INFECTIOUS DISEASES AFFECTING AFRICA

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Outline

- *Schistosomiasis*
  - *Schistosomiasis transmission*
  - *Schistosomiasis in Africa*
  - *Distribution of Schistosomiasis*
  - *Mathematical models of Schistosomiasis disease*

- *Onchocerciasis*
  - *Onchocerciasis transmission*
  - *Onchocerciasis in Africa*
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  - *Mathematical models of Onchocerciasis disease*

Schistosomiasis

What is Schistosomiasis?

- Schistosomiasis also known as Bilharziasis is a debilitating parasitic disease caused by the trematode worms of the genus Schistosoma species.[73,74]

Schistosomiasis Organism

Schistosoma haematobium, S. japonicum, S. mansoni, S. mekongi and S. intercalatum [73,74,76]

commonest in Sub-Saharan Africa

- S. Haematobium - urogenital schistosomiasis;
- S. mansoni - intestinal schistosomiasis

Infection is widespread in poor communities

Major risk group for schistosomiasis

Although the disease can affect all age groups and gender, Women, manual workers, fisherman school-aged male children are mostly affected [77]

Female genital schistosomiasis

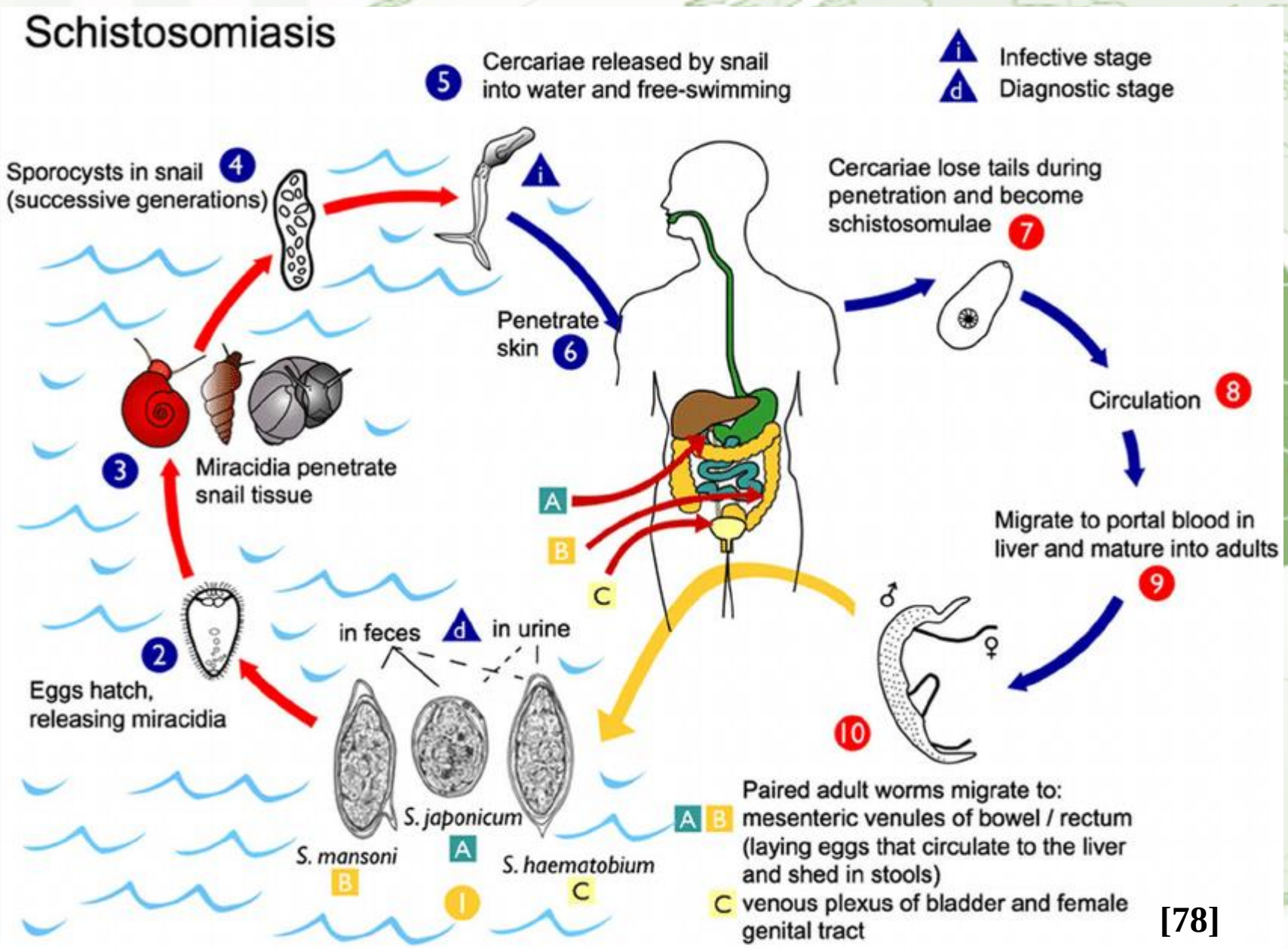
A major risk factor for HIV infection

Treatment

Praziquantel remains the drug of choice for the treatment of schistosomiasis.[75]

Globally, 76.9 million people received treatment for schistosomiasis in 2020 - 59.9 million were school aged children (55.2 million in African region) and 17 million adults (14.5 million in African region) [80].

Schistosomiasis Transmission



[78]

urogenital form - haematuria (blood in the urine), painful urination, bladder or kidney disease and the women, involvement of fallopian tube may cause infertility [74].

Intestinal form - diarrhoea, bloody stool, liver and or spleen enlargement, and portal hypertension alongside the associated complications [75].

Complications

Impaired learning difficulties and recurrent typhoid fever in children. [74,75].

Schistosomiasis in Africa

- About 78 countries have been reported to harbor schistosomiasis with 52 of them classified to have moderate to high transmission [73]
- 440 million people suffer from chronic schistosomiasis worldwide. [75]

- sub-Saharan Africa, Caribbean, Middle East, Asia and South America [74]
- Reported in some parts of Europe and North America largely due to climatic change and human migration [75]

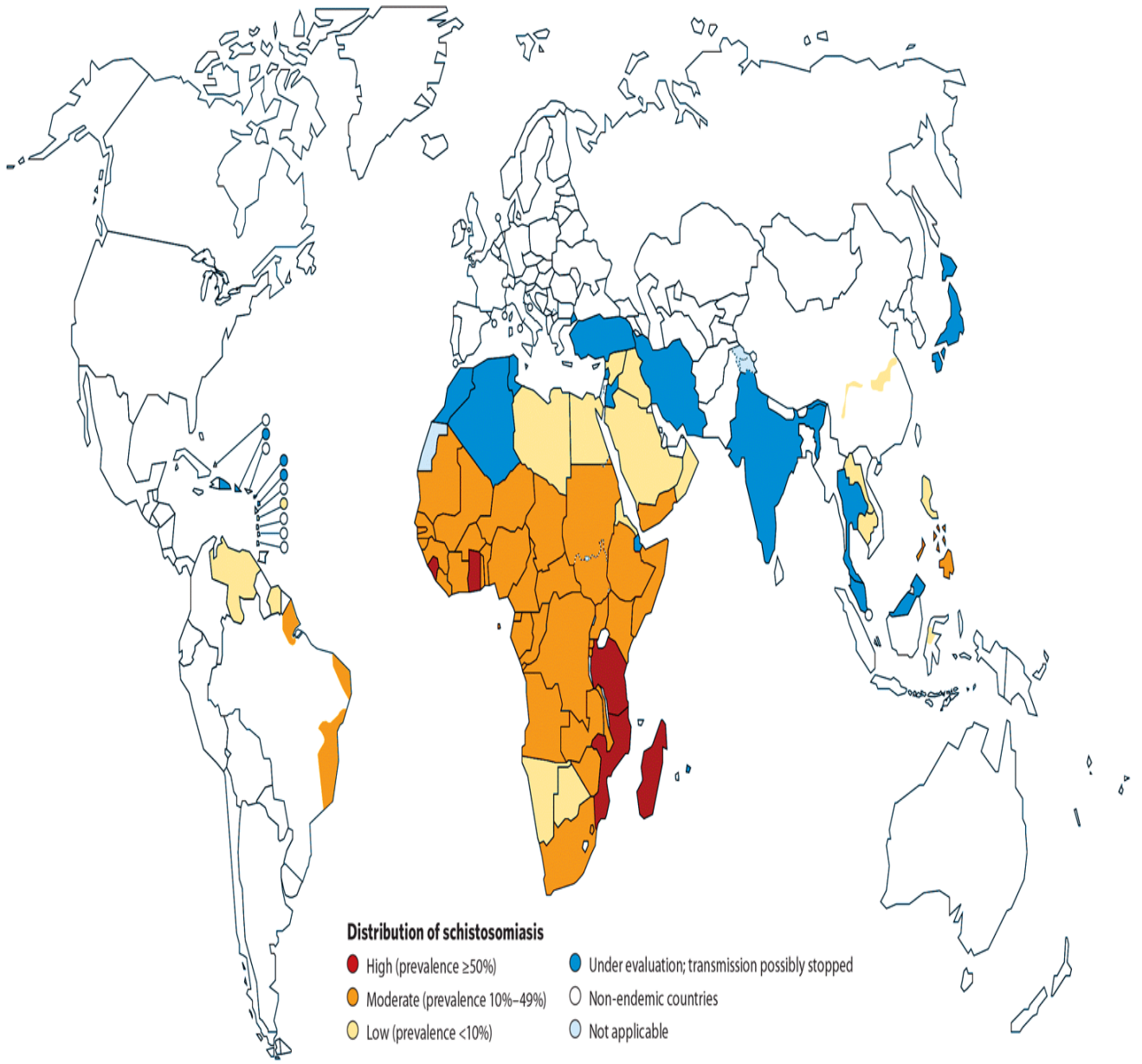
- Sub-Saharan Africa (SSA) accounts for more than 90% of human burden of schistosomiasis. [76]
- Within Africa, Western Africa, Central Africa, Eastern Africa and Southern Africa are mostly affected compared to Northern Africa. [77]

