Background

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

What is Onchocerciasis (River Blindness)?

Onchocerciasis is a skin and eye disease caused by the parasitic worm, *Onchocerca volvulus*. The infection is spread by blackflies that breed in fast-flowing water, giving it the common name “river blindness.” Onchocerciasis is the second leading cause of infectious blindness worldwide. Although there is no vaccine available to prevent *O. volvulus* infection, aggressive vector control and drug delivery programs have dramatically decreased disease incidence over the past thirty years.

Global Burden

Countries endemic for onchocerciasis *(WHO, 2002)*

Worldwide, there are an estimated 37 million people infected with *O. volvulus* and 90 million people remain at risk.[1] Approximately half a million people are visually impaired due to the disease and 270,000 have been blinded.[2] Onchocerciasis is found primarily in West and Central Africa, with 99% of infected individuals living in 30 endemic countries. The disease is also prevalent in Yemen and in a handful of Latin American nations.[3]

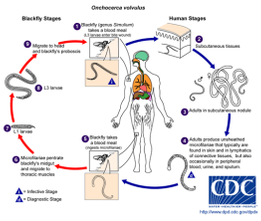
Onchocerciasis has traditionally been a major factor in decreasing the economic prosperity of affected regions. In the 1970s, the disease had blinded almost half of men over age 40 in some African communities.[2] The unrelenting itching can cause psychological problems, reduce productivity, and stigmatize infected individuals. The association of the disease with fast-flowing streams left fertile farmland abandoned. During this time period, economic losses resulting from onchocerciasis were estimated at $30 million per year.[2] The three-decade long Onchocerciasis Control Program in West Africa, which ended in 2002, used insecticide and drug administration to successfully treat an estimated 40 million infections and to prevent 600,000 cases of blindness; this program reversed the annual loss of ~1 million disability adjusted life years and made 25 million hectares of land safe for resettlement.[3,4]

Causative Agent and Transmission

Simulium spp. of flies that transmit onchocerciasis. (photo: WHO)

O. volvulus is filarial nematode worm that is transmitted to humans by blackflies of the genus *Simulium.* The blackfly acquires immature *O. volvulus* larva (termed microfilariae) by biting the skin of an infected individual. The microfilariae develop in the fly over a period of two weeks and then migrate to its mouthparts. The infectious larvae are then transmitted to a new human host during the next blood meal. Once inside the subcutaneous tissue, larvae form nodules and begin maturing into adult worms – a process that can take up to one year. The male and female adults, which can measure up to a meter in length, live coiled in mating pairs within the skin nodules. The female worms produce progeny microfilariae in numbers of up to 1000 per day for a lifespan of 15 years.

Microfilariae migrate throughout the body, including to the skin, where they are accessible to the bite of the blackfly. Death of the microfilariae in the sensitive organs of the skin and eye leads to the major symptoms of onchocerciasis, which usually appear between 9 months and 2 years after initial infection.



O. volvulus life cycle.
Click to view

Because the microfilariae cannot develop further inside the human body, the number of adult worms present in an individual is related to the number of times they have been bitten by infected blackflies. For this reason the disease is often not contracted by a single bite, and the most severe symptoms result from years of repeated exposure. Travelers spending less than three months in endemic areas are at little or no risk for the disease. For those who have been exposed, however, symptoms may appear years after leaving the endemic region, as the long-lived adult worms continue to produce microfilariae.[5,6]

Pathogenesis

The pathogenesis of onchocerciasis is caused by the microfilariae. These immature larvae migrate throughout the body, especially to the skin and eyes. Death of the microfilariae in these tissues results in an inflammatory immune reaction and causes a variety of pathologies. In the skin, the disease can manifest as rashes, lesions, and disfiguring conditions such as depigmentation, skin scaling, and atrophy. The death of microfilariae in the skin causes itching, which is so severe that it is estimated to account for 60% of the disease burden.[3] In the eyes, microfilariae can cause inflammation and bleeding, leading to itching, redness, and eventually vision impairment or blindness. Morbidity caused by onchocerciasis can reduce life expectancy by up to 15 years.[2]

Bacteria of the *Wolbachia* genus have been found to live inside *O. volvulus* worms. The relationship is symbiotic, as these bacteria are necessary for female worm fertility. *Wolbachia* also contribute to onchocerciasis pathogenesis, asthe release of bacteria upon death of the microfilariae contributes to the severity of the inflammatory response.[7]

