Module 1. Introduction to Targeted Neglected Tropical Diseases (NTDs)

Session 2. NTDs Overview
Reference Material for Group Exercise
LYMPHATIC FILARIOIS
Life Cycle (Vector) and Biology

**Adult female worms produce microfilariae which migrate to peripheral blood.**

**Mosquito takes blood meal, infecting person with L3 larvae.**

**Blood microfilariae ingested by mosquito.**

**Larvae develop into adult worms in lymphatic vessels.**
Lymphatic Filariasis

- Wuchereria bancrofti
- Brugia malayi, B. timori
Organism and Disease

- Passed from human to human by mosquitoes, which must survive at least ten days for maturation and transmission of infective larvae.
- Parasites live in the lymphatic system for 4-6 years, producing millions of microfilariae (mf).
- Infection acquired in childhood.
- Obstacle to healthy development.
Diagnostic Features mf

- Periodicity: at night in most places (daytime in Pacific islands)
- Length 250-300mm
- Width: about the diameter of a leukocyte
- Sheaths, sometimes visible with Giemsa
Effect of LF on the Lymphatic System

• Anatomy
  – Adults worms live in the lymphatic system
    • Cause initial dilation that leads to dysfunction

• Dysfunction
  – Accumulation of fluid (oedema) in tissues
  – Increased risk of infection
  – Transport of bacteria to lymph nodes is impaired, thus bacteria can multiply in the tissues
Adult LF Worms in Lymph Node
Suffering Caused by LF

- Physical
- Social
- Psychological
- Economic
Lymphatic Filariasis: the Poverty Cycle

- In India alone, US$1 billion is lost annually due to LF.
- Costs of managing the acute and chronic LF represent an enormous loss of resources.
- LF is primarily a disease of the poor because of its frequent prevalence in remote rural areas and impoverished peri-urban and urban areas.
- LF patients are physically incapacitated and cannot work, earn, or lead a normal life.
Twin Pillars of GPELF

- **Interrupt transmission**
  - Large-scale PC of “at risk” population for 5 years single-dose, once yearly 2-drug regimen

- **Morbidity control - relief of suffering**
  - Community-level care of those with LF
  - Management of lymphoedema, elephantiasis
  - Treatment of acute dermato-adeno-lyphadenitis
  - Surgical hydrocelectomy
Essence of the LF Elimination Strategy

- Reduce levels of mf in the blood.
- 5-6 rounds of ‘effective’ MDA will interrupt transmission.
- MDA will prevent new disease and halt early (subclinical) disease progression.
PC in Endemic Communities

In oncho co-endemic areas:
   Ivermectin (IVM) + Albendazole (ALB) 400 mg

In non oncho co-endemic areas:
   Diethylcarbamazine (DEC) 6 mg/kg + ALB 400 mg

Exclusion criteria:
   DEC + ALB: Children < 2 years of age
   Pregnant women
   IVM + ALB: Children < 90 cm tall
   Pregnant & women < 1 week post partum
   Very ill/very elderly
Target Population

- Whole communities if LF prevalence is ≥1%.
- MDA is based on the principle of directly observed treatment (DOT).
- ‘Effective’ MDA is defined by these goals:
  - Epidemiological coverage ≥65%
    # treated/total at risk population*100%
  - Geographic coverage should scale up to 100%
  - Program coverage ≥80% (before full scale up)
    # treated/total eligible targeted in endemic area*100%
  - National coverage ≥80% (when full scale up achieved)
    # treated/total eligible requiring PC at national level*100%
Onchocerciasis
Onchocerciasis - Transmission 1

- Caused by the nematode Onchocerca volvulus.
- Second leading cause of preventable blindness.
- Transmitted by the bite of an infected black fly: Simulium damnosum and other species, breeding in fast-flowing streams & rivers (well oxygenated water).
- Blindness caused by reactions precipitated by the death of the microfilaria (mf).
- People become blind early in life (20-30 years).
Interventions

- Larvicidal spraying of fast flowing rivers (OCP in 1974).
- Ivermectin use (from 1988).
- Onchocerciasis elimination Programme for the Americas (OEPA) established in 1992 (progress of programme very rapid because ‘vectors in the western hemisphere are less efficient than those elsewhere’).
- APOC in 1995 (CDTI).
- Since 2006 part of integrated PC implementation.
**OEPA:**