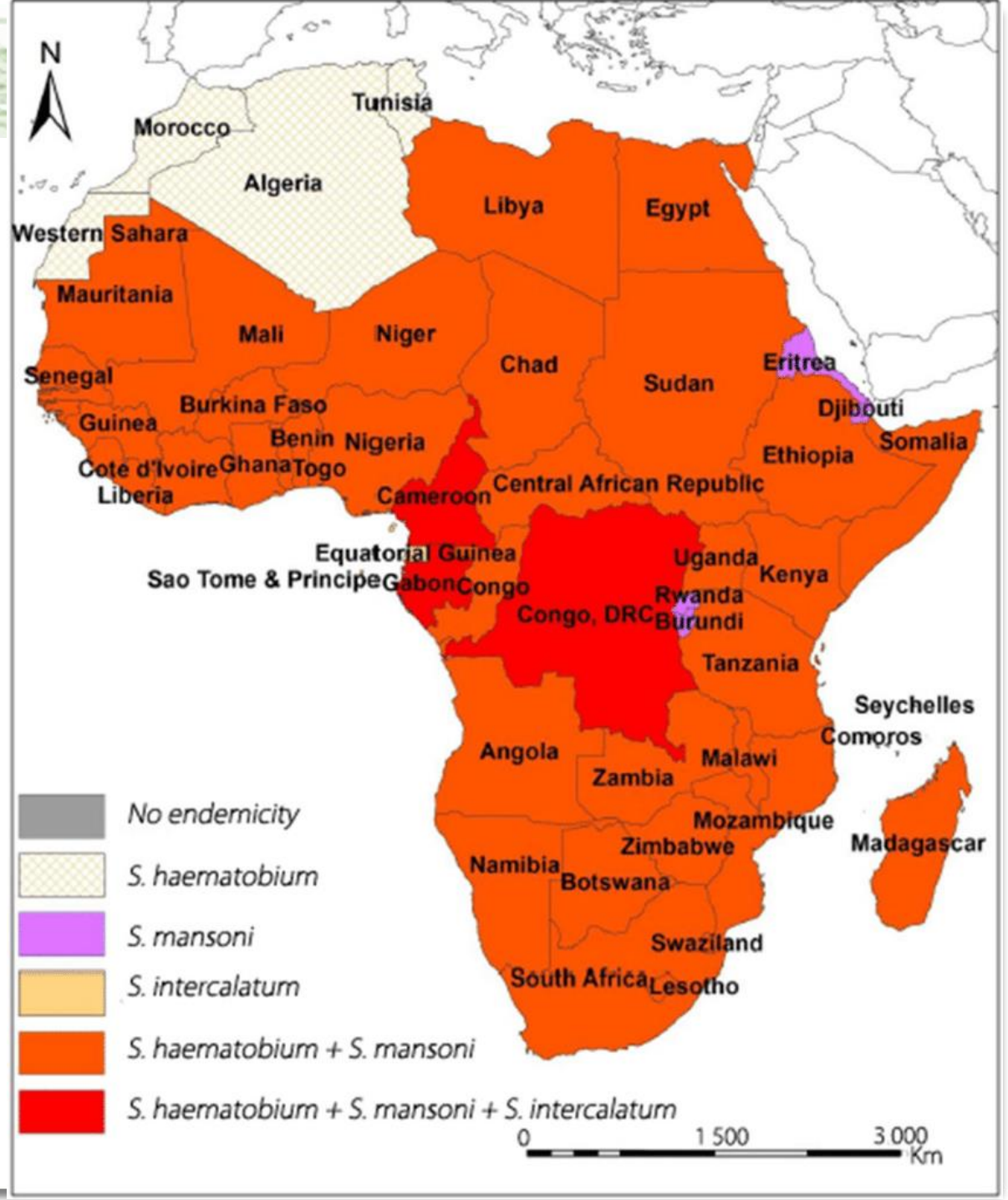
9 out of 10 infected people live in Africa

Diseases	Cases
Nigeria (West Africa)	29 million
Tanzania	23 million
DRC and Ghana	19 million
North Africa and the Middle East	12.7 million

[79]

Distribution of Schistosomiasis

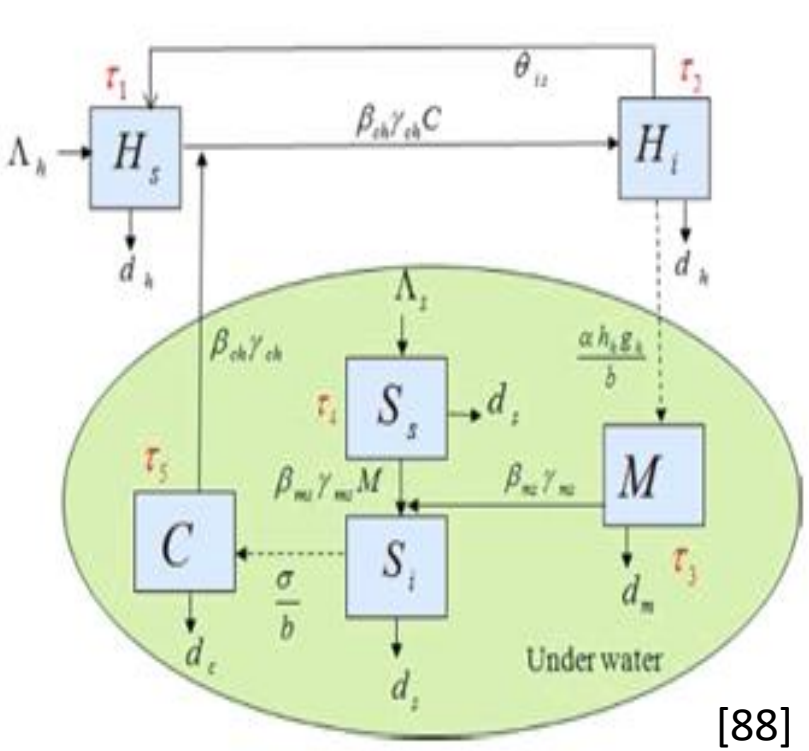




Early Mathematical Models of Schistosomiasis

- Macdonald [81] in 1965 developed the pioneering work on mathematical model of schistosomiasis using probability of pairing.
- Nåsell [82] and Goddard [83] built on Macdonald's model for schistosomiasis by relaxing some assumptions, Nasell considered snail latency as a deterministic model while Goddard detailed the Macdonald work.
- Feng et al. [84] - an age-structured model with multiple strains of schistosome and snail hosts with additional mammalian host and a competitor snail species considering treatment of human hosts by chemotherapy, and parasite resistance to the drug.
- Allen and Victory [85] - a mathematical model for schistosomiasis infection with human and snail hosts, and an additional mammalian host and a competitor snail species.
- Woolhouse [86] - Described different models that include the mean number of schistosomes per person and the prevalence of patent infections of snails. Various modifications are: prepatent infections of snails; loss of infection of snails; the effects of snail population dynamics; the effects of miracidia and cercariae population dynamics; miracidia searching efficiency; reservoir hosts; heterogeneous patterns of transmission; seasonality; and predisposition to infection; variation in levels of infection with age and the effects of acquired immunity to infection.

Delay Mathematical Model of Schistosomiasis



[88]

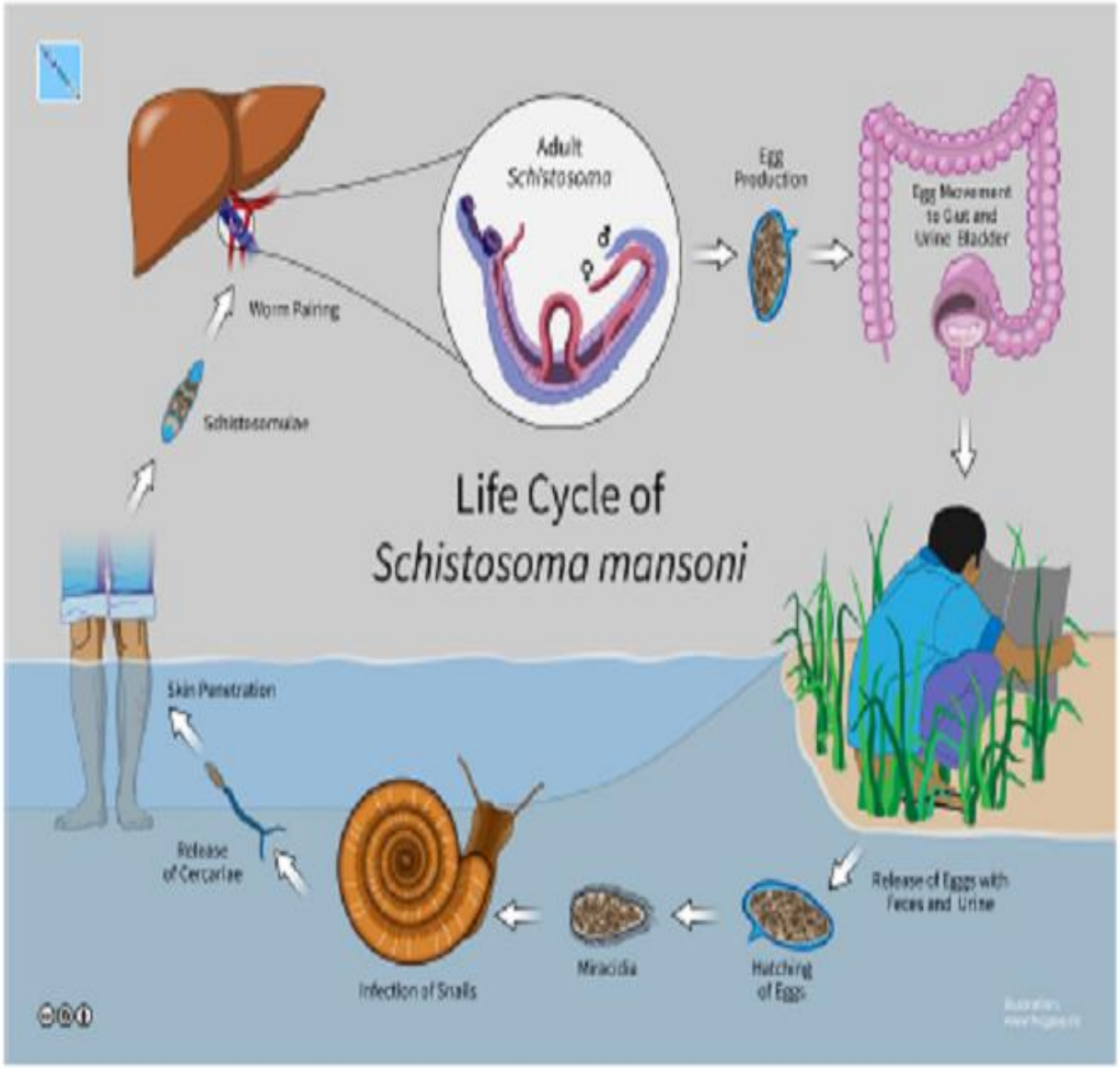
$$\begin{cases}
\frac{dH_s(t)}{dt} = \Lambda_h - \beta_{ch}\gamma_{ch}C(t-\tau_5)H_s(t-\tau_1) + \theta_{is}H_i(t) - d_hH_s(t), \\
\frac{dH_i(t)}{dt} = \beta_{ch}\gamma_{ch}C(t-\tau_5)H_s(t-\tau_1) - (\theta_{is}+d_h)H_i(t), \\
\frac{dS_s(t)}{dt} = \Lambda_s - \beta_{ms}\gamma_{ms}M(t-\tau_3)S_s(t-\tau_4)e^{-d_s\tau_4} - d_sS_s(t), \\
\frac{dS_i(t)}{dt} = \beta_{ms}\gamma_{ms}M(t-\tau_3)S_s(t-\tau_4)e^{-d_s\tau_4} - d_sS_i(t), \\
\frac{dC(t)}{dt} = \frac{\sigma}{b}S_i(t) - \beta_{ch}\gamma_{ch}C(t-\tau_5) - d_cC(t), \\
\frac{dM(t)}{dt} = \frac{\alpha h_h g_h}{b}H_i(t-\tau_2) - \beta_{ms}\gamma_{ms}M(t-\tau_3) - d_mM(t).
\end{cases}$$