Current Control Strategy

Several coordinated and aggressive control programs have been highly successful at limiting the burden of onchocerciasis over the past three decades. The Onchocerciasis Control Program in West Africa (1974-2002) began to control the disease vector through the aerial spread of insecticides. Following the donation of the drug ivermectin (Mectizan) by Merck in 1988, the program initiated mass treatment in high-risk communities. The African Program for Onchocerciasis Control was initiated in 1995 to limit the spread of the disease in the remaining endemic African regions. This program is directed by the affected communities themselves, who request donated ivermectin, distribute the medication, and monitor coverage. The Onchocerciasis Elimination Program for the Americas aims to reduce the burden of disease in Latin America through mass drug treatment campaigns.

Since ivermectin kills the microfilariae, but does not impact the adult worms, the treatment does not cure infection but merely relieves or delays its symptoms. Continuing success in the fight against Onchocerciasis therefore requires maintaining high treatment coverage with the drug for the lifespan of the adult worm.[3]

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Existing Products

Drugs

Onchocerciasis can be treated with an annual dose of ivermectin (Mectizan, Merck). This medication kills the parasite larva and relieves the severe skin itching caused by the disease.[2] Since it does not affect the adult worms, this drug does not cure infection. The effectiveness of ivermectin may be threatened by drug resistance. Also, ivermectin treatment cannot be used in regions that are co-endemic for another filarial parasite, *Loa loa,* due to the observation of serious adverse events.

Antibiotics target the bacteria *Wolbachia* and aim to kill the adult worms that rely on this endosymbiont. For example, doxycycline alone, or added to ivermectin, has been found to significantly reduce female worm viability and the number of microfilariae in the skin.[8] Short courses of antibiotics (rifampin and azithromycin) were not effective at reducing the number of worms, but these antibiotics may be a useful addition to other treatment regimens.[9] It is unclear what role antibiotics will play in future onchocerciasis control programs. There may be some impact of antibiotics through unrelated mass drug administration of antibiotics for the bacteria that cause trachoma, an infection of the eye.

Vaccines

There are currently no vaccines for the prevention of onchocerciasis.

Diagnostics

There are two predominant diagnostic techniques used for onchocerciasis:

- Skin biopsies (“snips”) or examination of excised nodules: Visualizing microfilariae in a skin sample is the standard diagnostic test for onchocerciasis. This technique is highly specific, but has poor sensitivity during the early stages of infection before significant numbers of microfilariae have been produced.
- Serological assays: Antibodies specific for the parasite can be found in the blood, but may not indicate active infection. Assays for O. volvulus antibodies include the Ov16 card test (to detect IgG4 targeting Ov16 antigen), ELISA to detect antibodies against cocktails of recombinant antigens (e.g., Ov20 and Ov33 or Ov7, Ov11 and Ov16), and dot blot assay using native adult parasite antigens.[6] These are currently available only in a research setting and are not approved for clinical diagnosis.

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References

1. Disease and Mortality in Sub-Saharan Africa. 2nd edition. Jamison DT, Feachem RG, Makgoba MW, et al., Eds. Washington (DC): World Bank; 2006.
2. WHO: Priority Eye Diseases
3. WHO (2010) Working to overcome the global impact of neglected tropical diseases: First WHO report on neglected tropical diseases.
4. Basáñez MG, Pion SD, Churcher TS, Breitling LP, Little MP, Boussinesq M. River blindness: a success story under threat? PLoS Med. 2006 Sep;3(9):e371
5. CDC: Onchocerciasis FAQs
6. Medscape: Onchosariasis
7. Saint Andre A et al. (2002) The role of endosymbiotic Wolbachia bacteria in the pathogenesis of river blindness. *Science*. 295:1892-5.
8. Hoerauf A et al (2009) “Efficacy of 5-week doxycycline treatment on adult Onchocerca volvulus.” Parasitology Research 104: 437-447.
9. Hoerauf A et al (2008) “Effects of 6-week azithromycin treatment on the Wolbachia endobacteria of Onchocerca volvulus.” Parasitology Research 103: 279-286.

