

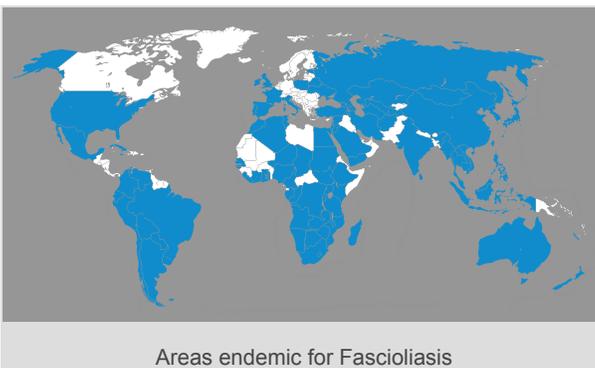
Background

Global Burden | Causative Agents & Transmission | Pathogenesis | Current Control Strategy | Existing Products | Get Involved

What is Fascioliasis?

Fascioliasis is caused by a parasitic flat worm that primarily affects the liver and bile duct. The parasite is transmitted by consumption of *Fasciola* spp. cysts on plants from contaminated fresh water. Chronic infection with fascioliasis can result in pain, abdominal inflammation and the formation of scar tissue and fibrosis in the bile duct, but it is not fatal.

Global Burden



Better known as a veterinary disease, human fascioliasis cases have been steadily rising since the 1970s, primarily in rural areas, and has until recently been severely neglected by the medical community. Due to its increased spread and chronic nature, it is now a disease of global human concern.¹

Fascioliasis has the widest geographic spread of any emerging vector-borne zoonotic disease and affects more than 51 countries worldwide. It is most prevalent in the Andean region, especially Bolivia and Peru.² Fascioliasis is a nearly-worldwide disease, also affecting people in Western Europe, Southeast Asia, and the Caspian Sea region, and less commonly in Africa, Oceania, and Eastern Europe. An estimated 17 million people are affected by fascioliasis.^{2,3} As fascioliasis has only more recently been recognized as a significant human disease, studies to determine the global morbidity caused by fascioliasis are ongoing.⁴ Indeed, most analyses of the global impact of fascioliasis focus on the economic impact caused by infections in domesticated herd animals. Depending on the disease prevalence in a herd, these losses can be significant. The direct economic impact of fascioliasis infection is increased condemnation of liver meat, but the far more damaging effects are decreased animal productivity, lower calf birth weight, and reduced growth in effected animals.^{5,6,16}

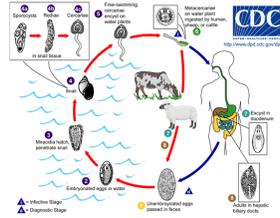
Parasite	Geographic Distribution
<i>F. hepatica</i>	Europe, South and Central America, Oceania, Asia, Africa
<i>F. gigantica</i>	Asia, Africa

Causative Agent and Transmission





Fascioliasis is caused by infection with flat worms of the genus *Fasciola* (either *F. hepatica* or *F. gigantica*). Commonly known as liver flukes, the parasites cause a zoonotic infection that affects domestic herd animals (such as cattle, sheep, donkeys, horses, camels, pigs) and wild animals. The parasite is transmissible from animal to human by human consumption of infected animal livers and from human to human through the fecal oral route.³



Fasciola life cycle

[Click to view](#)

Adult *Fasciola* flukes living in the bile duct release eggs, which are then passed through the host's stool into water. These eggs hatch in the water and develop through three larval stages. First stage, free swimming miracidia infect snails, where they develop further. The second, also free-swimming, cercariae stage of the parasite are released from the snail and attach to fresh water plants as third stage resting encysted metacercariae. Humans or animals that eat plants with encysted metacercariae, or drink water that is contaminated with these cysts, can be infected with the parasite.

