Acute Febrile Illnesses
Malaria and Dengue

Global Health Course
Center for Global Health
Colorado School of Public Health
University of Colorado Anschutz Medical Campus
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Formerly at Centers for Disease Control and Prevention
The Presentation

- Acute Febrile Illnesses
  - Definition, epidemiology, complexity
- Dengue
  - Life cycle, natural history and epidemiology
  - Diagnosis
  - Clinical course and management related to outcome
  - Prevention
- Malaria
  - Life cycle, natural history and epidemiology
  - Diagnosis
  - Treatment
  - Prevention
What is an Acute Febrile Illness (AFI) ?

- Frequently used criteria, since no internationally agree upon definition:
  - acute onset with temp $\geq 38^\circ$C (measured or reported)
  - ‘non-localizing’ signs / symptoms
  - 2-7 days duration

- Large number of infectious diseases have no pathognomonic signs/symptoms except for their most severe form. Fever is the ‘least common denominator’.

- Severe limitations in knowledge (global, regional) to guide clinicians – ‘what can I expect where I am working’
Etiology of Severe AFI in Low- / Middle-Income Countries

- **Systematic review of literature**
  - Studies from 1980-2013
  - Prospective assessment of patients admitted to ED or hospital
  - Rigorous laboratory-based case definitions

- **Results**
  - 2,729 studies → 863 met criteria for full review → 45 included
  - Locations: East Africa 54%; North Africa 19%; West Africa 5%; South Central Asia 8%; South East Asia 14%, and West Asia 0.4%. None from South and Middle Africa, Eastern Asia, Oceania, Latin America, Caribbean and European regions. None from LMICs
  - **Etiologies**
    - Bacterial and fungal infections – blood culture in (64%). 10.7% of illnesses attributed; 8.5% in children, 13.9% in adults
    - Plasmodium spp - most commonly identified organism
    - Bacterial zoonoses and viral infections – infrequent testing

Adapted from Prasad N, et al. PLOS ONE. 2015; DOI: 1371
Etiology of Severe AFI in Low- / Middle-Income Countries

- **Conclusions – Limitations**
  - Only representative of severe AFI. No OPD or primary care settings evaluated
  - Not geographically representative. Few rural areas, no LIMCs
  - Not representative of all age groups
  - Most studies could not determine seasonal variation or inter-annual periodicity
  - Insufficient data to assess role of HIV infection

Adapted from Prasad N, et al. PLOS ONE. 2015; DOI: 1371
Etiology of AFI in Asian Children Enrolled in Dengue Vaccine Trials

- Prospective, active surveillance for AFI among cohort of 2-14 y.o. healthy children (n=1500) followed for ~237 days
- Indonesia, Malaysia, Philippines, Thailand, Vietnam
- AFI = at least 2 days of temp $\geq 38^\circ$ C (axillary)
- 96.5% presented within 5 days after fever onset
- Laboratory diagnostics on acute and convalescent serum
  - DEN – NS1, IgM anti-DENV (seroconversion)
  - CHIK – IgM anti-CHIKV (seroconversion)
  - Leptospirosis - IHA (IgM / IgG)
  - *Salmonella typhi* - IgM anti-S. typhi
  - Rickettsia – IFA IgM/IgG
  - Influenza – IgM anti-influenza A
  - Hepatitis A – IgM anti-HAV

Adapted from Capeding MR, et al. PLOS NTD. 2013; 7(7): e2331
Etiology of AFI in Asian Children Enrolled in Dengue Vaccine Trials

- Febrile episodes = 374 = 33.6 / 100 person years (range 21-41)
- Clinical diagnoses (84%)
  - Pharyngitis, including nasopharyngitis - 33% (124/374)
  - Upper and lower respiratory tract infections – 19% (72 / 374)
  - Tonsillitis – 11% (39/374)
  - Viral infection excluding dengue - 10% (37/374)
  - Dengue - 9% (34/374)
  - Gastroenteritis – 2% (8/374)

Adapted from Capeding MR, et al. PLOS NTD. 2013; 7(7): e2331
Etiology of Acute Febrile Illness, Asian* Children 2-15 years, 2010-2011