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Pipeline & Analysis

Drugs | Vaccines | Diagnostics | Get Involved

Drugs

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Moxidectin	Pfizer Inc. World Health Organization					
Emodepside	Bayer AG					
Closantel	Scripps Research Institute					

ANALYSIS

New product needs for onchocerciasis include macrofilaricides and/or drugs that can be used in combination with ivermectin to shorten the timeframe for mass drug administration. A major focus is on repurposing antihelminth drugs that are currently in use in animals for the treatment of onchocerciasis in humans. One animal antihelminth, moxidectin (Pfizer), is currently in human clinical trials and two others, emodepiside (Bayer) and closantel (multiple generic manufacturers), have demonstrated efficacy in vitro.[1,2] Unfortunately, moxidectin has the same mechanism of action as ivermectin and is unlikely to be useful if drug resistance to ivermectin develops. In contrast, emodepiside and closantel have unique mechanisms of action relative to ivermectin and target GPCRs and chinases, respectively.

	Strengths	Weaknesses	Opportunities	Risks
Ion channel inhibitors				
Most advanced program: Ivermectin, on market (Most advanced new product, moxidectin, phase III)	Ivermectin has proven efficacy in mass drug administration	Kills microfilariae but not macrofilariae Existing and new product have same mechanism of action Ivermectin causes severe reaction in patients with Loa loa co-infection, unclear if moxidectin will overcome this	Combination therapy with repurposed animal antihelminthics with unique mechanisms of action	New product unlikely to overcome weaknesses of ivermectin

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Vaccines

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III

Anti-L3 vaccine (NYBC)	New York Blood Center					
Anti-L3 vaccine (LSTM)	Liverpool School of Tropical Medicine					

There are no vaccines in clinical development for onchocerciasis, but several research groups are exploring recombinant protein vaccines that use antigens from the L3 larval stage of the parasite. Protective immunity against *O. volvulus* L3 larva has been demonstrated in humans, mice, and cattle and several recombinant antigens capable of partial protection in mice have been identified. Because of the success of mass drug administration campaigns with ivermectin, investment in vaccines has been minimal. If drug resistance to ivermectin is detected or if mass drug administration proves to take 15 years due to the long life span of the adult worm, a vaccine would prove to be more valuable.

Diagnostics

There are four types of diagnostic in development for onchocerciasis:

- Antigen-based detection: Detection of parasite antigens can indicate active infection. The oncho-C27 dipstick assay can detect the C27 antigen in urine and tears in as little as 3 hours. The test showed good sensitivity and specificity during testing in Cameroon.[3]
- Immune response test: The Diethylcarbamazine (DEC) patch delivers a drug into the skin, which causes a localized dermal reaction if the worms are present.[4] DEC is not used as part of mass drug administration for onchocerciasis due to this reaction.
- Nucleic acid amplification tests: PCR of material from skin can increase diagnostic sensitivity.[5-8] Unfortunately, PCR is costly and requires specialized equipment, limiting the utility of this test in endemic regions.
- Metabolomics-based tests: A recent study used liquid chromatography-mass spectrometry to identify 14 biomarkers in the blood that correlate with *O. volvulus* infection.[9] Additional research will be needed to determine if these biomarkers can be developed into diagnostic assays that can be used in the field.
- Luciferase immunoprecipitation system (LIPS) to differentially diagnose onchocerciasis from other filarial infections (including the lymphatic filariasis species and Loa Loa). NIH researchers developing the test believe that it may be feasible for point of care use.

References

1. Hoerauf A (2008) “Filariasis: new drugs and new opportunities for lymphatic filariasis and onchocerciasis.” Curr Opin Infect Dis 21: 673-681.
2. Gloeckner C et al. (2010) “Repositioning of an existing drug for the neglected tropical disease Onchocerciasis.” PNAS 107: 3424-3429.
3. Ayong LS et al. (2005) “Development and evaluation of an antigen detection dipstick assay for the diagnosis of human onchocerciasis.” Trop Med Int Health 10: 228-233.
4. WHO clinical trail: “To determine the safety, tolerability and systemic absorption of Diethylcarbamazine (DEC) from a "patch" applied locally to the skin for the diagnosis of Onchocerca volvulus infection.” More information available here.
5. Zhang S et al. (2000) “Paper chromatography hybridization: a rapid method for detection of *Onchocerca volvulus* DNA amplified by PCR.” Am J Trop Med Hyg 63: 85-89.
6. Pischke S et al (2002) An internal control for the detection of *Onchocerca volvulus* DNA by PCR-ELISA and rapid detection of specific PCR products by DNA Detection Test Strips Trop Med Int Health 7: 526-531.
7. Rodríguez-Pérez MA et al. (2006) “Large-scale entomologic assessment of *Onchocerca volvulus* transmission by poolscreen PCR in Mexico.” Am J Trop Med Hyg 74: 1026-33.
8. Tang TH et al. (2010) “Nested PCR to detect and distinguish the sympatric filarial species *Onchocerca volvulus*, Mansonella ozzardi and Mansonella perstans in the Amazon Region.” Mem Inst Oswaldo Cruz 105: 823-828.
9. Denery JR et al. (2010) “Metabolomics-based discovery of diagnostic biomarkers for onchocerciasis.” PLoS Neglected Tropical Diseases 4: pii: e834.