Launched in 1991  
Covers 6 countries  
400,000 at risk  
Twice a year Treatment

**APOC:**

Launched in 1995  
Covers 19 nations  
115 million at risk  
Annual Treatment
Target Population and Effective Coverage

- Community Directed Treatment with Ivermectin (CDTI).
- Entire communities are treated.
- Single dose of IVM per annum can kill first stage larvae (mf) in those infected and prevent transmission.
- To be ‘effective’
  - Epidemiological (therapeutic/drug) coverage ≥65%
  - Geographic coverage 100%
CDTI

- Empowerment of communities.
- Community decides when to distribute.
- Community collectively selects distributors.
- Distribution at convenience of community (seasonal).
- DHMT/NGO helps with training and monitoring.
TRACHOMA
Chlamydia trachomatis

• A bacterium with lots of different strains that infect the lining cells of the eye and genital tract. Particular strains of C. trachomatis cause trachoma.

• An infected eye may show evidence of inflammation known as active trachoma. One of the signs of active trachoma is called “trachomatous inflammation-follicular” (TF).

• Repeated episodes of active trachoma over many years can lead to trachomatous trichiasis (TT), in which the eyelashes are diverted so that they touch the eyeball. This can damage the cornea, affecting vision.
Trachoma Cycle

INFECTION THE EYES
Flies carrying the microorganism land on children’s eyes, to feed on discharge.

FAMILY CONTACT
Women who take care of children also get the infection.

SPREADING OUT
Flies that breed in human feces spread the disease to others.

Dirty hands or face cloths also spread the disease.

Source: The Carter Center (Al Granberg)
PROGRAMME MANAGERS' TRAINING COURSE FOR NTDs
TARGETED FOR CONTROL OR ELIMINATION BY PREVENTIVE CHEMOTHERAPY INTERVENTIONS

Module 1. Introduction to Targeted NTDs
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TRACHOMA GRADING CARD

- Each eye must be examined and assessed separately.
- Use binocular loupes (x 2.5) and adequate lighting (either daylight or a torch).
- Signs must be clearly seen in order to be considered present.

The eyelids and cornea are observed first for injured eyelashes and any corneal opacity. The upper eyelid is then turned over (everted) to examine the conjunctiva over the stiffer part of the upper lid (tarsal conjunctiva).

The normal conjunctiva is pink, smooth, thin and transparent. Over the whole area of the tarsal conjunctiva there are normally large deep-lying blood vessels that run vertically.

TRACHOMATOUS INFLAMMATION – FOLLICULAR
(TF): the presence of five or more follicles in the upper tarsal conjunctiva.

Follicles are round swellings that are paler than the surrounding conjunctiva, appearing white, grey or yellow. Follicles must be at least 0.5mm in diameter; i.e., at least as large as the dots shown below, to be considered.

TRACHOMATOUS INFLAMMATION – INTENSE (TI): pronounced inflammatory thickening of the tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels.

The tarsal conjunctiva appears red, rough and thickened. There are usually numerous follicles, which may be partially or totally covered by the thickened conjunctiva.

TRACHOMATOUS SCARRING (TS): the presence of scarring in the tarsal conjunctiva.

Scars are easily visible as white lines, bands, or sheets in the tarsal conjunctiva. They are glaering and fibrous in appearance. Scarring, especially diffuse fibrosis, may obscure the tarsal blood vessels.

TRACHOMATOUS TRICHIASIS (TF): at least one eyelash rubs on the eyeball.

Evidence of recent removal of irritated eyelashes should also be graded as trichiasis.

CORNEAL OPACITY (COI): easily visible corneal opacity over the pupil.

The pupil margin is blurred viewed through the opacity. Such corneal opacities cause significant visual impairment (less than 6/18 or 0.3 vision), and therefore visual acuity should be measured if possible.

TF: give topical treatment (e.g. tetracycline 1%).
TI: give topical and consider systemic treatment.
COI: refer for eyelid surgery.