Symbol	Description
τ_1	Prepatent period of schistosome in human body
τ_2	Incubation period for egg hatching
τ_3	Time delay for miracidium
τ_4	Maturation duration of the sporocyst in snails
τ_5	Maturation lag for cercarial growing into schistosoma larva
Λ_h	Recruitment rate of suspectable human
d_h	Natural death rate of humans
θ_{is}	Transmission rate from infected humans to recovered humans
β_{ch}	Transmission rate from cercaria to susceptible human
γ_{ch}	Contact rate(frequency) between humans and cercaria
Λ_s	Natural birth rate of snails
d_s	Natural death rate of snails
β_{ms}	Infected rate from miracidia to snails
γ_{ms}	Contact rate between miracidia and snails
d_m	Natural death rate of miracidia
α	Hatching rate of miracidia from eggs
g_h	Stool production one person
h_h	Eggs production per gram stool
d_c	Natural death rate of cercaria
σ	Cercaria production per infected snail
a	Cercaria habitat area
b	Surface water area

$H_s(t)$ - susceptible humans
$H_i(t)$ - infected humans
$S_s(t)$ - susceptible snails,
$S_i(t)$ - infected snails,
$M(t)$ - mean spatial density of miracidia
$C(t)$ - mean spatial density of cercaria

- Kouton et al. [87] investigated the impact of latent period of parasites within the snail and human hosts on schistosomiasis prevalence incorporating distributed delays.
- Yang and Xiao [89] - A discrete delay model for schistosomiasis transmission where the delay appears in the incidence term including masse action SI
- Guiro et al. [90] - a delay deterministic model of schistosomiasis disease with human and snail hosts and two general incidence functions.

Schistosomiasis transmission



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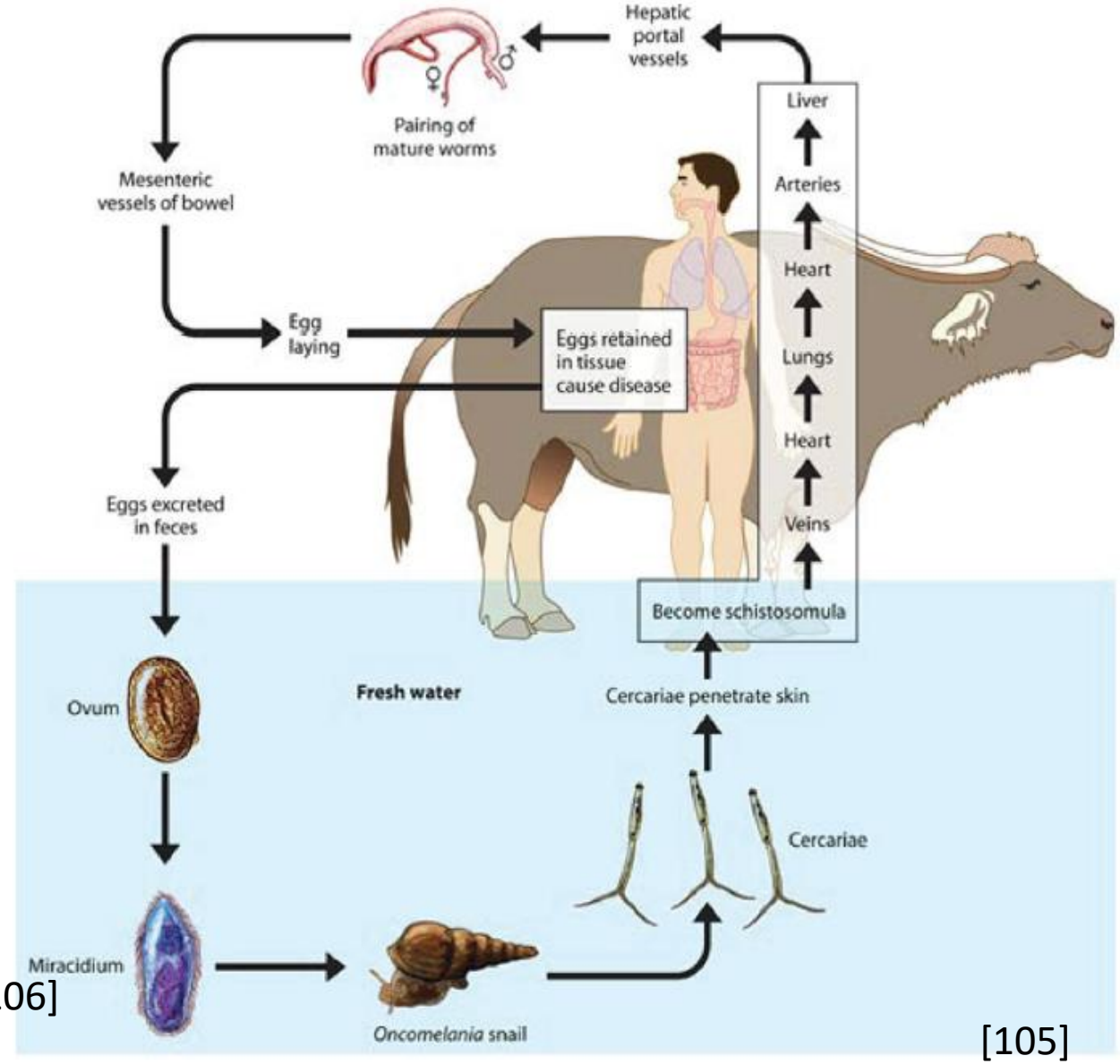
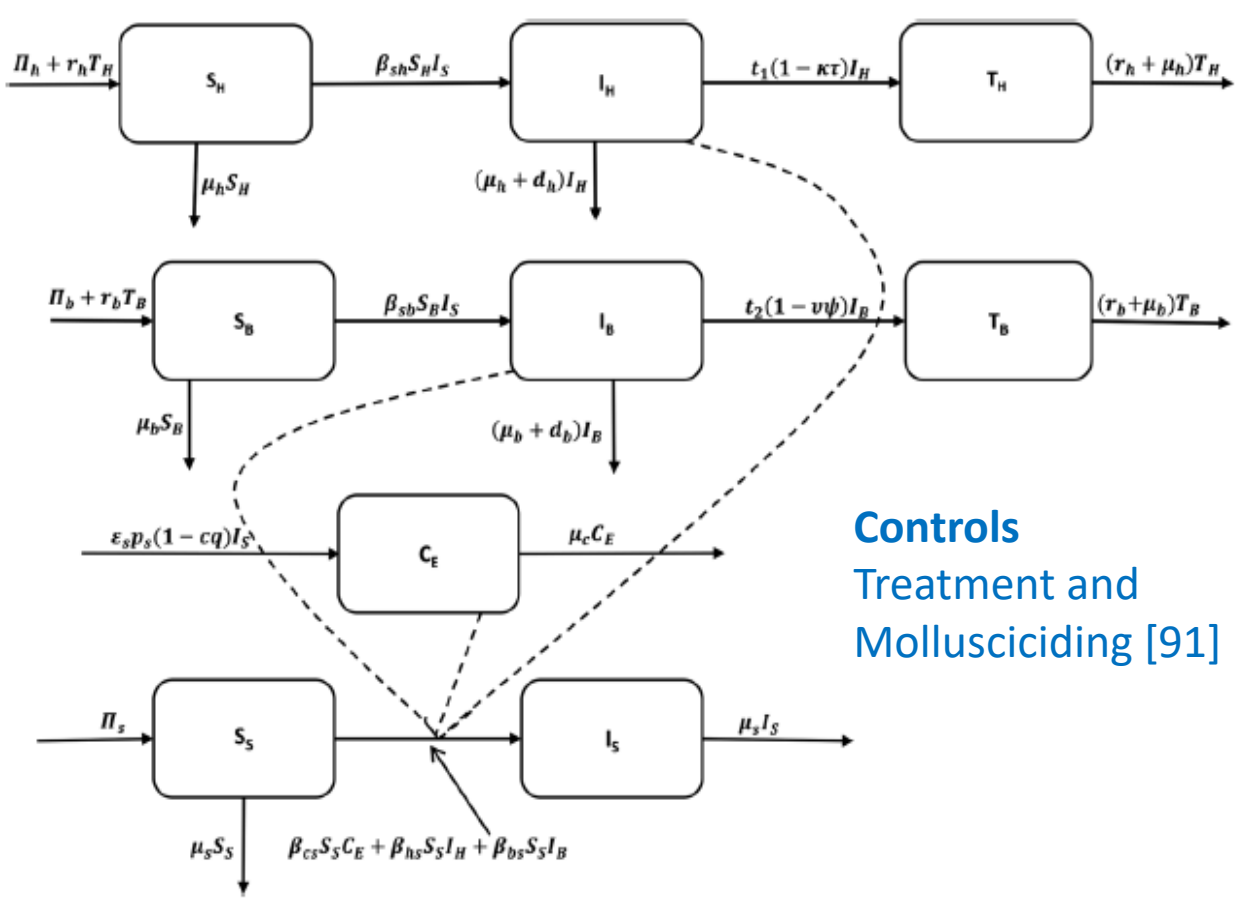