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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 onchocerciasis. 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 onchocerciasis are extremely limited.

Drug Development Tools

Basic Research: Target Identification	Target Validation	Screening: Hit/Lead Identification Optimization	Pre-clinical Validation	Clinical Validation
Genome: cDNA assembly sequences available for nuclear genome. Complete mitochondrial genome has been sequenced. **Key databases:** Wellcome Trust | Sanger Institute Broad Institute Genome Index ***In vitro* culture:** Adult worms and larvae can survive in vitro; L3 molting occurs in vitro. No onchocercal cell line exists.	**Gene knock-outs:** No **Conditional gene knock-outs:** No **Transposon mutagenesis:** No **RNAi:** Yes **Other antisense technology:** Yes **Viability assays:** Yes, e.g., MTT (3-(4,5 dimethylthiazol-2yl)-2,5 diphenyl tetrazolium bromide) staining of L3 larvae. **Transcription microarrays:** Yes, but only limited studies have been performed **Proteomics:** Yes, but only limited studies have been performed **Crystal structures:** Yes	**Whole-cell screening assays:** Yes, eg. Molting assay of L3 larvae. **Enzymatic screening assays:** Yes	**Animal models:** *O. volvulus* infects chimpanzees, gorillas, and cynomolgus monkeys but does not cause ocular disease. Cytomegalous monkeys can also be infected with *O. lienalis*. Mangabey monkeys and patas monkeys can be infected with *Onchocerca* spp. *Onchocerca* spp. infect dogs and cause ocular symptoms. Cattle can be infected with *O. ochengi*. Mice are infectable with *Onchocerca* spp.	**Monitoring treatment efficacy:** Yes **Availability of endpoints:** Yes. Sustained absence of microfilariae in skin biopsies Killing of adult worms (macrofilaricidal or curative effects) **Availability of surrogate endpoints:** No **Access to clinical trial patients/sites:** Yes

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Vaccine Development Tools

Basic Research: Antigen Identification	Immune Response Characterization	Clinical Validation
See drug development	**Predictive animal models:** Non-human primates and bovine	**Surrogate markers of**

tools above	models are best available. **Detection of endogenous antigen specific response in clinical samples:** Yes, e.g., antibodies **Natural immunity well characterized:** Yes, protective immunity targets the infectious larva (L3). Concomitant immunity develops with age.	**protection:** No **Challenge studies possible:** Control programs have used volunteers exposed to wild blackflies to collect the insects for study.

Diagnostic Development Tools

Basic Research: Biomarker Identification	Biomarker Validation	Clinical Validation
See drug development tools above	**Biomarkers known:** Yes, metabolite biomarkers recently mapped. **Access to clinical samples:** Yes **Possible sample types:** Skin, blood	**Access to clinical trial patients/sites:** Yes **Treatment available if diagnosed:** Yes, ivermectin

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Product Details

Anti-L3 vaccine (LSTM)

Synonyms:
Anti-L3 vaccine (LSTM)

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
Yes

Target/Technology:
Recombinant/purified protein vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

19901988

Anti-L3 vaccine (NYBC)

Synonyms:
Anti-L3 vaccine (NYBC)

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Product Type:
Vaccine

PRV Elegible?
Yes

Target/Technology:
Recombinant/purified protein vaccines

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

Closantel

Synonyms:
Closantel

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Chitinase

Mechanism of Action:
Prevents molting of infectious larvae

Molecule Class:

Administration Route:

Notes:

In use for animals.