Support from the partners of the WHO Alliance for the Global Elimination of Trachoma is acknowledged.
SAFE Strategy

S = Surgery for people with TT to prevent blindness

A = Antibiotics to clear infection

F = Facial Cleanliness: encourage improved hygiene

E = Environmental improvement: increased access to water and sanitation
Elimination Goals

• Elimination of trachoma as a public health problem by 2020:
  – TF in children aged 1-9 years < 5%, AND
  – TT less than 1 case unknown to the health system per 1,000 total population, both at district level

• SAFE intervention thresholds: if, at district level:
  – TF1-9 ≥30.0%: A,F,E (incl. MDA) for 5 years before re-survey
  – TF1-9 10.0-29.9%: A,F,E for 3 years before re-survey
  – TF1-9 5.0-9.9%: A,F,E for 1 year before re-survey
  – TF1-9 <5%: no A needed at community level; F&E if required
‘S’ - Surgery

• Simple and the most cost-effective procedure to prevent blindness.
• Trichiasis (TT) is a painful condition that affects sight and life.
• 3 procedures mostly used: BTR, Trabut, Cuenod-Nataf.
• All aim to re-establish the correct lid margins position and avoid corneal damage.
• Quality of surgical outcomes improves with:
  – Good surgical training
  – Good surgical materials
  – Good counseling of the patients
  – Good follow up (at 7-8 days)
‘A’ - Antibiotics

• Tetracycline eye Ointment (TEO)
  – For: people aged <6 months or who can’t take azithromycin
  – Dosage: both eyes BID for 6 weeks (~2 tubes)

• Azithromycin oral solution/tablets
  – For: people aged ≥6 months
  – Dosage: 20mg/kg to a maximum of 1g. Usually height-based dosing is used

• Azithromycin eye drops
  – No age restriction, no pregnancy restriction
  – Dosage: both eyes, BID for 3 days
‘F’- Facial Cleanliness

- Facial cleanliness is thought to be important because the flies that transmit *C. trachomatis* are attracted to discharges around the eyes.
  - Measuring facial cleanliness properly is difficult
  - Education sessions are useful and need to continue during SAFE implementation and after the achievement of the UIG
‘E’- Environmental Improvement

• ‘E’ aims at:
  – Increasing accessibility and use of latrines
  – Increasing accessibility of water in quantities that allow its use for personal hygiene

• ‘F’ and ‘E’ go together, as behavioral change can not happen if latrines and water are not accessible.

• Messages and demonstrations can be delivered best by non-medical staff (village leaders, religious leaders) and need to be repeated for a long time to have an effect.
Soil Transmitted Helminthiasis (STH)
Common Features of STHs

• Endemic in rural areas: most common diseases among the 2.7 billion people living <$2/day.
• Chronic diseases → long-term disability.
• ↑ risks related to pregnancy (adverse outcomes).
• Affect adult productive capacity.
• In children
  – hinder normal growth
  – intellectual & cognitive development
• Geographically confined
  – although communicable
  – strictly linked to the environment
  – complex reproductive cycles
**STHs Targeted in PC**

- **Ascariasis** (*Ascaris lumbricoides*)
  - Roundworm

- **Trichuriasis** (*Trichuris trichiura*)
  - Whipworm

- **Hookworm disease** (*Ancylostoma duodenale, Necator americanus*)

- **Strongyloidiasis** (*Strongyloides stercoralis*)
  - Threadworm
Ascaris Life Cycle

[Diagram showing the life cycle of Ascaris, including stages such as infective stage, diagnostic stage, fertilized egg, and unfertilized egg.]
Tissue Migration

• Through liver, then lungs (1-14 days post infection).
• Associated with eosinophilia, asthma-like complaints.
• Pneumonitis may be seasonal in some areas.
• Heavy infections may cause hepatosplenomegaly.
Intestinal Phase

- Pre-patent period 60-75 days.
- Vague abdominal complaints.
- May block bile or pancreatic ducts.
- Rarely intestinal obstruction.
**Trichuris Life Cycle**
Hookworm Life Cycle
Morbidity

- Adult hookworms tissue and blood feeders.
- Anemia related to worm burden.
- Significant public health problem, especially among women of child-bearing age (WCBA).
- Trichuris-associated rectal prolapse.
**Strongyloides stercoralis: Life Cycle**

1. Eggs deposited in intestinal mucosa, hatch, and migrate to lumen.
2. Rhabditiform larvae in the intestine are excrated in stool.
3. Eggs are produced by fertilized female worms.
4. Rhabditiform larvae hatch from embryonated eggs.
5. The rhabditiform larvae develop into infective filariform.
6. Infective filariform larvae penetrate the intact skin initiating the infection.
7. The filariform larvae enter the circulatory system, are transported to the lungs, and penetrate the alveolar spaces. They are carried to the trachea and pharynx, swallowed, and reach the small intestine where they become adults.
8. Adult female worm in the intestine.
9. Autoinfection: Rhabditiform larvae in large intestine, become filariform larvae, penetrate intestinal mucosa or perianal skin, and follow the normal infective cycle.
10. Development of adults
11. Development of infective larvae