[105]

Heterogeneous model for Schistosomiasis transmission dynamics



Controls
Treatment and Molluscicide [91]

$$\frac{dS_H}{dt} = \Pi_h - \beta_{sh} S_H I_S + r_h T_H - \mu_h S_H,$$
$$\frac{dI_H}{dt} = \beta_{sh} S_H I_S - (t_1(1-\kappa\tau) + \mu_h + d_h) I_H,$$
$$\frac{dT_H}{dt} = t_1(1-\kappa\tau) I_H - (r_h + \mu_h) T_H,$$
$$\frac{dS_B}{dt} = \Pi_b - \beta_{sb} S_B I_S + r_b T_B - \mu_b S_B,$$
$$\frac{dI_B}{dt} = \beta_{sb} S_B I_S - (t_2(1-\upsilon\psi) + \mu_b + d_b) I_B,$$
$$\frac{dT_B}{dt} = t_2(1-\upsilon\psi) I_B - (r_b + \mu_b) T_B,$$
$$\frac{dS_S}{dt} = \Pi_s - (\beta_{cs} C_E + \beta_{hs} I_H + \beta_{bs} I_B) S_S - \mu_s S_S,$$
$$\frac{dI_S}{dt} = (\beta_{cs} C_E + \beta_{hs} I_H + \beta_{bs} I_B) S_S - \mu_s I_S,$$
$$\frac{dC_E}{dt} = \varepsilon_s p_s (1-cq) I_S - \mu_c C_E.$$

t_1, t_2: Disease progression rates,

k, ν: Fraction of humans and bovines treated,

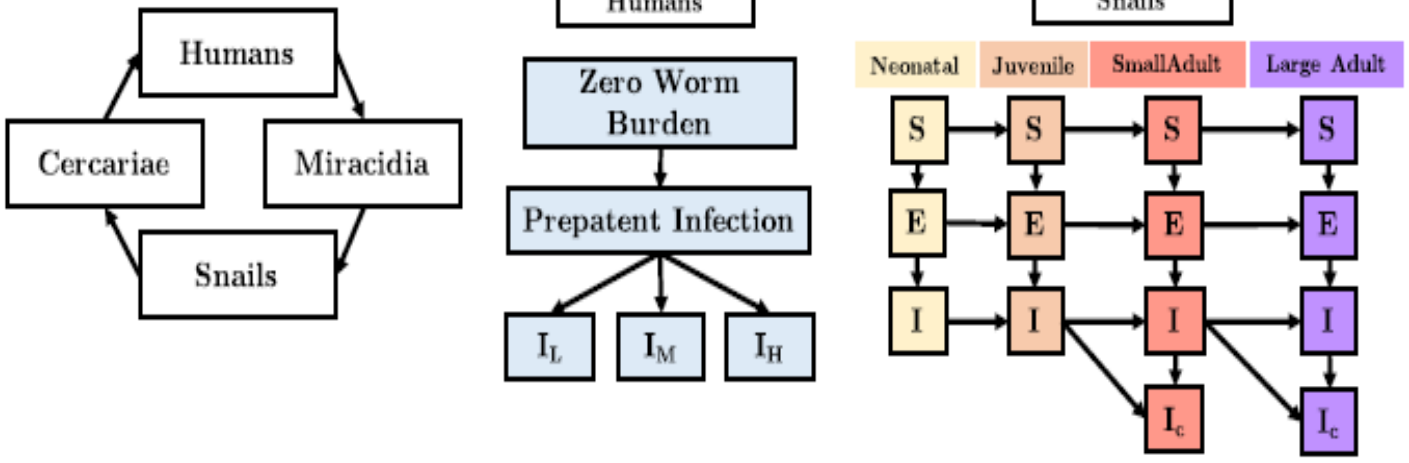
τ, ψ: Effectiveness of treatment in humans and bovines

S_H: Susceptible humans, I_H: Infected humans, T_H: Treated humans, S_B: Susceptible bovines, I_B: Infected bovines, T_B: Treated bovines,
S_S: Susceptible snails, I_S : Infected snails, C_E: Contaminated environment

- Madubueze et al. [92] proposed a heterogeneous model (Cattle, human and snail) with snail control measure.
- Chen et al. [93] studied the human-cattle-snail transmission of Schistosomiasis in Hubei Province, China

Age structure model within the intermediate host population

a



b

Snail Age Group	Model Structure: Completely Stratified (N+J+S+L)	Neonatal & Juvenile &Large (N+J+L)	Juvenile & Small & Large (J+S+L)	Juvenile &Large (J+L)	Small & Large (S+L)	No Age Stratification: All Large (L)
Neonatal (0-5mm)						
Juvenile (5-9mm)						
Small Adult (9-11mm)						
Large Adult (11+mm)						

a Diagrams of the model framework illustrating the complete transmission cycle, the human infection status with variable *Schistosoma mansoni* worm burden, and the age-stratified snail population. *S* Susceptible class, *E* exposed class, *I* infected class, I_C infected and castrated snails; I_L infected humans with a low *S. mansoni* burden, I_M infected humans with a moderate *S. mansoni* burden, I_H infected humans with a heavy *S. mansoni* burden.

b The completely stratified model for the snail population includes neonatal (*N*), juvenile (*J*), small (*S*) and large (*L*) adult age classes; this is simplified in various combinations in later model structures. The *colors* represent the way in which the age classes are combined in each model structure. The missing age groups in all models, excluding the completely stratified model, are subsumed into the larger age class.

For example, in the neonatal and juvenile and large (*N+J+L*) model, small adults are subsumed into the large adult age class. In the small and large (*S+L*) model, neonatal and juvenile snails are subsumed into the small adult snail class. In every version of the model the snails can still be assigned to any of the infection statuses [94].

Complex models for Schistosomiasis transmission

- Aziz-Alaoui1 et al. [95] - the impact of human behavior on schistosomiasis diseases using $S_h I_h \mathrm{M} S_s I_s \mathrm{C}$ model and special functions for the human transmission and treatment rates, and shedding rates of the infected humans and infected snails.
- Kamara et al. [80] – the effect of treatment, public health education, and chemical control interventions using $S_h I_h \mathrm{M}\ S_s I_s \mathrm{C}$ model and saturation incidence functions with Cercariae (C) and miracidia (M).
- Gao et al. [96] - the effect of treatment and snail control on schistosomiasis transmission using $S_h I_h \mathrm{M} S_s I_s \mathrm{P}$ model with saturation incidence function of free-living pathogen (P) and Holling's type III functional response of miracidia (M).
- Das et al. [97] - Impulse optimal control of snail population and sanitation and treatment on schistosomiasis transmission with only two-third of total Cercariae entering a human body, pair up to produce eggs and logistic growth for the snail population.
- Nur et al. [98] - the effect of health education and snail control on schistosomiasis transmission using $S_h E_h I_h \mathrm{M}$ $S_v I_v$ C model with mass action force of infections for M and C.

Complex models for Schistosomiasis transmission

- Kanyi et al. [99] - the effect of treatment and sanitation on schistosomiasis transmission using $S_hE_hI_hT_hN_mS_sI_sN_c$ model and saturation incidence functions with Cercariae (N_c) and miracidia (N_m).
- Ding et al. [100] - the impact of incubation period of parasite in human body and optimal controlling of some parameters such as transmission rate from Cercariae to exposed human, awareness level and temperature using $H_sH_eH_iMS_sS_iC$ model with mass action force of infections for M and C .
- Feng et al. [101] - impact of migrating human population in persistence of Schistosomiasis using two migrating human groups and infection-age density of infected snails which the human population was extended to n human populations.
- Kalinda et al. [102] - Optimal control temperature-dependent Schistosomiasis model using Snail natural predator crayfish as biological control and molluscicide as chemical control.

Co-infection models of Schistosomiasis transmission

- Okosun and Smith? [103] - Optimal control analysis of malaria-schistosomiasis co-infection dynamics.
- Okosun et al. [104] – Cholera schistosomiasis coinfection dynamics

Further research possibility on Schistosomiasis

- Delay in incubation period in infected definitive hosts by drug treatment,
- Impulsive differential equation where periodic water treatments are modeled as periodic pulses.
- Saturation treatment function to take into account due to limitation in treatment of infected humans
- Model separate states for vulnerable age or demographic group
- Incorporating seasonality with temperature and rainfall as weather variations effect snail populations
- Individual-based stochastic model incorporating spatial transmission
- Co-infection of Schistosomiasis and typhoid as Salmonella species which cause typhoid fever hides in the sanctuary sites provided by the terminal spines of Schistosoma eggs and prevent antibiotics for typhoid from reaching them.
- Host heterogeneities in human with age-stratified snail population and dispersal in the model.
- Time-delayed differential for Schistosomiasis transmitted among humans, animals, and snails.
- Incorporation of combined control interventions like treatment, public health education, chemical control and snail control intervention strategies.

Further research possibility on Schistosomiasis

- Immigration of infectious humans
- **Application of molluscicide**: what is minimum level of application of molluscicide to achieve the desired outcome in practice, the toxicological consequences on water and/or soil pollution, and the ecological consequences of removing a large fraction of the snail population from the food chain and the overall stability of the ecosystem is vital.
- immune responses and their effects on schistosome establishment, fecundity and mortality.
- Determining the specific human age-group to be targeted for mass drug administration.
- Diverting the cercariae to non-sensitive snails (to minimize the population of cercaria producing snails) by the incorporation of a competitor non-sensitive snail population.
- The introduction of the population of predator fishes that prey on sensitive snails
- Using behavioral contact and/or shedding rate functions is not simple prevalence-dependent functions.
- The spatial dynamics (reaction–convection–diffusion model) of snails and/or cercariae.
- Fractional derivatives such as Atangana–Baleanu derivative will give a more realistic description of the disease.