Clinical Trials:

Publications:

20142509

21534605

Diethylcarbamazine (DEC) patch test

Synonyms:

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Portability:
Handheld

Technology:
Unknown

Sample of Type:
Other

Training Required:
Minimal

Notes:

Clinical Trials:

Publications:

17207156

DNA detection test strips

Synonyms:

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Portability:
Peripheral laboratory

Technology:
Nucleic acid based

Sample of Type:
Blood

Training Required:
Moderate

Notes:

Clinical Trials:

Publications:

12031075

Emodepside

Synonyms:
Emodepside

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
GPCR

Mechanism of Action:

Molecule Class:

Administration Route:

Notes:

In use in animals. Although in vitro data exist, it is not clear if this product is being actively pursued for human use.

Clinical Trials:

Publications:

18978537

Metabolomics-based biomarker discovery program

Synonyms:
Metabolomics-based biomarker discovery program

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Portability:
Unknown

Technology:
Unknown

Sample of Type:
Blood

Training Required:
Unknown

Notes:

Clinical Trials:

Publications:

20957145

Moxidectin

Synonyms:
Moxidectin

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Ion channels

Mechanism of Action:
Glutamate-gated chloride ion channel inhibitor

Molecule Class:

Administration Route:

Notes:

In use for treatment of heartworm in animals.

Clinical Trials:

NCT00790998
NCT01035619
NCT00300768

Publications:

Multi-antigen luciferase immunoprecipitation systems (LIPS)

Synonyms:

Disease:
Onchocerciasis (River Blindness)

Specific Indication:
antibody detection, differentiation from other filarial infections (Ss, Wb, Ll)

Portability:
Peripheral laboratory

Technology:
Immunoassay

Sample of Type:
Blood

Training Required:
Advanced

Notes:

Clinical Trials:

Publications:

19436728

Oncho-C27 antigen dipstick

Synonyms:

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Technology:
Immunoassay

Sample of Type:

Antigen detection

Portability:
Peripheral laboratory

Urine

Training Required:
Moderate

Notes:

Clinical Trials:

Publications:

15730506

Paper chromatography hybridization assay

Synonyms:

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Portability:
Peripheral laboratory

Technology:
Nucleic acid based

Sample of Type:
Blood

Training Required:
Moderate

Notes:

Clinical Trials:

Publications:

11358002

Developer Details

National Institutes of Health (United States)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Onchocerciasis (River Blindness)	Multi-antigen luciferase immunoprecipitation systems (LIPS)	Pre-clinical

University of Yaounde I

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Onchocerciasis (River Blindness)	Oncho-C27 antigen dipstick	

University of Dschang (Cameroon)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Onchocerciasis (River Blindness)	Oncho-C27 antigen dipstick	

Ministry of Technical Scientific Research (Cameroon)

Type	Disease	Product/Research Program	Current Phase

Diagnostic	Onchocerciasis (River Blindness)	Oncho-C27 antigen dipstick

World Health Organization (Switzerland)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Onchocerciasis (River Blindness)	Diethylcarbamazine (DEC) patch test	Clinical

World Health Organization (Switzerland)

Type	Disease	Product/Research Program	Current Phase
Drug	Onchocerciasis (River Blindness)	Moxidectin	Phase III

College of Dermatology, University of Nigeria (Nigeria)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Onchocerciasis (River Blindness)	Diethylcarbamazine (DEC) patch test	Clinical

Scripps Research Institute (United States)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Onchocerciasis (River Blindness)	Metabolomics-based biomarker discovery program	Pre-clinical

Scripps Research Institute (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Onchocerciasis (River Blindness)	Closantel	Pre-clinical

Washington University in St. Louis, School of Medicine (United States)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Onchocerciasis (River Blindness)	Paper chromatography hybridization assay	Pre-clinical

Bernard Nocht Institute for Tropical Medicine (Germany)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Onchocerciasis (River Blindness)	DNA detection test strips	Pre-clinical

Bayer AG (Germany)

Type	Disease	Product/Research Program	Current Phase
Drug	Onchocerciasis (River Blindness)	Emodepside	Pre-clinical

New York Blood Center (United States)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Onchocerciasis (River Blindness)	Anti-L3 vaccine (NYBC)	Discovery

Liverpool School of Tropical Medicine (United Kingdom)

Type	Disease	Product/Research Program	Current Phase
Vaccine	Onchocerciasis (River Blindness)	Anti-L3 vaccine (LSTM)	Discovery

Merck & Co., Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Onchocerciasis (River Blindness)	Ivermectin (Onchocerciasis)	Approved

Pfizer Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Onchocerciasis (River Blindness)	Moxidectin	Phase III