165 (57%) children with positive diagnostic testing

- CHIK (35%)
- S. Typhi (29%)
- DEN (24%)
- Influenza (12%)
- Rickettsia (4%)
- Hep A (1%)

*Indonesia, Malaysia, Philippines, Thailand, Vietnam
Differential Diagnosis of AFI

- Chikungunya
- Malaria
- Influenza
- Leptospirosis
- Typhoid
- Meliodosis
- Rickettsiodoses
- Bacterial sepsis
- Zika fever
- Measles
- Enterovirus
- Hepatitis A
- Erythema infectiosum (5th disease)
- Roseola infantum (6th disease)
- HIV seroconversion illness
- Rubella
- Epstein-Barr virus
- Scarlet fever
- Meningococcemia
- Adenovirus infections
- Viral hemorrhagic fevers
  (Hantavirus, Crimean-Congo HF virus, Ebola)
Dengue
Flaviviruses

- Tick-borne encephalitis virus
  - West Nile Virus
  - Murray Valley Encephalitis Virus
  - Japanese Encephalitis Virus
  - St. Louis Encephalitis Virus
  - Zika
  - DENV 1
  - DENV 3
  - DENV 2
  - DENV 4
  - Yellow Fever Virus

Flaviruses
Dengue Virus Transmission

Mosquito acquires virus during feeding
virus replicates in mosquito

Mosquito infects susceptible person

Mosquito infects humans – virus in lymph nodes, other organs blood

Mosquito acquires virus during feeding
virus replicates in mosquito
The Mosquito Vectors

- **Aedes aegypti**
  - Well adapted to transmit DENV
    - Human blood meal
    - Breeds year round
  - Day biter
  - Breeds near human habitation

- **Aedes albopictus**
  - Less adapted to transmit DENV
    - Multiple animal blood meals
    - Goes into diapause when cold
  - Day biter
  - Breeds near human habitation
Outcome of Dengue Virus Infection

Infection Incidence
~1-5% / year

- Asymptomatic: 75%
- Symptomatic: 25%
  - Dengue Fever: 80-85%
  - Severe Dengue: 15-20%

Survive

Death: 0.1 - 5%

Adapted from Vaccine 2004; 22: 1275-1280
Dengue is a Global Problem

Adapted from Bhatt, S et al Nature 2013; 496: 504-507
Dengue in Africa

- 4 DENV types
- 22 countries = local transmission & dengue in returning travelers
- 12 countries = only travelers
- Anti-DENV prevalence = 13 – 40% in limited studies
- Aedes aegypti present in 66% of countries

From: Emer Infect Dis 2011; 17:1349-54
How Many Dengue Deaths Occur?

- WHO – 20,000 / year
- No population based studies until recently
- Problem
  - deaths occur among people with an AFI syndrome
  - difficult to know if dengue
- Expert opinion – deaths poorly reported if reported at all
Dengue Deaths in Puerto Rico

- **2007**: retrospective chart review of dengue deaths
  - Only 25% of death certificates listed ‘dengue’ as 1° or 2° cause

- **2010-2012**: EFASS - prospective, active case finding
  - Active surveillance for suspect cases identified by AFI symptoms
  - Early identification with systematic specimen collection

- **Results**
  - (n=311 AFI deaths)
  - 91% had serum or tissue specimens
  - 40% had pathogen identified; dengue (19%), lepto (11%), staph & strep (3%), influenza (1%), 0.3% each Neisseria, Burkholderia, Proteus, Clostridium, Cryptococcus, Klebsiella
  - 3-fold > than estimated by conventional surveillance

Dengue Epidemiology

- An acute febrile illness (AFI syndrome)
- Incidence: high endemic + cyclical epidemics
- Highly seasonal (rainy season)
- Often several circulating DENV types
- Peak age of incidence varies by region

Dengue Not Just a Disease of Children
Age Distribution of Dengue, Puerto Rico, 2010

