SLIDE 1 Technical Seminar - Malaria

Malaria is an extremely important cause of mortality in different parts of world. In this technical seminar, I'll discuss the rationale for classifying areas as high, low or no risk, using examples from different countries. We'll also look at the difficulty in even making a clinical diagnosis, and the rationale for choosing anti-malarials.

SLIDE 2 Malaria - Overview

In Africa and parts of Asia, *Plasmodium falciparum* is widespread, contributing to an estimated 1 million pediatric deaths worldwide annually — mostly children under age 5 (1). Repeated infections, either clinical or sub clinical, build immunity in the exposed child or adult, resulting in a much lower mortality rate in them.

In several African countries in sub-Saharan Africa, malaria is the leading cause of death in children under five.

However, there is variable epidemiology based on different ecological settings. In most of tropical Africa, the risk of contracting malaria is high but less so in urban areas, in semi-arid areas and in highland areas. In Asia and the Americas, there may be a variable risk for developing malaria with marked seasonal variation. This epidemiology is further complicated by mosquitoes’ increased resistance to insecticides, travel between malarious and non-malarious areas, and the aggregation of large groups of displaced persons such as refugee camps.

SLIDE 3 Malaria - Overview (continued)

This variable epidemiology makes it important to classify areas and countries with malaria as areas with high risk, low risk, or no risk using these risk assessments.
In **high risk** areas where mortality is a major problem, all children with febrile diseases can be assumed to have malaria. In **low risk** areas, only children with no other diagnoses should be considered to have malaria, since the specificity of testing will be low. In areas where there is **no risk** of developing malaria, anti-malarials should not be used.

Because of the widespread use of anti-malarials, there is **growing anti-malaria resistance**. This causes increased rates of hospitalization for severe disease, since treatment of parasites resistant to anti-malaria drugs results in progression of the disease. Furthermore, these children may develop severe anemia and, ultimately, die.

**SLIDE 4   What is Malaria?- Case definition**

There is **no specific clinical case definition** for malaria, and in non-severe disease, there is **no adequate gold standard** (2).

Thus, in highly endemic areas, **even healthy children have more than 5,000 parasites per µl.**

In endemic areas, **children have anemia from repeated attacks of malaria and from nutritional deficiencies.** In these areas, severe anemia is not uncommon due to either malaria or other endemic diseases.

**SLIDE 5   Cerebral Malaria - Kills quickly**

Children with very severe febrile disease — those with fever who have a danger sign — in high or low malaria risk areas **may have cerebral malaria.**

This can be a very rapid killer of children — they can progress from lethargy to unconsciousness to death in less than 24 hours. **Rapid treatment after onset of fever is essential.**
Where there is a high risk of malaria, **every child with a severe febrile disease** classification should receive intramuscular Quinine and should be urgently referred for continued management in hospital.

Health care workers **should not take chances if theirs is a high risk area or season, or if the child is non-immune.** Acting quickly in these cases can save lives.

**SLIDE 6   Malaria Risk - High**

Areas can be classified as high risk for three reasons.

Areas **where malaria is endemic** are described as high-risk areas. In some countries where malaria is highest during the rainy season — and greater than 5 percent of febrile children have malarial parasites — **seasonality** and a **history of travel** also become important in determining malaria risk (2).

In high-risk malaria areas, the sensitivity of “any fever” for classification of malaria varies between 98 and 100 percent. However, the specificity is low, varying from 6 to 13 percent. This leads to over treatment with anti-malarials in high-risk areas. But **classifying all children with fever as “malaria”** is considered an acceptable strategy because the risk of developing cerebral malaria or other complications of malaria is very high in young infants and children. To be classified with malaria, the child either has **fever by history, by touch or by measurement in the clinic** (3). In Papua New Guinea, the presence of fever, **anemia and splenomegaly** in the absence of other obvious causes of fever was highly predictive of malaria (3).

In the high malaria risk setting, **the value of microscopy is limited.** During malaria season, the number of patients coming to an outpatient facility with fever may be very high. If every child were examined, there would be **poor quality control** due to the large number, which would result in false negatives. In this circumstance, it would be harmful for the child not to be treated. In addition, in very high malaria risk areas where more than 50 percent of febrile children have parasitemia, **the cost involved** in screening and the distinct possibility of false
negatives suggest that microscopy would result in little cost savings and result in non-treatment of potentially severe disease. Other disadvantages of microscopy are that quality control is often difficult, the time involved in reading smears from many patients may result in inordinate delays in treatment, and good technique with adequate lighting is essential for making the diagnosis. For these reasons, the WHO malaria program does not recommend routine malarial parasite examination in uncomplicated malaria. It should be restricted to cases that are failures of therapy. More on this later in the seminar.