[Back to Top](#)

Pathogenesis

After ingestion, *Fasciola* cysts open in the small intestine. The acute stage of the disease occurs as the worms migrate through the lining of the small intestine into the liver and bile duct. While often asymptomatic, the onset of this stage can produce gastrointestinal bleeding, inflammation, abdominal pain, and diarrhea. The chronic phase of the disease occurs when the worms reach the bile duct. The long-term presence of the worms causes progressive inflammation from scar tissue and debris that can lead to fibrosis and obstruction of the ducts.^{7,3}

Current Control Strategy

Because fascioliasis in humans is so poorly characterized compared to the infection in animals, control measures are difficult to devise and implement. However, as understanding of the human health impact of this disease increases, support for control measures has increased as well. This effort is buoyed by the World Health Organization's (WHO) designation of fascioliasis as an extremely neglected disease.^{1,3}

Because the infection can be difficult to detect and can be transmitted in so many ways, control of fascioliasis has represented a significant challenge. The role of domestic and wild animal reservoirs, coexistence of the various *Fasciola* and snail species, and varying types of endemic situations have rendered the creation of a universal control strategy unrealistic.¹ Current WHO guidelines recommend that hospitals maintain stockpiles of triclabendazole and that further classification studies regarding the nature of fascioliasis endemicity be undertaken in each endemic country, which vary widely in geography and socioeconomic status from endemic France to hyperendemic Peru and Bolivia.^{8,1}

Existing Products

▶ Drugs

The primary treatment for fascioliasis is a single oral dose of triclabendazole. Triclabendazole, a benzimidazole that inhibits parasitic

microtubule formation, is highly safe and effective against both immature and adult parasites, and is donated by Novartis in developing endemic countries.³ Most *Fasciola* infections are cleared with a single oral dose of triclabendazole, though some heavy infections require two. Bithionol was formerly used to treat fascioliasis but is no longer frequently used primarily due to its long treatment schedule and ambiguous dosage as compared to the more effective triclabendazole.⁹

Triclabendazole was originally developed as a veterinary drug for animals infected with fascioliasis. Veterinary resistance to the drug is spreading but there have been no reports of resistance in humans. However, this underscores the need for multiple drugs.

▶ Vaccines

There is currently no vaccine for the prevention of fascioliasis.

▶ Diagnostics

Diagnosis of fascioliasis is often limited in resource-poor settings to discovery of eggs in a patient's stool. This detection method can result in under-diagnosis, since the eggs do not appear in the stool until after the acute phase of infection. Additionally, in some cases, repeated stool ova tests occur with a negative result despite a laboratory-confirmed diagnosis of fascioliasis. If laboratory resources are available, ELISA or Western blot testing can confirm a diagnosis. Ultrasonic detection of liver lesions can determine the extent of the tissue damage from the parasite.¹⁰

[Back to Top](#)

References

1. Mas-Comas et al (2009). "Chapter 2. *Fasciola*, *lymnaeids* and human Fascioliasis, with a global overview on disease transmission, epidemiology, evolutionary genetics, molecular epidemiology and control." *Advanced Parasitology* 69.
2. Marcos et al (2008) "Natural History, Clinicoradiologic Correlates, and Response to Triclabendazole in Acute Massive Fascioliasis." *American Journal of Tropical Medicine and Hygiene* 78 (2).
3. WHO Fascioliasis Factsheet.
4. WHO Collaborating Centres Global Database.
5. Njeruh et al (2004). "Prevalence and Economic Importance of Fascioliasis in Cattle, Sheep and Goats in Kenya." *Kenya Veterinarian* 27.
6. Hillver, G.V. (2005). "Fasciola antigens as vaccines against Fascioliasis and Schistosomiasis." *Journal of Helminthology* 79.
7. Khandewal et al. (2008). "Biliary Parasites: Diagnostic and Therapeutic Strategies." *Current Treatment Options in Gastroenterology* 11.
8. WHO Bulletin - New Opportunities for Fascioliasis Control, 1999
9. Keiser J. and J. Utzinger (2010). "The Drugs We Have and the Drugs We Need Against Major Helminth Infections." *Advances in Parasitology* 73.
10. Shabrawi et al (1997). "Human Fascioliasis: Clinical Features and Diagnostic Difficulties in Egyptian Children." *Journal of Tropical Pediatrics* 43.
11. Favennec et al (2003). "Double-blind, randomized, placebo-controlled study of nitazoxanide in the treatment of fascioliasis in adults and children from northern Peru." *Alimentary Pharmacology and Therapeutics* 17(2).
12. Tendler M and A Simpson (2008). "The biotechnology-value chain: Development of Sm14 as a Schistosomiasis vaccine." *Acta Tropica* 108 (2).
13. Intapan et al (2004). "Development of Rapid Agglutination Test Using Fasciola Gigantica Specific Antigen for Serodiagnosis of Human Fascioliasis." *Southeast Asian Journal of Tropical Medicine & Public Health* 35 (1).
14. Rahimi et al (2010). "Evaluation of Fast-ELISA versus Standard-ELISA to Diagnose Human Fasciolosis." *Archives of Iranian Medicine* 14 (1).
15. Hillver, G. and M Soler de Galanes (1991). "Initial Feasibility Studies of the FAST-ELISA for the Immunodiagnosis of Fascioliasis." *The Journal of Parasitology* 77(3).
16. Kaplan R. (2001). "Fasciola hepatica: A review of the economic impact in cattle and considerations for control." *Veterinary Therapeutics* 2(1).