47% of cases in adults
Dengue Diagnostic Testing

**Incubation Period**

**Febrile Phase**

**Critical Phase**

**Convalescent Phase**

**Fever Onset**

**MAC ELISA for IgM anti-DENV**

**Exposure**

**Days Post Onset of Fever**

IgG anti-DENV of no use in acute illness diagnosis

Combined Sensitivity of Dengue Diagnostic Tests*

*DENV rRT-PCR + IgM anti-DENV

*DENV rRT-PCR or NS1 antigen

Days Post Illness Onset

Sensitivity (%)

*Comparison to IgM anti-DENV seroconversion

### Dengue Diagnostic Testing Algorithm

**Days Post-Onset of Illness (DPO)**

<table>
<thead>
<tr>
<th>Day Post Onset of Illness</th>
<th>Diagnostic Tests</th>
<th>Probability to confirm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>rRT-PCR NS1: +, IgM anti-DENV: -</td>
<td>~90%</td>
</tr>
<tr>
<td>3-7</td>
<td>rRT-PCR NS1: +, IgM anti-DENV: +</td>
<td>~90%</td>
</tr>
<tr>
<td>&gt;7</td>
<td>rRT-PCR NS1: -, IgM anti-DENV: +</td>
<td>~90%</td>
</tr>
</tbody>
</table>

Dengue Rapid Diagnostic Tests

- A number of tests available
- Differ in analytes
  - IgM anti-DENV
  - NS1
  - NS1 & IgM anti-DENV
- Differ in performance
  - Overall - modest sensitivity and good specificity
  - Combination NS1 & IgM anti-DENV perform best
- When to use (assuming a good test)
  - If established laboratory testing not available
  - To identify dengue outbreaks
  - If (+) = dengue, if (-) = must use clinical judgment

Hunsperger EA, et al. PLOS Negl Trop Dis. 2014; 8:e3171
Laboratory vs Clinical Diagnosis of Dengue
Ratchaburi, Thailand, 2006 - 2009

- Acute Febrile Illnesses among cohort of 5-13 y.o.
- Laboratory-based dengue definition = 394 cases
  - (fever + DENV viremia)

<table>
<thead>
<tr>
<th>WHO Clinical Case Definitions*</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated Fever (UF)</td>
<td>210</td>
<td>53.3</td>
</tr>
<tr>
<td>Dengue Fever (DF)</td>
<td>142</td>
<td>36.0</td>
</tr>
<tr>
<td>Dengue Hemorrhagic Fever (DHF)</td>
<td>42</td>
<td>10.7</td>
</tr>
<tr>
<td>Total</td>
<td>394</td>
<td>100</td>
</tr>
</tbody>
</table>

*WHO 2004 or 2009

From Sabchareon, A et al. PLoS NTD 2012; 6: e1732
Proper Case Management Critical to Survival

- Timely diagnosis improves prognosis
- Need to recognize severe dengue
  - Recognition of “warning signs”
  - Recognition of compensated or decompensated shock
  - A subset of individuals develop dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS)
  - Life threatening, requires critical, supportive care
- Proper case management reduces fatality rate to < 1%
  - Proper fluid management and resuscitation of plasma-leakage

CDC Dengue Case Management
E-Learning Course

Dengue Case Management Educational Tool
- Designed for healthcare providers
- Includes case management steps recommended by WHO and incorporated in many dengue endemic countries

Free CME Training:  cdc.gov/dengue/training/cme.html
Clinical Course of Dengue

**Mosquito bite**
- Range: 3 to 14 d; usually 4 to 7 days

**Incubation**
- Range: 2 to 7 days; usually 3 to 5 days

**Viremia**
- 1 to 3 days; usually <48 hrs

**Febrile Phase**
- Usually 3 to 5 days

**Critical Phase**
- Usually 3 to 5 days

**Convalescent Phase**
- Typically uncomplicated DHF/DSS lasts for 10 to 12 days
Febrile Phase

- Corresponds to fever which lasts 2 – 7 days and can be biphasic
- Defervescence occurs on day 3 – 8 of illness
  - Defined as when body temperature drops to less than 38.0°C & remains below this level
Clinical Manifestations in Febrile Phase

Sudden onset of fever:
Flushed or erythema of the face, neck, and chest for 1 to 2 days. May have injected pharynx and red lips.