**SLIDE 7 Malaria Risk - Low**

There is not a simple specific method for diagnosing malaria in low risk areas and a **good clinical definition is lacking**.

In areas with low malaria risk or where malaria is seasonal, malaria accounts for a very small proportion of febrile diseases. In order to restrict anti-malarial overuse, **more restrictive criteria** should be applied.

Even with these restrictive criteria, a potentially high proportion of children are **misdiagnosed**. In this setting, only children with a history of fever or fever and no other major cause of fever, such as an upper respiratory tract infection or measles, should be classified as malaria (4).

The **current guidelines still have a very low specificity in low malaria risk areas**. Based on data from the Philippines (5) and Tanzania (6), the requirement for intermittent fever or fever accompanied by chills, sweats or shaking did not improve the specificity of the classification of malaria. Additionally, in a study from the Gambia (7) during the non-rainy season, these factors were not found to be of value in discriminating between children with malaria — those with greater than 5,000 parasites per ml — and those without malaria. “Shaking chills” was only 35 percent sensitive, while rapid breathing had some value. However, the presence of fever in low malaria risk areas is only specific in 8 to 9 percent of cases. **This means overtreatment for 9 out of 10 patients occurs in low malaria risk areas.** Trying to increase the specificity using the absence of fast
breathing and pallor makes the recommendations much more complex, and in the pretest in Gondar, Ethiopia (8), and in the field test in Arusha, Tanzania (9), these complex guidelines had to be simplified in order to make the charts useable at first-level health facilities.

**SLIDE 8  Malaria Risk - How to Assess**

WHO has developed a **specific methodology for assessing the risk of malaria** because of the danger of children dying of cerebral malaria and the development of resistance to antimalarials due to over usage of these drugs for children with fever (10,11).

The methodology uses **systematic sampling** of children age 2 months to 59 months presenting at outpatient health care facilities with a history of fever or in whom fever is detected by routine screening. All patients should be included, whether or not disease is severe and whether or not they are referred from other areas.

The sample should be well defined, for example, those attending one day per week. It should avoid bias, and should allow inclusion of 50 children per month when the incidence of malaria is high or 100 children when the incidence of malaria is low.

A **microscopist and a clinician must be available** throughout the study. All children are examined by the clinician who records the clinical diagnosis or the IMCI classification. A slide is taken and the result recorded. Normally, greater than 100 oil immersion fields of Giemsa-stained thick film should be examined for malarial parasite. The result should be recorded quantitatively and the species noted.

**SLIDE 9  Malaria Risk - How to Assess (continued)**

It is important that the **quality of laboratory diagnosis should be assured before the start of the study**. IMCI recommends that a slide positive rate of 5 percent or less indicates low
malaria risk. Thus, the definition of high, low and no malaria risk varies not only by area, but also by season.

The rationale for dividing areas into high, low, or no malaria risk comes from studies in Africa and in Asia.

In Gambia in West Africa (7), with seasonal malaria during the rainy season, the relative risk of fever with parasitemia was 5 times greater in children with no clear cause of fever than in those with a clear cause of fever. In the dry season, there was no association.

In Ethiopia, during the pretest in Gondar (8), malaria was uncommon in children living in the highlands but a travel history to a low-lying area resulted in quite a few false negatives. This necessitated the inclusion of travel history in the IMCI guidelines.

Finally, during the field test of training materials in Arusha, Tanzania (9), the diagnosis of malaria in low-risk areas was simplified to exclude a runny nose, measles and other causes of fever. These examples underlie the vast complexity of differentiating between high, low and no malaria risk areas.

**SLIDE 10  Low Malaria Risk - Classification**

Based on what we just discussed about low malaria risk areas, children with fever measured in the clinic or a history of fever with no runny nose, no measles and no other identifiable cause of fever should be classified as having malaria.

**SLIDE 11  IMCI Guidelines - Adaptation**

The generic chart and modules discuss high and low malaria risk areas, while countries have adaptations.

In some countries such as Ethiopia (8), the adaptations include high, low and no malaria risk. For example, in the first pretest in Ethiopia, because it was conducted in the mountains, there are areas with no malaria risk.
In some countries, such as Tanzania and Uganda, the whole country is considered high risk and every child with a fever is treated with an anti-malarial.