Onchocerciasis

What is Onchocerciasis?

Onchocerciasis, also called African river blindness, is a severe debilitating parasitic disease caused by the nematode *Onchocerca volvolus* transmitted through the repeated bite of a vector, female infected blackfly, *Simulium species* [107, 108]. Onchocerciasis is an eye and skin disease and the second most important cause of infectious blindness worldwide after trachoma.

Where the blackfly breeds

The blackflies breed along fast-flowing rivers and streams, close to remote villages located near fertile land where people rely on agriculture.

Symptoms

Symptoms are caused by the microfilariae that move around the human body and induce untense inflammatory responses when they die.

severe itching, disfiguring skin conditions, and visual impairment, including permanent blindness.

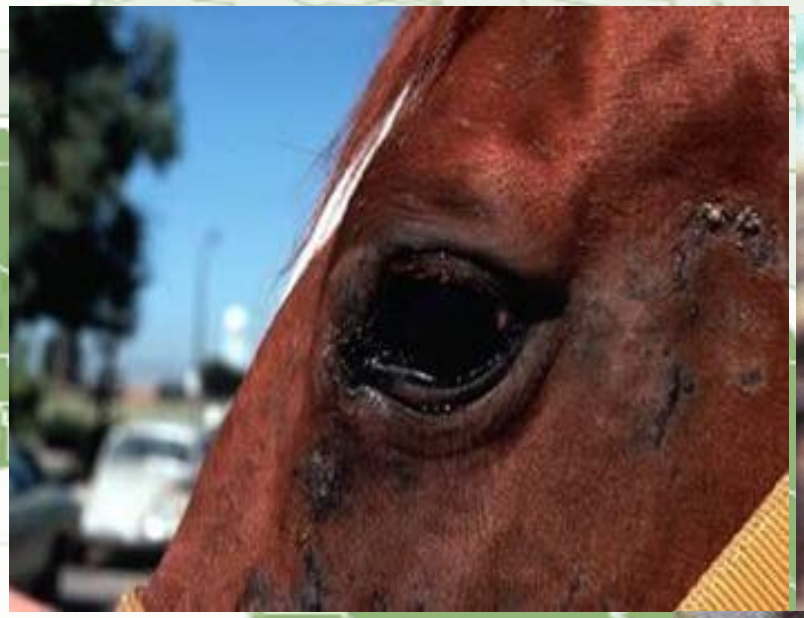
Life cycle of Onchocerca volvulus

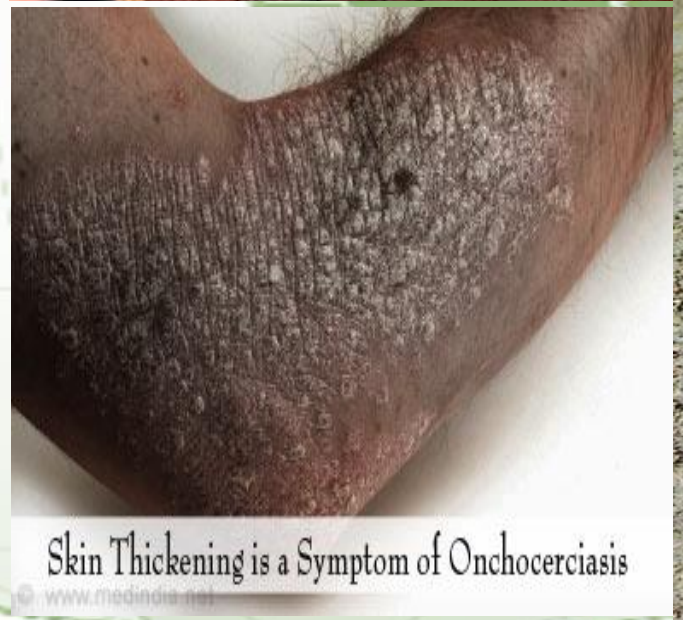
- O. volvulus in the human host comprises adult worms referred to as macrofilaria and infective larvae forms called microfilariae.
- The macrofilariae accumulate beneath skin to form nodules called onchocercomas,
- Microfilariae migrate through the skin to eyes and other organs [111].
- Each macrofilaria produces a thousand microfilaria per day and has a life span of 11 – 12 years
- Microfilariae has life span of 1—2 years [109, 110].
- The vector female blackflies gets infected with microfilariae during blood meal when it bites an infected human with onchocerciasis.
- The microfilariae in blackfly undergo through several stages and move to the proboscis where it uses to pierce the human skin during blood meal.

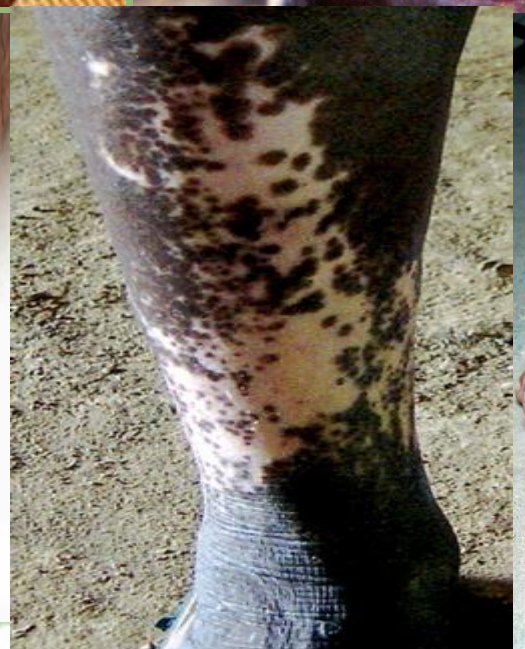
Clinical Features of Onchocerciasis

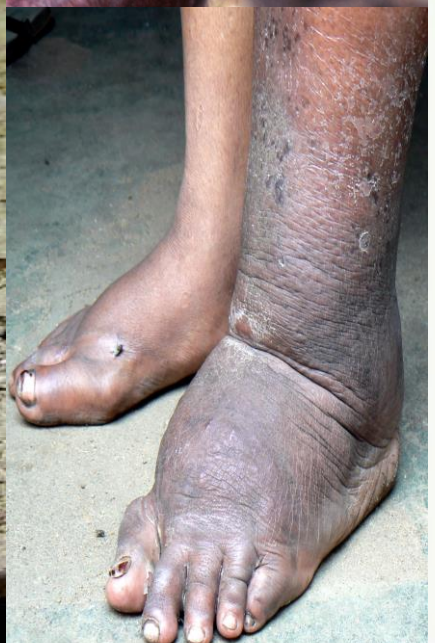
The inflammatory reactions provoked by the presence of microfilariae in the body

- In the skin: provoke itching leading to chronic dermatitis called onchodermatitis, lizard skin and leopard skin.
- Microfilariae can block the lymphatic channels to cause elephantiasis of the lower limbs and scrotum.
- Microfilariae in the eyes elicit reactions that cause blindness. [108, 111, 110, 112]

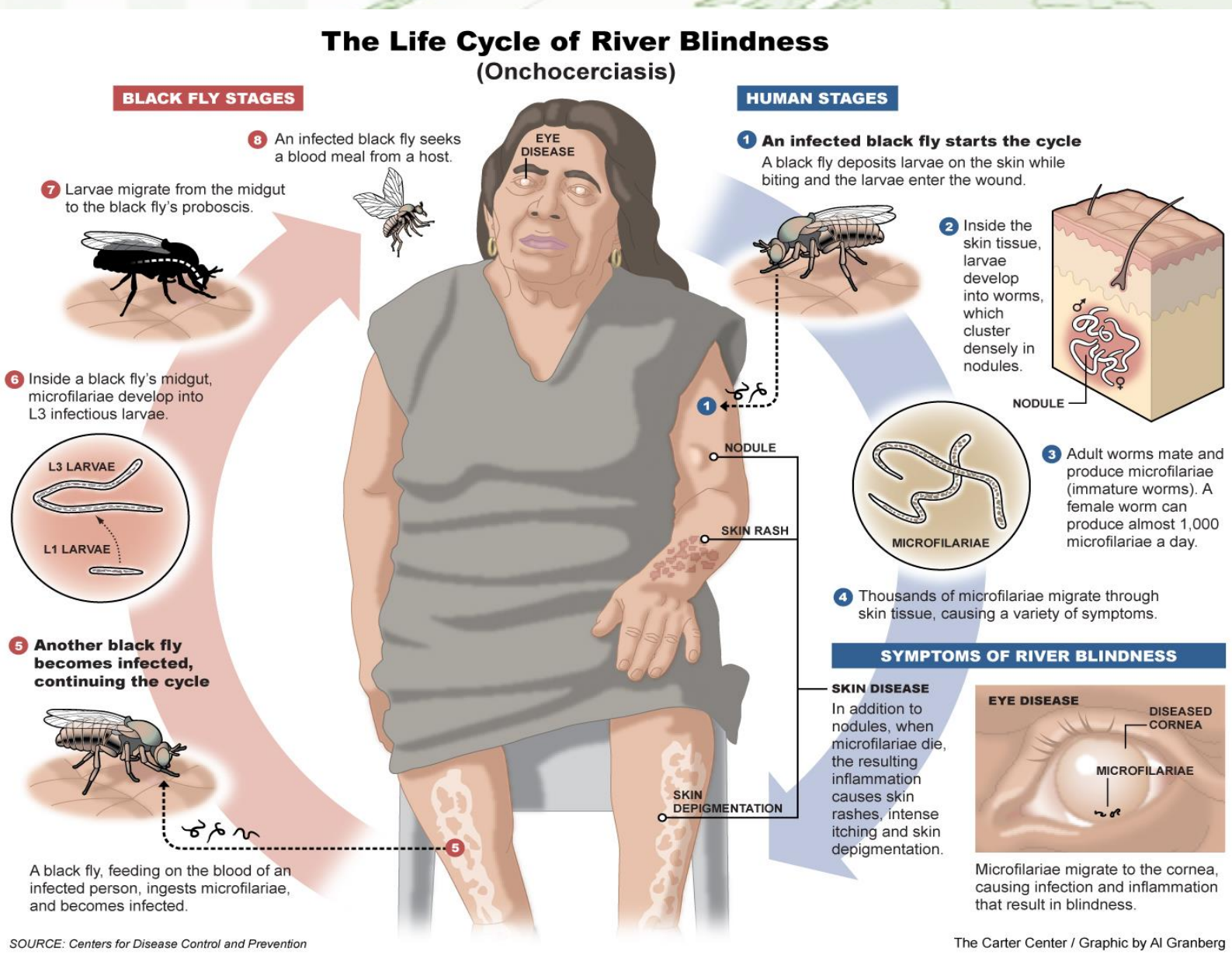








Onchocerciasis Transmission



- The people most at risk for acquiring onchocerciasis are those who live or work near streams or rivers where there are Simulium blackflies.
- blackflies are found are rural agricultural areas in sub-Saharan Africa in the countries
- Onchocerciasis has been associated with epilepsy and nodding syndrome which are suspected to be due to cross-reactions of onchocerciasis specific antibodies with the nervous system [109].
- Long-term missionaries, Peace Corps volunteers, field researchers, and other long-term travelers to the endemic areas of onchocerciasis are at risk becoming infected [113].
- **It affects poor people in remote areas.**