**Legend:**
- = Infective Stage
- = Diagnostic Stage
Diagnosis

- Kato Katz for STH but not suitable for the detection of larvae of S. stercoralis.
- Baermann test (and Koga Agar plate culture) for S. stercoralis.
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**STH Control**

The diagram illustrates the life cycle of *Ascaris lumbricoides*, an intestinal nematode. The cycle begins with the embryonated egg, which is infective when ingested. The egg hatches in the intestine, releasing larvae that can infect the lungs, trachea, pharinx, and finally the small intestine. Eggs are passed in faeces, completing the cycle. The diagram is adapted and redrawn from NCDC.
### WHO Recommended PC for STH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole (ALB)</td>
<td>400mgs</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Mebendazole (MBD)</td>
<td>500mgs</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Pyrantel</td>
<td>10mg/kg</td>
<td></td>
</tr>
<tr>
<td>Levamisole</td>
<td>2.5mg/kg</td>
<td>Single dose for school-aged children (SAC): 80 mg</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>200µg/kg</td>
<td>in preparation</td>
</tr>
</tbody>
</table>
Target Populations

- School-aged children (SAC, 5<15 years).
- Pre-school children (PSC) 1-4 years.
- Women of childbearing age (15-39 years).
- Women in ANCs in 2nd and 3rd trimesters.
Benefits of STH Treatment

- ↓ School absenteeism by 25%.
- ↓ Wasting malnutrition by 60%.
- ↓ Moderate anaemia by 59%.
- Improvement of growth
  - 20% in weight
  - 7% in height
- Benefits of a hookworm-free childhood at
  - 45% of adult wages
- Increase in per capita income by 45%.
- Control of STH can contribute to poverty reduction.
Better Access to Sanitation and Safe Water...

- Long term measure.
- Slow impact but long-lasting.
- More expensive.
- Reduction of transmission.
- Other health benefits.
- Community involvement.
...Better Hygienic Practices Through Health Education

- Low cost.
- Difficult to assess.
- Additional health benefits.
- Community involvement.
- Impact on the new generation.
- Use to reduce transmission.
STH Programs in Schools

• Expanded donations of de-worming drugs provide a new opportunity to develop school health packages.
  – Nutrition
  – Safe water
  – Hygiene education
  – Sanitation
  – De-worming
Schistosomiasis
Schistosome Life Cycle
Schistosome Species

- *Schistosoma haematobium* (African, urinary)
- *Schistosoma mansoni* (African/South American, intestinal)
- *Schistosoma intercalatum* (African, intestinal)
- *Schistosoma japonicum* (Asian, intestinal)
- *Schistosoma mekongi* (Asian, intestinal)
Common Features of Schistosomes

- Transmission linked to contaminated fresh water in rural areas.
- Most infections without symptoms.
- Chronic diseases leading to long-term disability.
- Affect adult productive capacity.
- Increase the risks related to pregnancy (adverse outcomes).
- In children:
  - hinders normal growth,
  - intellectual and cognitive development
- Geographically confined:
  - although communicable, strictly linked to the environment (presence of adequate snail species)
Pathology of Urogenital Schistosomiasis

- Pathology is due to immune response to eggs (not to the adult worm).
- Egg deposition in genitourinary tract leads to:
  - Hematuria
  - Female genital schistosomiasis
  - Bladder calcifications
  - Bladder cancer
Pathology of Urogenital Schistosomiasis

- Pathology is due to immune response to eggs (not to the adult worm).
- Egg deposition in intestinal tract and tissues causes:
  - Intestinal pathology
  - Anemia
  - Weight loss
  - Hepatosplenic disease including ascites/cirrhosis
Epidemiology & Transmission Patterns

- Transmission can be quite focal and is facilitated by:
  - Poor sanitation
  - Human activities that bring people into contact with contaminated water
  - Environmental modifications affect vector’s ecosystem
**Schistosomiasis Control**

- **Health education**
- **Safe water supply**
- **Behavior change**
- **Snail control:**
  - Molluscicides
  - Management of water scheme