In some countries in Asia and South America, there is no malaria risk; in other areas there is no *P. falciparum* and only *P. vivax* is present — some areas in India, for example. In other areas both *P. falciparum* and *P. vivax* are problems — such as the Philippines. Since *P. vivax* malaria very rarely results in mortality, and *P. vivax* does not respond to anti-microbials containing sulfa drugs, these adaptations become much more complex.

**SLIDE 12  Diagnostic - Microscopy**

The routine use of microscopy is discouraged because of the many reasons described in an earlier slide. However, it can be of value if good technique is used, the number of indications from microscopy is restricted, and results are available to patients in the clinic.

**SLIDE 13  Diagnostic - Microscopy (continued)**

Let’s discuss some scenarios where microscopy may be effective (2).

- **Treatment failures** with anti-malarials can identify resistant malaria or, if no parasites are found, identify another cause for failure of therapy.
- In the situation where no prior anti-malarials are used, severe malaria can be excluded by repeated examinations of the blood. In the circumstance where referral is impossible, this would have major implications for therapy.
- In the low-risk malaria setting, microscopy can be very useful in identifying the few patients with malaria. This could be used in conjunction with the clinical definitions used in IMCI, and would increase the specificity significantly.
• In circumstances where both *P. vivax* and *P. falciparum* occur and treatments are different, microscopy is useful. In the situation where chloroquine-resistant *P. falciparum* is very common and the second-line drug is sulfa pyrimethamine which has low activity against *P. vivax* malaria, the identification of *P. vivax* would necessitate treatment with chloroquine and *P. falciparum* with sulfa pyrimethamine.

• In areas where borreliosis is common, microscopic examination would reduce the non-specific treatment of febrile children with an anti-malarial.

• In high-risk areas where only moderate number of febrile children have positive smears, it may be cost effective to use microscopy.

As we said in an earlier slide, one of the major limitations of microscopy is the time involved and the quality of microscopy. Dip sticks have been developed that are very sensitive and specific for *P. falciparum* malaria; however, they are currently more expensive than the treatment itself, making microscopy a non-viable public health option.

**SLIDES 14 & 15  Treatment - Choice of Anti-malarials**

Drug resistant *P. falciparum* malaria is becoming increasingly common. Even if malaria prevalence is low, there should always be **two lines of therapy** for non-severe malaria (10). The first-line drug is chosen by the National Drug Policy Program, which assesses the rate of resistance to different anti-microbials and decides on the first-line treatment for uncomplicated malaria. The second-line drug is used for children with uncomplicated malaria who have not been cured with the first-line drug or in whom the first-line drug is contra-indicated, such as a drug reaction with prior use.

It is important to note that the **second-line drug should be available at the same facility** where the first-line drug is administered. The primary reason is the rapidity with which malaria can progress. Also, if resistance levels to first-line drugs are more than 5 to 10 percent, a significant proportion of children will return to the first-level health facility for a second-
line drug. In these circumstances, sending a child to a referral facility may result in a huge number of false referrals.

For severe malaria, indicated by very severe febrile disease, only intramuscular Quinine is currently recommended. Quinine resistance, fortunately, is not common.

**SLIDE 16  Treatment - Updating a Policy for Uncomplicated Malaria Treatment**

Increasing drug resistance necessitates that national policies be active in detecting ineffective first-line treatment. Policies should be changed before they lead to significant increases in malaria-associated morbidity and severe disease.

The first step in detecting ineffective first-line treatment is determining the precise proportion of treatment failures in a given population. This involves post-treatment checks and some follow-up clinical assessment, and should be performed only in patients who are sick from a malarial infection. The outcomes measured may vary — different treatments may yield a similar proportion of clinical admissions within 2 or 3 days but a very different proportion of clinical relapses after 7 days. Clinical relapses up to day 14 are practically unaffected by re-infection, however, a test with a 14-day follow-up may not be feasible.

Should a country’s first-line treatment be changed? Ask these questions.

- Can improving compliance reduce clinical failure? It may be important to assess compliance where a decrease in effectiveness can be attributed to a decrease in compliance.

- Is there an unacceptable proportion of clinical failures? We propose that 25 percent of clinical failures is a upper limit which should not be reached. Changing this proportion would be premature if it leads to rapid exhaustion of available treatment options. On the contrary, changing the proportion would be warranted if it could prevent severe and complicated malaria and mortality. Another consideration is that the withdrawal of a first-line drug may result in less
selective pressure and/or return to sensitivity after several years. All these options complicate the decision by a national program to decide what proportion of clinical failures is unacceptable.