Onchocerciasis Treatment

- Treatment for onchocerciasis is the use of ivermectin 150 mcg/kg given once or twice a year depending on the level of individual disease burden and community endemicity [114].
- WHO recommends treating onchocerciasis with ivermectin drug at least once yearly for 10 to 15 years [115].
- Ivermectin kills the microfilariae and inhibited the macrofilariae from releasing microfilariae for up to 2 years after a single dose [108].
- It does not kill macrofilariae and the macroflariae dies off after 11—12 years [108, 111].
- Mass drug administration of ivermectin via community directed treatment with ivermectin (CDTi) remains the standard for the treatment of onchocerciasis [116].
- More than 100 million people are treated each year under a donation program [114].
- Doxycycline is a promising treatment that kills the adult worms by killing the Wolbachia bacteria on which the adult worms depend in order to survive [113].
- Ocular complications associated with onchocerciasis were treatable, are managed by standard ophthalmic treatment protocols.
- It is advise to treat an infected with both with ivermectin and with doxycycline.

Drawback of ivermectin - does not kill adult worm

Higher prevalence of onchocerciasis- Male gender, a distance less than 2 km from the riverbank, noncompliance to ivermectin therapy, and age of above 35 years [114].

Coinfection of O. Volvulus with Loa loa

- In some patients infected with onchocerciasis, there is coinfection with Loa loa, another parasite, concomitant loiasis (African eye worm), that is endemic in the west and central Africa, where Onchocerca volvulus also exists.[117, 118]
- Treatment with ivermectin in people with this coinfection can cause severe life-threatening adverse effects, including encephalitic reaction as a result of the Loa loa infection contributing to the heavy burden of microfilariae.[117, 119].
- The inability of ivermectin to kill adult worm is a drawback to eradication efforts in these endemic areas of coinfection with Loa loa [116].

- Treatment strategies may need to be adjusted, by following the Mectizan Expert Committee (MEC)/APOC recommendations for the prevention and management of severe adverse events [115].
- Preventive chemotherapy should be given yearly for duration not less than the life span of the adult worm.
- Intervention measures should take cognizance of life spans of macrofilariae and microfilariae when designing frequency of preventive chemotherapy and other non-pharmaceutical controls.

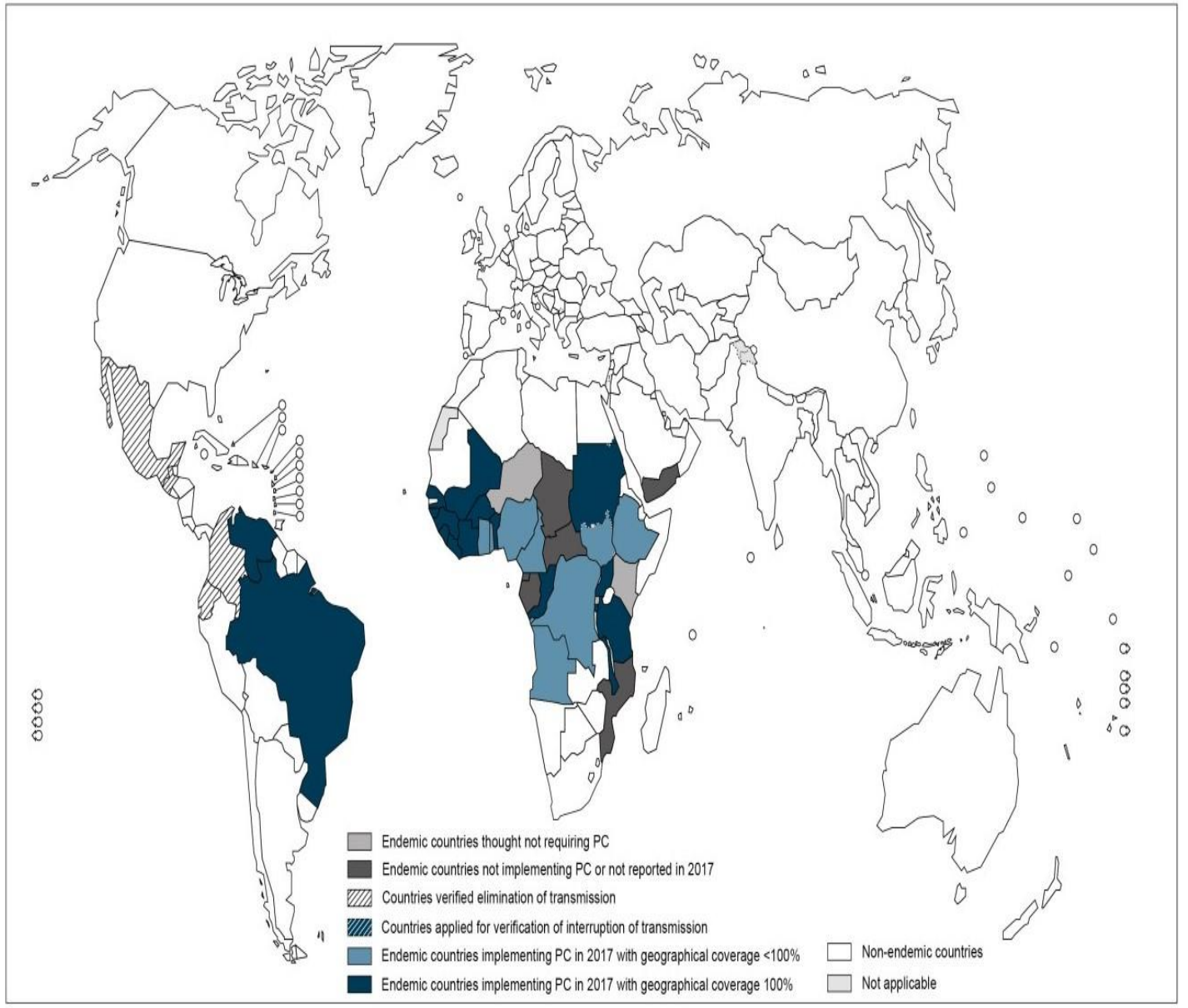
Alternative Treatment Strategies for Onchocerciasis

- **Increasing coverage, adherence and frequency of ivermectin Treatment**: increasing the frequency of ivermectin treatment (to twice or four times per year if possible), as highlighted by the Latin American experience.
- **Other microfilaricidal therapies (moxidectin)**: Moxidectin has not yet been licensed for human use but have pass phase II and phase III clinical trials conducted in Africa to assess its safety and efficacy for the treatment of human onchocerciasis.
- **Macrofilaricidal therapies (doxycycline):** Doxycycline is effective against adult O. volvulus and also safe for treatment of coinfected patients with Loa loa. It is used with the combination of ivermectin.
- **Vector Control**: Large-scale vector control, by weekly spraying of blackfly breeding sites with larvicidal insecticides and highly complementary to annual ivermectin MDA even in highly endemic settings.
- **Onchocerciasis Vaccine:** Onchocerciasis Vaccine for Africa (TOVA) Initiative has been established and developed three candidate antigens that have proven efficacious in three different filariae-animal systems.

Drawback of doxycycline- It is expensive for widespread community-based control and contraindications in children under eight years and in pregnancy

Burden of Onchocerciasis disease in Africa

- In 2019, it was projected that 217.2 million people in 31 countries in Africa, six in Americas and Yemen in Asian, 99% of whom were in sub-Saharan Africa, were at risk of onchocerciasis and required preventive chemotherapy [120, 121].
- 14.6 million of the infected people already had skin disease [115]
- The disease is endemic in 31 sub-Saharan African countries.
- Vision loss due to onchocerciasis is estimated to affect 1.15 million population [114].



Onchocerciasis Prevention and Control Programs

Personal protection measures against biting insects

- Wearing insect repellant such as N,N-Diethyl-meta-t oluamide (DEET) on exposed skin,
- Wearing long sleeves and long pants during the day when blackflies bite, and wearing permethrin- treated clothing [113].
- Avoid sleeping outside during the day time.

Vector Control

- The Onchocerciasis Control Programme in West Africa (OCP); Time : 1774 – 2022.
- **Aim:** To eliminate river blindness as a public health problem and as an obstacle to socioeconomic development [122].

Onchocerciasis Control Programme in West Africa (OCP)

- OCP: treating the breeding sites of disease-transmitting blackflies with larvicides to kill the larva over a long enough time that the adult worms would all die out [122].
- Cover Burkina Faso and six neighboring countries
- Later double the coverage to 11 countries in 1986 and supplemented by large-scale distribution of ivermectin in 1989 [122].

Onchocerciasis Prevention and Control Programs

African Programme for Onchocerciasis Control (APOC)

- launched in 1995 to end 2015
- objective: controlling onchocerciasis in the remaining endemic countries in Africa, 19 countries in East and Central Africa [115].
- Its main strategy: Establishment of sustainable community-directed treatment with ivermectin (CDTI) and vector control with environmentally-safe methods where appropriate [115].