Get Involved

To learn how you can get involved in neglected disease drug, vaccine or diagnostic research and development, or to provide updates, changes, or corrections to the Global Health Primer website, please view our FAQs or contact us at globalhealthprimer@bvgh.org.

Pipeline & Analysis

Drugs | Vaccines | Diagnostics | Get Involved

Drugs

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Nitazoxanide	London School of Hygiene and Tropical Medicine					
Artesunate	Hospital for Tropical Diseases University of Oxford					
OZ78	Swiss Tropical and Public Health Institute University of Nebraska					
Artemether	Queens University of Belfast Medical Center Swiss Tropical and Public Health Institute University of Nebraska					

[Back to Top](#)

ANALYSIS

Because of the high cure rates of triclabendazole, drug development for fascioliasis is not seen as a priority. However, due to concerns about rising veterinary resistance to triclabendazole, development of alternative treatments may become necessary.

New drug development for fascioliasis is primarily building on drug development programs for other parasitic infections. Nitazoxanide, an anti-helminthic used to treat cryptosporidium, has achieved moderately successful cure rates in clinical trials.¹ Based on the antischistosomal properties of artemisinin-derived malaria drugs, testing is underway to determine their efficacy against fascioliasis. Artemether and artesunate have both undergone proof of concept studies in animal models with encouraging results.² The synthetic endoperoxide OZ78 has been shown to be effective in a murine model. None of the drugs in development have progressed to the clinical stage, and for now, triclabendazole is more effective than any drug in development.²

Vaccines

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Sm14 (Fascioliasis)	Brazilian Ministry of Health Oswaldo Cruz Foundation					

ANALYSIS

Several purified recombinant *F. hepatica* antigens are being studied for their immunogenic potential in domestic animals. Many of these cross-protect against Schistosomiasis infection. While not entirely preventing *F. hepatica* infection, these candidates reduced total fluke burden, decreased egg production, and reduced the severity of liver lesions as compared to controls. Primary preclinical testing of these antigens has been done in ruminant, murine, and sylvatic models, but no vaccines have yet reached the clinical stage and it is unclear whether any are being developed for use in humans. Sm14, an antigen being pursued by the Brazilian Ministry of Health for *S. mansoni* immunization, may cross-protect against fascioliasis. Lack of funding for this neglected disease remains problematic, and co-development of an *S. mansoni*/*F. hepatica* vaccine may be the surest way to success.^{3,4}

Diagnosics

Accurate, rapid, and affordable point of care diagnostics that can detect both species of the parasite are a critical need to improve patient care. More specifically, there is a need for fascioliasis rapid diagnostic tests (RDTs) to improve the accuracy of field diagnoses. A latex agglutination test platform – previously used to develop tests for *T. cruzi* and *T. gondii* – has been shown to be 75% sensitive and 99% specific at diagnosing fascioliasis, and results are ready in five minutes without laboratory equipment.⁵

A fast ELISA test is in development that offers the same diagnostic accuracy as a standard ELISA test but with quicker results. While the test cuts down the result time to within a single patient visit, it is still a laboratory assay that requires laboratory infrastructure and a skilled technician, and therefore still prohibitive in some endemic areas that lack the facilities to perform the test.^{6,7}

[Back to Top](#)