- How does one know that a critical proportion of clinical failures has been reached? The WHO recommends that the national drug policy include regular monitoring of the efficacy of recommended treatments. However, such monitoring is rarely carried out and may not have a great impact on decision making.

**SLIDE 17  Treatment - Updating a Policy for Uncomplicated Malaria Treatment (continued)**

In developing a new policy for first-line treatment, a country must take into account not only a drug’s resistance and clinical efficacy, but also its compliance rate, cost, availability and side effects, and what areas of the country should be covered by the policy (11).

- What affordable and safe alternatives are available? Once the least expensive first-line drugs develop resistance, effective alternative treatments are likely to much more expensive. Factors that need to be considered are:
  
  - the difference in cost between the new and old first-line treatments
  - the economic cost of treatment failure and its re-treatment
  - the proportion of treated uncomplicated cases that could be prevented from becoming severe
  - the total cost of a case of severe complicated malaria or severe anemia

- To what area should the recommendation apply? This decision is often difficult and limited since areas with resistant parasites often cross artificial boundaries and country borders. This necessitates harmonization of drug policies between neighboring countries.
SLIDE 18  Treatment - Intramuscular Quinine

The use of intramuscular Quinine has been controversial for many years but recent studies provide evidence that it is safe and achieves adequate levels in the blood compared to intravenous administration, even in children with severe malaria (12, 13).

Complications can be avoided with good administration technique.

One complication of intramuscular administration is that it can result in skin narcosis if inadvertently given subcutaneously. IV administration requires careful regulation of the drip — often not possible at first-level health facilities — as rapid infusion of Quinine is associated with cardiac arrhythmias and hypoglycemia, and subsequent mortality from IV therapy itself. Quinine can be administered in a hospital setting with cardiac monitoring and close monitoring for arrhythmia and hypoglycemia.

The major complication of intramuscular administration is development of muscle necrosis and abscess formation that may be related more to the preparations containing urethane and other irritants and poor injection technique. For example, administration in the buttock can result in injury to the sciatic nerve. These complications can be avoided by good technique and choosing the correct site of administration.

Intramuscular Quinine is well tolerated if diluted adequately. Concentrated Quinine solutions are very painful.

SLIDE 19  Treatment - Intramuscular Quinine (continued)

Current WHO guidelines on administration of IM Quinine involves a loading dose of 20 mg salt per kg in 2 doses of 10 mg/kg, followed by a maintenance dose of 10 mg/kg given at intervals of 8 to 12 hours after the last administration.

The generic guidelines recommend 12 hourly dosing if referral is not possible. In areas of adequate Quinine sensitivity of P.
*falciparum*, the 12 hourly regimen has been shown to give good therapeutic and pharmacological results and is much easier to deliver at a first-level health facility (14). It is also less expensive than the 8 hourly regime. The Quinine maintenance should be **reduced to 5 to 7 mg per kg if more than 48 hours of therapy is required**.

As soon as the child can swallow, **full oral treatment should be initiated** — Quinine tablets 8 mg base per kg 3 times a day — with sulfa pyrimethamine (15,16).

Please note, however, that in the generic guidelines, Quinine **should not be administrated to young infants under 2 months of age and to any child age less than 4 months** in a low malaria risk area. In these areas, risk of malaria is low in this age group.

**SLIDE 20  Treatment - Why Not IM Chloroquine?**

IM chloroquine is not recommended for these reasons (15):

- chloroquine resistant malaria is common and spreading
- the intramuscular absorption is erratic and dangerous
- sometimes transient high levels can result in hypotension since chloroquine is a potent vasodilator. In these instances, fatal hypotension has resulted.

In comparison, intramuscular Quinine can be used since Quinine resistance is very rare and absorption is more reliable and safe if used with good technique.

**SLIDE 21  Severe Malaria in Young Infants - Risk**

In a low or high malaria setting, the prevalence of severe malaria in young infants is generally low because **protective maternal antibodies** and the high hemoglobin F content of newborn babies’ erythrocytes inhibit parasite development.

Thus, the **generic guidelines recommend** that Quinine not be given to a young infant under 2 months of age in high or low
malaria settings or to any child age less than 4 months in a low malaria risk area.

However, in some areas with very high malaria risk, even young infants may suffer from cerebral malaria with a very high mortality. In this circumstance, **young infants with possible serious bacterial infection may need to be treated with IM Quinine.**

This policy decision needs to be made very carefully after examining data on the **prevalence of malaria** in the newborn and the young infant.
REFERENCES