Aim: Eradication of the disease in Africa

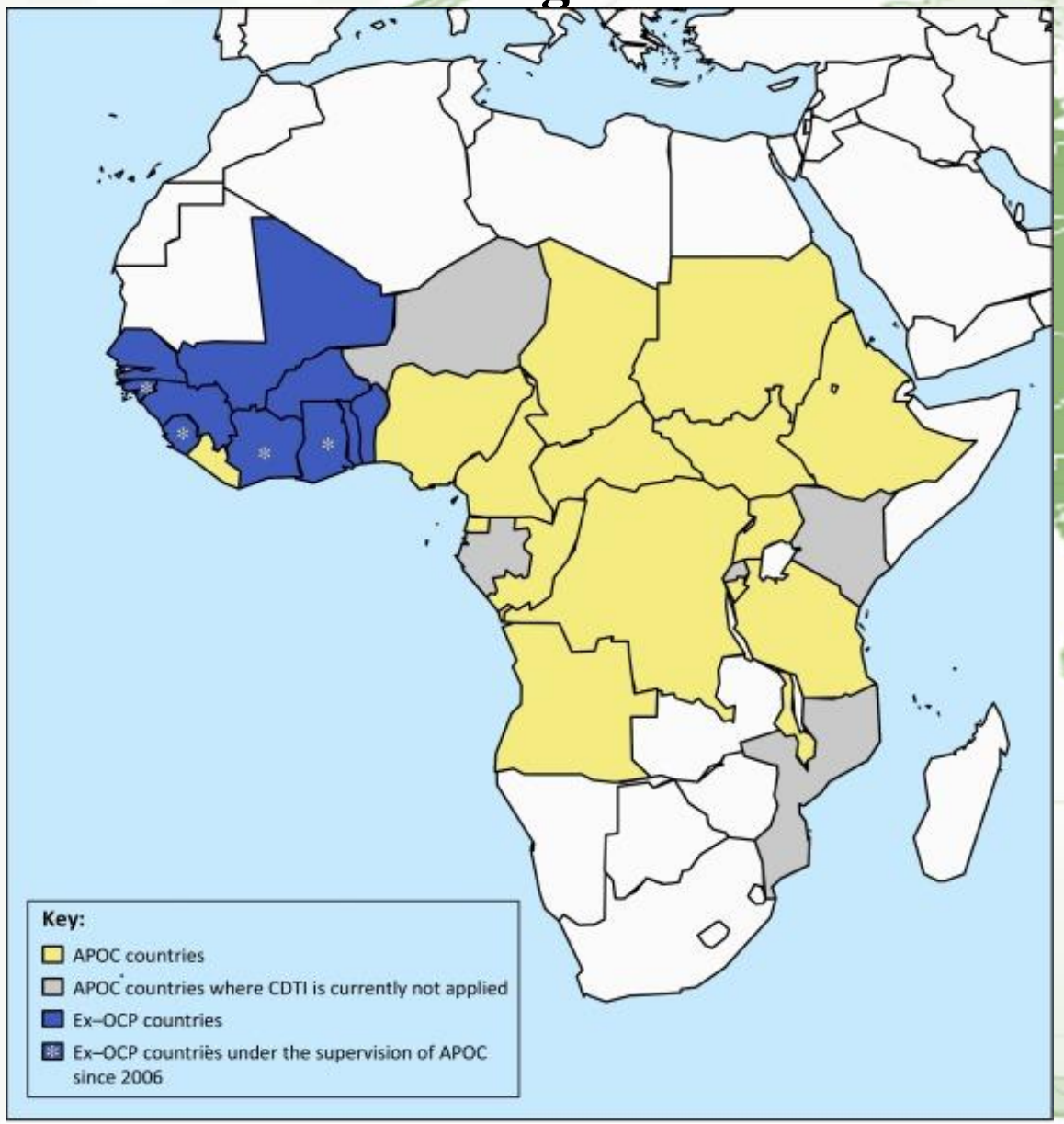
Result of OCP

- Relieved 40 million people from infection,
- Prevented blindness in 600 000 people,
- Ensured that 18 million children were born free from the threat of the disease and blindness [115].

Result of APOC

- more than 119 million people were treated with ivermectin
- many countries had greatly decreased the morbidity associated with onchocerciasis
- More than 800,000 people in Uganda and 120,000 people in Sudan no longer required ivermectin by the time that APOC closed. [115]

Onchocerciasis Prevention and Control Programs



Elimination major challenges

- incomplete elimination mapping of all transmission zones;
- co-endemicity of onchocerciasis and loiasis;
- possible emergence of ivermectin resistance;
- uncoordinated cross-border elimination efforts;
- conflict and civil war;
- suboptimal program implementation;
- technical and financial challenges [123].

Research priorities

- Optimizing strategies to reach marginalized and migratory populations.
- Validating mapping and safe intervention strategies in settings where onchocerciasis and loiasis are con-endemic.
- Defining starting and stopping thresholds for MDA.
- Development of robust diagnostics tools to support programme decision-making.
- Demonstrating the programmatic utility of vector control measures.
- Testing new therapeutic regimens.
- Optimizing survey design through the use of new geostatistical tools.
- Developing post-verification strategies.
- Exploring opportunities to integrate surveillance.

WHO Roadmaps

WHO 2012 roadmap

To overcome the impact of NTDs through the identification of global and regional targets for the eradication, elimination, and control of NTDs by 2020 [124].

2012 Roadmap strategies

i. preventative chemotherapy
ii. intensified disease management
iii. vector and intermediate host control,
iv. veterinary public health
v. provision of safe water and sanitation [124].

WHO 2021 roadmap

To achieve Sustainable Development Goal (SDG) targets on NTD by 2030 [125].

2021 Roadmap strategies

i. Increase accountability for impact by using impact indicators instead of process indicators and accelerate programmatic action.
ii. To move away from siloed, disease-specific programmes by mainstreaming programmes into national health systems and intensifying cross-cutting approaches with adjacent sectors such as education, WASH, agriculture, environment, livestock, wildlife (One Health approach) centred on the needs of people and communities.
iii. To change operating models and culture to facilitate greater ownership of programmes by countries [125].

NTD Modelling Consortium

- In 2014, WHO 2012 roadmap and the London Declaration on NTDs provided the impulse for the establishment of the Bill & Melinda Gates Foundation-supported NTD Modelling Consortium.
- **Motivation:** Recognizing many urgent policy issues for the control and elimination of NTDs via the use of quantitative tools, which can only be achieved through strong collaborations between modellers, epidemiologists, policy makers and field epidemiologists [126].
- **Questions to address**:

1. where (and under which epidemiological scenarios) do models predict that onchocerciasis can be eliminated with current strategies by the timelines proposed in the WHO (2012) roadmap.
2. In those scenarios where elimination cannot be achieved using the current strategy, which (and where) alternative and complementary intervention strategies should be deployed to facilitate/accelerate progress towards elimination.

Note: These questions formed part of the national health programmes and APOC's closure at the end of 2015 for onchocerciasis control and elimination.

Onchocerciasis Models

There are two basic models which Onchocerciasis models are build from: **EPIONCHO** and **ONCHOSIM**

EPIONCHO

EPIONCHO is a deterministic, population-based model that uses partial differential equations to describe, with respect to time and host age, the rate of change of the mean numbers of nonfertile and fertile, adult female worms per host; of microfilariae per milligram of skin and of infective (L3) larvae, per blackfly vector.

Bas a~nez and Boussinesq [127] gave a protype of the EPIONCHO without explicit age structure.

Filipe et al. [128] extended Basa~nez and Boussinesq [129] to incorporate host age and sex to account for varying age- and sex-specific microfilarial profiles in endemic areas of northern Cameroon, central Guatemala and southern Venezuela.

1. Parasite population regulation in humans

- **Parasite establishment**

A decreasing function that depends on vector biting rate and the mean number of L3 larvae per fly is assumed for L3 larvae establishment (and development into adult worms) within the human host [130].

Duerr et al. [131] assumed that the parasite establishment rate is an increasing (positive density-dependent) function of the number of adult worms already established. describing a phenomenon of immunosuppression that would explain profiles of microfilarial load that increase with host age.

- **Mating probability of female adult worms**

May [132] proposed that the probability that a female worm is mated depends on: i. the sex ratio (assumed to be 1:1 in Onchocerca volvulus); ii. the sexual system (assumed to be polygamous) and iii. the distribution of adult worms among the human host population

Onchocerciasis Models

- **Excess human mortality**

Walker et al. [133] proposed a density-dependent relationship between microfilarial load and relative risk of mortality (human excess mortality).

Little et al. [134] - relationship between microfilarial load and blindness incidence.

2. Parasite population regulation in vectors

- **Parasite establishment**

The probability of microfilariae (ingested by the vector) developing into L3 larvae is a decreasing (negative density-dependent) function of microfilarial load [135, 136].

- **Excess vector mortality**

Microfilarial intake and the rate of vector mortality has a density-dependent relationship such that the life expectancy of infected flies decreases with the number of ingested microfilariae [135].

3. Pre-treatment parasite dynamics

- **Endemic equilibrium situation**

Filipe et al. [128] presented an EPIONCHO model for the situation of endemic equilibrium before the inception of treatment control interventions.

- **Transmission seasonality**

Transmission of blackflies being confined to be more during the rainy months when the vectors have repopulated the breeding sites; this used a sinusoidal functional [137].

4. Post-treatment parasite dynamics

- **Ivermectin**

Basanez et al. [138] modelled ivermectin treatment with the standard dose of 150 mg/kg on the dynamics of skin microfilarial load and the proportion of adult female worms producing live microfilariae.

- **Moxidectin**

Awadzi et al. [139] studied moxidectin's effects by fitting the functions used by Basanez et al. [138]. It is a temporal dynamics of skin microfilarial loads.

Onchocerciasis Models

- **Coverage and adherence**

Basanez et al. [140] subdivide the human population into

i. fully compliant group who; takes treatment every round;
ii. two semi compliant groups who take treatment every other round alternately;
iii. a systematically non compliant,
iv. group who never takes treatment.

- **Infection dynamics**

The dynamics of infection intensity in human and vector hosts under treatment with ivermectin (or moxidectin) with hosts sex and adherence to treatment [140].