Classic signs and symptoms: headache, retro-orbital eye pain, arthralgia, myalgia, or hemorrhagic manifestation. Encephalitis can present early while febrile.

Days 2 to 6 post onset:
Macular or maculopapular truncal rash that spreads to face and extremities.
Laboratory Findings in Febrile Phase

- Leukopenia
- Mild-to-moderate thrombocytopenia
- Normal or slightly increased HCT
- Elevated AST and ALT
Critical Phase

- Occurs around time of defervescence
  - Lasts for 24 to 48 hours
  - Most patients improve but a proportion (15-25%) develop clinically significant plasma leakage due to an increase in vascular permeability
  - Signs of plasma leakage:
    - Increasing HCT
    - Hypoproteinemia
    - Pleural effusions
    - Ascites
Petechiae may appear, especially on lower extremities. **Warning signs of severe dengue** may develop:

- Severe abdominal pain
- Persistent vomiting
- Ascites, pleural effusion
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- Drop in PLT with increase in HCT

- Intravascular volume depletion secondary to plasma leakage
- Severe hemorrhage may occur especially if there is prolonged shock
- Severe organ impairment may occur: hepatitis, myocarditis, pancreatitis, neurodengue

**Clinical Manifestations in Critical Phase**

Days

-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

- Incubation
- Viremia
- Critical Phase
- Convalescence

1 to 2 days
Laboratory Findings in Critical Phase

- Leukopenia
- Moderate-to-severe thrombocytopenia
- Increased HCT
- Elevated AST and ALT
Convalescent Phase

- Gradual re-absorption of extravascular fluid takes place in 48–72 hours, and diuresis ensues

- General well being improves, hemodynamic status stabilises, and patient may become bradycardic

- Laboratory
  - HCT stabilises or may lower due to dilutional effect of reabsorbed fluid
  - WBC usually starts to rise soon after defervescence
  - Recovery of platelet count is typically later than WBC
Basic Steps to Patient Assessment

- **Differential diagnosis:** Is it dengue?
  - Clinical and laboratory diagnosis

- **Assessment of dengue patient**
  - Which **phase** of dengue? (febrile/critical/convalescent)
  - Are there **warning signs** for severe disease?
  - What is **mental status**?
  - What is **hydration** and **hemodynamic status**?
  - Signs/symptoms of **plasma leakage** or **bleeding** present?
  - Does patient require hospitalization?
# Management of Dengue

<table>
<thead>
<tr>
<th><strong>Group A</strong></th>
<th><strong>Group B</strong></th>
<th><strong>Group C</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>(all of following)</td>
<td>(any of following)</td>
<td>(any of following)</td>
</tr>
<tr>
<td><em>Home</em></td>
<td><em>Hospitalization</em></td>
<td><em>Hospitalization</em></td>
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</table>

### Group A
- Getting adequate volume of oral fluids
- Passing urine at least once every 6 hours
- Does not have any warning signs
- Has stable hematocrit and hemodynamically stable
- Does not have co-existing conditions

### Group B
- Has warning signs
- Has co-existing condition: diabetes mellitus, renal failure, or is infant, pregnant or elderly
- Has social circumstances such as living alone or living far away without a reliable means of transport

### Group C
- Severe plasma leakage with shock and/or fluid accumulation with respiratory distress
- Severe bleeding as per clinician
- Severe organ impairment: AST or ALT $\geq 1000$ and/or impaired consciousness
Identify Early Signs of Shock

Important to identify early signs of shock including narrowing pulse pressure with rising diastolic, delayed capillary refill and tachycardia in absence of fever.
Intravenous Fluids And Dengue

• **What?**
  - Use isotonic solutions (Ringer’s Lactate, Normal Saline)
  - Colloids (albumin) preferred if blood pressure has to be restored urgently (e.g., Group C)

• **When?**
  - Limit IV fluids in febrile phase unless dehydrated and/or not able to take enough liquids by mouth
  - Plasma leakage occurs for 24 - 48 hours. IV fluids are usually needed for only 24 to 48 hours.