**Drugs:** PZQ

**Snails**
- **S. m.**
- **S. j.**
- **S. h.**

**Cercaria**
- Free-swimming
- Penetrates in skin

**Human**
- Mature in intrahepatic portal blood
- in faces
- in urine

**Snail control:**
- Molluscicides
- Management of water scheme

**Sanitation**
- Drugs: PZQ
Why Treat Schistosomiasis?

• To cure and prevent chronic morbidity by reducing the worm burden (and therefore number of eggs in the body).
• To prevent healthy people to become infected by reducing the source of infection (interrupting transmission).
• To promote health education and integration with other programmes.
Target Groups for Preventive Chemotherapy

- Total population if prevalence is high.
- School-aged children (5<15 years old).
- Women of childbearing age (15-39 years old).
- Special occupational groups:
  - Workers in water irrigation schemes
  - Fishermen
Praziquantel (PZQ) Delivery

- Treatment dose: based on a height pole, weight can also be used.
- Side effects are diminished by administering PZQ after food.
- Can be safely combined with ALB as part of a de-worming program.
- PC intervention should be considered if prevalence is > 10%.
Food-Borne Trematodiases
Overview

- FBT life cycle
- FBT in liver
  - Asian liver fluke (adult worm in bile ducts)
    - *Opisthorchis viverrini*
    - *Clonorchis sinensis*
  - Large liver fluke (*Fasciola hepatica, F. gigantical*)
- FBT in intestinal tract
  - Minute intestinal flukes
- FBT in lung
  - Lung trematode (*Paragonimus westermani*)
FTB Life Cycle
Asian Liver Flukes

- 2 species
  - *Opisthorchis viverrini*
  - *Clonorchis sinensis*
- Adult worm live in bile duct of liver: provoking morbidity
- Transmission: consumption of raw or insufficiently cooked fresh water fish
- Diagnosis: identifying eggs in faeces using parasitological techniques (e.g. Kato-Katz) → confusion with eggs of minute intestinal flukes!
- Treatments: Praziquantel
Asian Liver Fluke

- Adult in bile ducts of human, cat, & dogs

Cyprid Fish:
- length: 5-10 cm
Distribution – Opisthorchis viverrini
Clinical Manifestations and Consequences

- Obstructive jaundice
- Cholangitis
- Choleystitis
- Gallstones
- Hepatomegaly
- Cholangiocarcinoma
Cholangiocarcinoma (CCA) Development

Exposure

Inflammation
Periportal fibrosis
Advanced periportal fibrosis
Hepatobiliary abnormalities

Preclinical
Clinical
Disease

Intervention efficacy
High
Low

Likelihood of progression

CCA

OV Infection

TRENDS in Parasitology
Risk Factors for CCA in Thailand

- Host immune research: HLA type, susceptibility gene
- Xenobiotic metabolism
- Familial/genetic susceptibility
- Others: smoking, environment

Liver fluke
Carcinogens
Other factors
Liver Morbidity Assessment
Suspected CCA Case

Lao patient (male, age 65 years): solid mass lesion with well-defined contour in right liver lobe (left); mechanical bile duct dilation due to the mass (right).
Control

Prevent raw food consumption

Praziquantel:
= individual
= mass-treatment

Snail Control:
environmental modifications
Large Liver Fluke (*Fasciola sp.*)

- 2 species endemic in the region:
  - *Fasciola hepatica*
  - *Fasciola gigantica*
- Adult worm live in liver (less in bile ducts) → liver morbidity
- Transmission: consumption of water weeds (vegetables) contaminated with metacercarieae.
- Diagnosis: clinical signs, parasitological and serological tools
- Treatments: Triclabendazole
**Fasciola sp. – eggs**

Large eggs: 80 x 140 μm;
Non-embryonated, with operculum → confusion with MIF
Control

Prevent raw food consumption

Triclabendazole:
= individual
= mass-treatment

Control in reservoir hosts
Minute Intestinal Flukes

- Several species of small adult flukes living in the intestinal tract → minute intestinal flukes (MIF)

- Eggs are small and with similar shape as *Opisthorchis/Clonorchis* eggs → confusion possible
  - Specific diagnostic tests required (PCR, etc.)

- Signs/symptoms:
  - Unspecified abdominal signs and symptoms (most infections asymptomatic)

- Treatment: Praziquantel
Lung Fluke (*Paragonimus spp.*)
Saykham, Vientiane, Lao PDR
Control Prevent raw food consumption

Praziquantel:
- individual
- mass-treatment

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