Other extension of EPIONCHO model

- Mating probability [141]
- Cumulative effect of treatment on female worm fertility [140]

The details of the modification and extension of ONCHOSIM can be found in [140]

ONCHOSIM

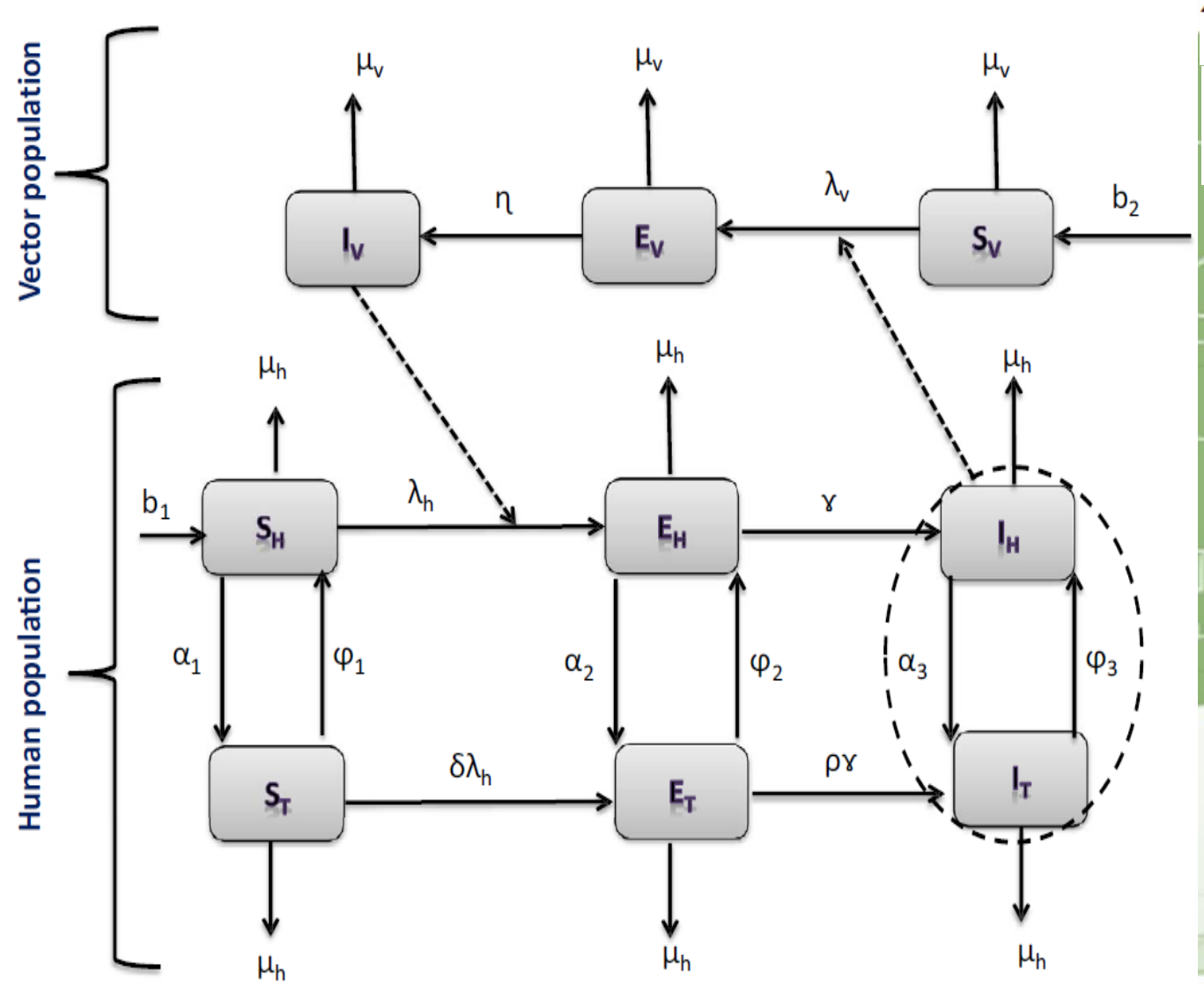
- ONCHOSIM is a stochastic, individual-based model for the transmission and control of onchocerciasis.
- The human population is represented as discrete number of individuals.
- The tracks changes in human population and individual infection status is in one-month steps and age.
- Human transmission is captured by deterministic submodel, representing the blackfly population dynamics and the fate of the parasite in the fly [140].

Modification and Extension of ONCHOSIM

1. Human population demography
2. Parasite population regulation in humans
   - Exposure to fly bites
   - Parasite establishment
   - Mating probability of female adult worms
   - Microfilarial counts in skin snips
   - Blindness and excess human mortality
3. Parasite population regulation in vectors
   - Parasite establishment
   - Transmission probability

Recent Mathematical Models of Onchocerciasis Transmission

Omondi et al. [142] presented an optimal control for onchocerciasis



$$\lambda_v(t) = \frac{q\beta(I_H + \kappa I_T)}{N},$$

$$\lambda_h(t) = \frac{p\beta V}{N}\frac{I_V}{V} = \frac{p\beta I_V}{N}$$

Three controls considered

i. personal protection against,
ii. black-fly, enhanced treatment,
iii. insecticide spraying.

Parameter	Description
b_1	Human recruitment rate
μ_h	Death rate of the human
β_h	The rate of transmission of the disease from black-fly to human
γ	Transfer rate from E_H to I_H class
α_1	Uptake rate of ivermectin
α_2	Uptake rate of ivermectin
α_3	Uptake rate of ivermectin
φ_1	Waning rate of ivermectin
φ_2	Waning rate of ivermectin
φ_3	Waning rate of ivermectin
κ	Modification parameter
ρ	Modification parameter
δ	Modification parameter
b_2	Vector recruitment rate
β_v	The rate of transmission of the disease from human to black-fly
η	Transfer rate from E_V to I_V class
μ_v	Death rate of the black–fly
u_1	Control parameter
u_2	Control parameter
u_3	Control parameter
r_0	Control efficacy

Recent Mathematical Models of Onchocerciasis Transmission

Omondi et al. [142] presented an optimal control for onchocerciasis

$$
\begin{aligned}
\dot{S}_H &= b_1 + \varphi_1 S_T - \lambda_h S_H(1-u_1(t)) - (u_2(t)\alpha_1 + \mu_h)S_H,\\
\dot{E}_H &= \lambda_h S_H(1-u_1(t)) + \varphi_2 E_T - (u_2(t)\alpha_2 + \gamma + \mu_h)E_H,\\
\dot{I}_H &= \gamma E_H + \varphi_3 I_T - (u_2(t)\alpha_3 + \mu_h)I_H,\\
\dot{S}_T &= u_2(t)\alpha_1 S_H - \delta\lambda_h S_T(1-u_1(t)) - (\varphi_1 + \mu_h)S_T,\\
\dot{E}_T &= u_2(t)\alpha_2 E_H + \delta\lambda_h S_T(1-u_1(t)) - (\rho\gamma + \varphi_2 + \mu_h)E_T,\\
\dot{I}_T &= u_2(t)\alpha_3 I_H + \rho\gamma E_T - (\varphi_3 + \mu_h)I_T,\\
\dot{S}_V &= b_2 - \lambda_v S_V(1-u_1(t)) - \mu_v S_V - r_0 u_3(t) S_V,\\
\dot{E}_V &= \lambda_v S_V(1-u_1(t)) - (\eta + \mu_v)E_V - r_0 u_3(t) E_V,\\
\dot{I}_V &= \eta E_V - \mu_v I_V - r_0 u_3(t) I_V,
\end{aligned}
$$

Omondi et al. [143] presented onchocerciasis Model with impulses : With pulse treatment of onchocerciasis with ivermectin that occurs every six months.

Reproduction Number

$$R_0 = \sqrt{\mathscr{R}_0} = \sqrt{R_0^h R_0^v},$$

where

$$R_0^h = \beta_h \gamma \mu_h^2 \phi^2 \left[\frac{\Phi_4 + u_2\alpha_1\delta(\varphi_2(Q_6 + u_2\alpha_3\kappa) + Q_2\rho(Q_3\kappa + \varphi_3))}{b_1 Q_1 Q_2 Q_3 Q_4 Q_5 Q_6 (1-\Phi_1)(1-\Phi_2)(1-\Phi_3)} \right],$$

$$R_0^v = \frac{\phi^2 b_2 \beta_v \eta}{Q_7^2 Q_8}, \quad \Phi_2 = \frac{u_2\alpha_2\varphi_2}{Q_2 Q_5}, \quad \Phi_3 = \frac{u_2\alpha_3\varphi_3}{Q_3 Q_6},$$

$$\Phi_4 = Q_4[Q_5(Q_6 + u_2\alpha_3\kappa) + u_2\alpha_2\rho(Q_3\kappa + \varphi_3)].$$

$$Q_1 = \alpha_1 u_2 + \mu_h, \quad Q_2 = \alpha_2 u_2 + \gamma + \mu_h, \quad Q_3 = \alpha_3 u_2 + \mu_h,$$

$$Q_4 = \varphi_1 + \mu_h, \quad Q_5 = \rho\gamma + \varphi_2 + \mu_h, \quad Q_6 = \varphi_3 + \mu_h,$$

$$Q_7 = \mu_v + r_0 u_3, \quad Q_8 = \eta + \mu_v + r_0 u_3, \quad \Phi_1 = \frac{u_2\alpha_1\varphi_1}{Q_1 Q_4}, \quad \phi = 1 - u_1.$$

Challenges and Future Directions

- **Relationship between operational endpoints, transmission breakpoints and stochastic fade-out**

- **Estimating basic and effective reproduction ratios:**

For O. volvulus, R_0 is defined as the number of mature female worms produced, on average, by a female worm during her reproductive lifespan in the absence of density-dependent constraints (the equivalent of the beginning of an epidemic in microparasites, when nearly all the host population is susceptible) [144].

- **Modelling the diagnostic performance of the skin snip method and serological assays in near-elimination scenarios**

- **Modelling hypoendemic onchocerciasis**

- **Spatial models of onchocerciasis transmission**

Hypoendemic Disease

A disease that is constantly present at a low incidence or prevalence and affects a small proportion of individuals in the area.

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