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Intravenous Fluids And Dengue

• How much?
  – Give minimum IVFs required to maintain good perfusion and urine output of at least 0.5 ml/kg/hr.
  – Volume based on ideal body weight if overweight.
  – Reduce IV fluids gradually when rate of plasma leakage decreases towards end of critical phase. Indicated by:
    • Increasing urine output and adequate oral fluid intake
    • Hematocrit decreases below baseline value in a stable patient.

REMEMBER: This is not acute gastroenteritis. Extravasated fluids remain in body and need to be reabsorbed

CDC Dengue Case Management E-Learning Course

Dengue Case Management Educational Tool
- Designed for healthcare providers
- Includes case management steps recommended by WHO and incorporated in many dengue endemic countries

Free CME Training: cdc.gov/dengue/training/cme.html
The Dengue Prevention Framework

Primary Prevention
- Integrated Vector Control
- Vaccines
- Surveillance
- Diagnostics

Secondary Prevention
- Case Management

Adapted from:
Malaria
Malaria, 2015

- Cases: 214 million globally (range 149-303 million)
- Deaths: 438,000 (range 236,000 – 635,000)
  - 91% occur in sub-Saharan Africa
- Population at risk: 3.2 billion (50% of world’s population)
- Affected countries: 97 countries and territories with ongoing transmission

From: Roll Back Malaria Partnership www.rollbackmalaria.org
Species of Plasmodium

- *Plasmodium falciparum* - responsible for majority of deaths globally and most prevalent species in sub-Saharan Africa
- *Plasmodium vivax* - prevalent in Southeast Asia and Latin America. Has dormant liver stage, which can reactivate with clinical symptoms
- *Plasmodium ovale* – accounts for small percentage of infections. Has dormant stage that can reactivate
- *Plasmodium malariae* – accounts for only a small percentage of infections
- *Plasmodium knowlesi* – infects primates and has led to human malaria, but the exact mode of transmission is unclear
Animated lifecycle of the malaria parasite

**TRANSMISSION TO MAN**

- Sporozoites
- Oocysts
- Ookinete
- Diploid Zygote
- Macrogametocyte (Exflagellation)
- Macrogametocyte

**LIVER**

- Sporozoites
- Nucleus
- Hypnozoite
- Infected Hepatocyte
- Schizont
- Merozoites
- Erythrocyte
- Gametocytes
- Ring
- Trophozoite
- Schizont

**43 – 48 h**

Cycle leading to clinical symptoms

**P. vivax dormant stage**

**TRANSMISSION TO MOSQUITO**

- Macro-gametocyte
- Diploid Zygote
- Ookinete
- Oocysts
- Sporozoites

**9 days**

15 mins

**5.4 days**

1h

12-36h

9-12 days

15-30 mins

9 days

5.4 days

12-36h

9-12 days
The Global Malaria Mapper http://www.worldmalariareport.org/
Rates of *P. falciparum* parasitemia, children 2-10 years, Africa, 2000-2015

Source: http://www.nature.com/doifinder/10.1038/nature15535
Incidence of *P. falciparum* Malaria, Africa, 2000-2015

Source: [http://www.nature.com/doifinder/10.1038/nature15535](http://www.nature.com/doifinder/10.1038/nature15535)
The Bible

http://www.who.int/malaria/publications/atoz/9789241549127/en/
Disease Classification

- **Uncomplicated malaria** - caused by all *Plasmodium sp*
  - Symptoms present (fever) but no signs / symptoms or laboratory findings of organ dysfunction

- **Severe malaria** – can occur with *P. falciparum, vivax and knowlesi*
  - If initial infection not promptly treated, can progress to severe malaria
  - **Symptoms:** impaired consciousness, prostration, multiple convulsions, hypoglycemia, acidosis, severe anemia, renal impairment, pulmonary edema, jaundice, significant bleeding, shock, hyperparasitemia (>10%) 

- **Cerebral malaria** - only caused by *P. falciparum*
  - manifests with CNS symptoms, such as coma.
Diagnosis

