection could enhance understanding of infection dynamics [28].

Therapeutic innovations focus on exploring various intervention strategies and refining models to improve predictive capabilities [29]. Combining traditional anti-parasitic treatments with novel compounds, such as disodium glycyrrhizinate and curcumin, shows promise in preclinical studies, suggesting potential pathways for enhancing treatment efficacy and reducing liver damage [7].

Establishing high software engineering standards for epidemiological simulators is essential for reliability and effectiveness. Future research should mandate these standards, ensuring models are developed with the same rigor as critical infrastructure [38]. Enhancing software based on user feedback and real-world applications will further improve modeling capabilities and usability, contributing to more effective public health interventions [36].

Finally, exploring generalizations of network modeling approaches beyond degree distributions to account for global topological characteristics could provide a more comprehensive understanding of transmission networks [37]. Addressing these future directions can lead to innovative diagnostic and therapeutic solutions that effectively mitigate the impact of *Clonorchis* and *Opisthorchi* infections on public health.

8 Conclusion

Addressing *Clonorchis* and *Opisthorchi* infections requires a multifaceted public health strategy that transcends traditional biomedical approaches. Effective control measures must integrate ecological and socio-cultural dimensions to ensure sustainable interventions. Emphasizing disease tolerance as a component of host defense against helminths offers new therapeutic avenues aimed at enhancing host resilience and fitness. The interplay between ecological systems and helminthiasis spread necessitates the development of ecological-economic frameworks to support sustainable regional development.

Collaborative regional efforts and extensive data collection are crucial for advancing diagnostic and therapeutic strategies, highlighting the importance of coordinated actions in combating these infections. Understanding the acute inflammatory responses in early *C. sinensis* infections can inform timely interventions and improve disease management by elucidating host-parasite dynamics. The identification of parasites in environmental vectors underscores the need for ongoing research and public health initiatives to mitigate transmission risks.

Innovative modeling techniques, such as structured and decorated cospan, offer valuable methodologies for describing complex systems and guiding public health interventions. Continued research and modeling are imperative for deepening our understanding of liver fluke infections and developing targeted strategies to mitigate their public health impact. By integrating diverse data and employing interdisciplinary approaches, public health strategies can be enhanced, ultimately improving health outcomes for affected communities.

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