References

1. Favennec et al (2003). “Double-blind, randomized, placebo-controlled study of nitazoxanide in the treatment of fascioliasis in adults and children from northern Peru.” *Alimentary Pharmacology and Therapeutics* 17(2).
2. Keiser J. and J. Utzinger (2010). “The Drugs We Have and the Drugs We Need Against Major Helminth Infections.” *Advances in Parasitology* 73.
3. Hillver, G.V. (2005). “*Fasciola antigens as vaccines against Fascioliasis and Schistosomiasis.*” *Journal of Helminthology* 79.
4. Tendler M and A Simpson (2008). “The biotechnology-value chain: Development of Sm14 as a Schistosomiasis vaccine.” *Acta Tropica* 108 (2).
5. Intapan et al (2004). “Development of Rapid Agglutination Test Using *Fasciola Gigantica* Specific Antigen for Serodiagnosis of Human Fascioliasis.” *Southeast Asian Journal of Tropical Medicine & Public Health* 35 (1).
6. Rahimi et al (2010). “Evaluation of Fast-ELISA versus Standard-ELISA to Diagnose Human Fasciolosis.” *Archives of Iranian Medicine* 14 (1).
7. Hillver, G. and M Soler de Galanes (1991). “Initial Feasibility Studies of the FAST-ELISA for the Immunodiagnosis of Fascioliasis.” *The Journal of Parasitology* 77(3).

Get Involved

To learn how you can get involved in neglected disease drug, vaccine or diagnostic research and development, or to provide updates, changes, or corrections to the Global Health Primer website, please view our FAQs or contact us at globalhealthprimer@bvgh.org.

Tools

Drugs | Vaccines | Diagnostics | Get Involved

The following series of tables describe the availability of tools for research, discovery, and development of novel drugs, vaccines, and diagnostics for fascioliasis. The tools listed in the following tables are not intended to be an all-inclusive list but rather capture the most common tools used for drug, vaccine, and diagnostic development. The tools for fascioliasis are extremely limited.

Drug Development Tools

Basic Research: Target Identification	Target Validation	Screening: Hit/Lead Identification Optimization	Pre-clinical Validation	Clinical Validation
<p>Genome: <i>Fasciola Hepatica</i> GenBank library available. <i>Fasciola gigantica</i> is reported to be sequenced, but the genome is unavailable.</p> <p>Key databases: GenBank</p> <p>In vitro culture: <i>F. hepatica</i> adult worms have been maintained in the laboratory for at most 3 days after being taken from the livers of dead cattle, and no reliable in vitro culture models exist.</p>	<p>Gene knock-outs: No</p> <p>Conditional gene knock-outs: No</p> <p>Transposon mutagenesis: No</p> <p>RNAi: Yes</p> <p>Other antisense technology: Yes</p> <p>Viability assays: Possible with adult flukes</p> <p>Transcription microarrays: No</p> <p>Proteomics: Limited, primarily only for analysis of excreted parasite products (in larval and adult stages)</p> <p>Crystal structures: Yes</p>	<p>Whole-cell screening assays: No</p> <p>Enzymatic screening assays: Yes</p>	<p>Animal models: Yes</p> <p>Sheep, buffalo, cattle and mouse models</p> <p>Both species of fluke can infect the same animals, but susceptibility to the species varies among the animal models: Buffalos are most susceptible to <i>F. gigantica</i>. Sheep susceptibility to each species varies by breed.</p>	<p>Monitoring treatment efficacy: Yes</p> <p>Availability of endpoints: Yes, resolution of abdominal pain is commonly used. (More accurate endpoints are needed)</p> <p>Availability of surrogate endpoints: No</p> <p>Access to clinical trial patients/sites: Yes, but primarily in rural populations</p>

[Back to Top](#)

Vaccine Development Tools

Basic Research: Antigen Identification	Immune Response Characterization	Clinical Validation
<p>See drug development tools above</p>	<p>Predictive animal models: Sheep and goats most commonly used.</p>	<p>Surrogate markers of protection: No</p>

	<p>Detection of endogenous antigen specific response in clinical samples: No</p> <p>Natural immunity well characterized: Not well characterized</p>	<p>Challenge studies possible: Not in humans, but challenge studies have been done in sheep.</p>
--	---	---

Diagnostic Development Tools

Basic Research: Biomarker Identification	Biomarker Validation	Clinical Validation
<p><i>See drug development tools above</i></p>	<p>Biomarkers known: Yes</p> <p>Access to clinical samples: Yes</p> <p>Possible sample types: Stool</p>	<p>Access to clinical trial patients/sites: Yes</p> <p>Treatment available if diagnosed: Yes</p>

[Back to Top](#)

Get Involved

To learn how you can get involved in neglected disease drug, vaccine or diagnostic research and development, or to provide updates, changes, or corrections to the Global Health Primer website, please view our FAQs or contact us at globalhealthprimer@bvgh.org.