- In malaria-endemic areas, malaria should be suspected in patients presenting with a history of fever ≥ 37.5 °C and no obvious cause.
- Patients with suspected malaria should have parasitological confirmation with either microscopy or RDT before antimalarial treatment is started.
- Treatment based on clinical grounds should only be given if diagnostic testing is not accessible within 2 hours, particularly if suspected severe malaria.
- Both microscopy and RDTs must be supported by a quality assurance program.
- Where *P. vivax* is common and microscopy not available, a combination RDT that allows detection of *P. vivax* (pLDH antigen from *P. vivax*) or pan-malarial antigens (Pan-pLDH or aldolase) should be used.
- Antimalarial treatment should be limited to cases with positive tests, and patients with negative results should be reassessed for other common causes of fever and treated appropriately.

Treatment of Uncomplicated Malaria

- Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in 1st trimester) with one of the following recommended ACTs: (see WHO Guidelines for dosing)
  - artemether + lumefantrine
  - artesunate + amodiaquine
  - artesunate + mefloquine
  - dihydroartemisinin + piperaquine
  - artesunate + sulfadoxine–pyrimethamine (SP)
- Duration: ACT regimens should provide 3 days treatment
- Objectives: To cure infection as rapidly as possible and prevent progression to severe disease. The public health objectives are to prevent onward transmission of infection to others and prevent the emergence and spread of resistance to anti-malarial drugs.

Treatment of Recurrent Malaria - I

• Recurrence of *P. falciparum* malaria can result from re-infection or recrudescence (treatment failure).

• Treatment failure = drug resistance, or sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics or substandard medicines. Important to determine if treatment failure and the reason.

• Treatment failure should be confirmed parasitologically - use of microscopy or LDH-based RDTs since RDTs that detect histidine-rich protein-2 (PfHRP2) may remain positive for weeks after the initial infection (false positive).

• To not miss treatment failures, new malaria patients should be asked whether they received antimalarial treatment within the preceding 1–2 months.

Treatment of Recurrent Malaria - II

• FAILURE WITHIN 28 DAYS: The recommended second-line treatment is an alternative ACT known to be effective in the region.

• FAILURE AFTER 28 DAYS: Recurrence of fever and parasitaemia > 4 weeks after treatment may be due to either recrudescence or a new infection. The distinction can be made only by PCR genotyping of parasites from the initial and the recurrent infections.

• As PCR is not routinely used in patient management, all presumed treatment failures after 4 weeks of initial treatment should, from an operational standpoint, be considered new infections and be treated with the first-line ACT. However, reuse of mefloquine within 60 days of first treatment is associated with an increased risk for neuropsychiatric reactions, and an alternative ACT should be used.

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA IN SPECIAL RISK GROUPS

- First trimester of pregnancy
- Lactating women
- Infants less than 5kg body weight
- Patients co-infected with HIV
- Non-immune travelers
- Uncomplicated hyperparasitemia (density ≥4%)

TREATMENT OF SEVERE P. FALCIPARUM MALARIA

• Mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%.
• Prompt, effective antimalarial treatment and supportive care drops the rate to 10–20%.
• Within the broad definition of severe malaria some syndromes are associated with lower mortality (e.g. severe anemia) and others with higher mortality rates (e.g. acidosis).
• Risk for death increases in the presence of multiple complications.

TREATMENT OF SEVERE P. FALCIPARUM MALARIA

• Treat adults and children (including infants, pregnant women in all trimesters, lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT.
  – Dosing modifications for artesunate indicated for young children
  – Parenteral alternatives when artesunate is not available - use artemether in preference to quinine

• Intensive treatment required for the signs and symptoms associated with Severe Malaria

NATIONAL ADAPTATION and IMPLEMENTATION

• The choice of ACT in a country or region should be based on optimal efficacy, safety and adherence.

• When possible: use fixed-dose combinations rather than co-blistered or loose, single agent formulations; and for young children and infants, use pediatric formulations, with a preference for solid formulations (e.g. dispersible tablets) rather than liquid formulations

Malaria Elimination – Strategy