Product Details

0Z78

Synonyms:
0Z78

Disease:
Fascioliasis

Target/Technology:
Artemisinin-related

Specific Indication:
F.hepatica

Mechanism of Action:

Product Type:
Drug

Molecule Class:
trioxolanes

PRV Eligible?
Yes

Administration Route:

Notes:

Clinical Trials:

Publications:

17028093
17905370

Artemether

Synonyms:
Artemether

Disease:
Fascioliasis

Target/Technology:
Artemisinin-related

Specific Indication:
F. hepatica

Mechanism of Action:

Product Type:
Drug

Molecule Class:
artemisinins

PRV Eligible?
No

Administration Route:

Notes:

**Clinical
Trials:**

Publications:

Proof-of-concept studies in sheep and rats have indicated that artemether may be an effective fasciocide against triclabendazole-resistant strains.

17905370
18481085

Artesunate

Synonyms:
Artesunate

Disease:
Fascioliasis

Target/Technology:
Artemisinin-related

Specific Indication:
acute human fascioliasis

Mechanism of Action:

Product Type:
Drug

Molecule Class:

Administration Route:

PRV Eligible?

No

Notes:

Artesunate as a treatment for fascioliasis has undergone proof-of-concept in animal models, and a randomized-controlled human pilot study, comparing it to triclabendazole.

Clinical Trials:**Publications:**

18337331

Nitazoxanide**Synonyms:**

Nitazoxanide

Disease:

Fascioliasis

Target/Technology:

Unknown

Specific Indication:**Mechanism of Action:****Product Type:**

Drug

Molecule Class:

thiazolides

PRV Eligible?

No

Administration Route:**Notes:**

Nitazoxanide is FDA-approved to treat cryptosporidium infections, and has been tested in vitro and in placebo-control trials in Egypt and Peru as a treatment for fascioliasis, with 40-60% cure rates.

Clinical Trials:**Publications:**

12534412

Sm14 (Fascioliasis)**Synonyms:**

Sm14 (Fascioliasis)

Disease:

Fascioliasis

Target/Technology:

Recombinant/purified protein vaccines

Specific Indication:**Mechanism of Action:****Product Type:**

Vaccine

Molecule Class:**PRV Eligible?**

Yes

Administration Route:**Notes:****Clinical Trials:****Publications:**

18834847

Developer Details**World Health Organization (Switzerland)**

Type	Disease	Product/Research Program	Current Phase
------	---------	--------------------------	---------------

Drug	Fascioliasis	Triclabendazole	Approved
------	--------------	-----------------	----------

Novartis AG (Switzerland)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	Triclabendazole	Approved

Innothera (France)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	Bithionol	Approved

Swiss Tropical and Public Health Institute (Switzerland)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	0Z78	Pre-clinical

Swiss Tropical and Public Health Institute (Switzerland)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	Artemether	Pre-clinical

University of Nebraska (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	0Z78	Pre-clinical

University of Nebraska (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	Artemether	Pre-clinical

London School of Hygiene and Tropical Medicine (United Kingdom)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	Nitazoxanide	Phase I

Oswaldo Cruz Foundation (Brazil)

--	--	--	--

Type	Disease	Product/Research Program	Current Phase
Vaccine	Fascioliasis	Sm14 (Fascioliasis)	Phase I

Brazilian Ministry of Health (Brazil)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Fascioliasis	Sm14 (Fascioliasis)	Phase I

University of Oxford (United Kingdom)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	Artesunate	Phase I

Hospital for Tropical Diseases (Vietnam)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	Artesunate	Phase I

Queens University of Belfast Medical Center (Ireland)

Type	Disease	Product/Research Program	Current Phase
Drug	Fascioliasis	Artemether	Pre-clinical