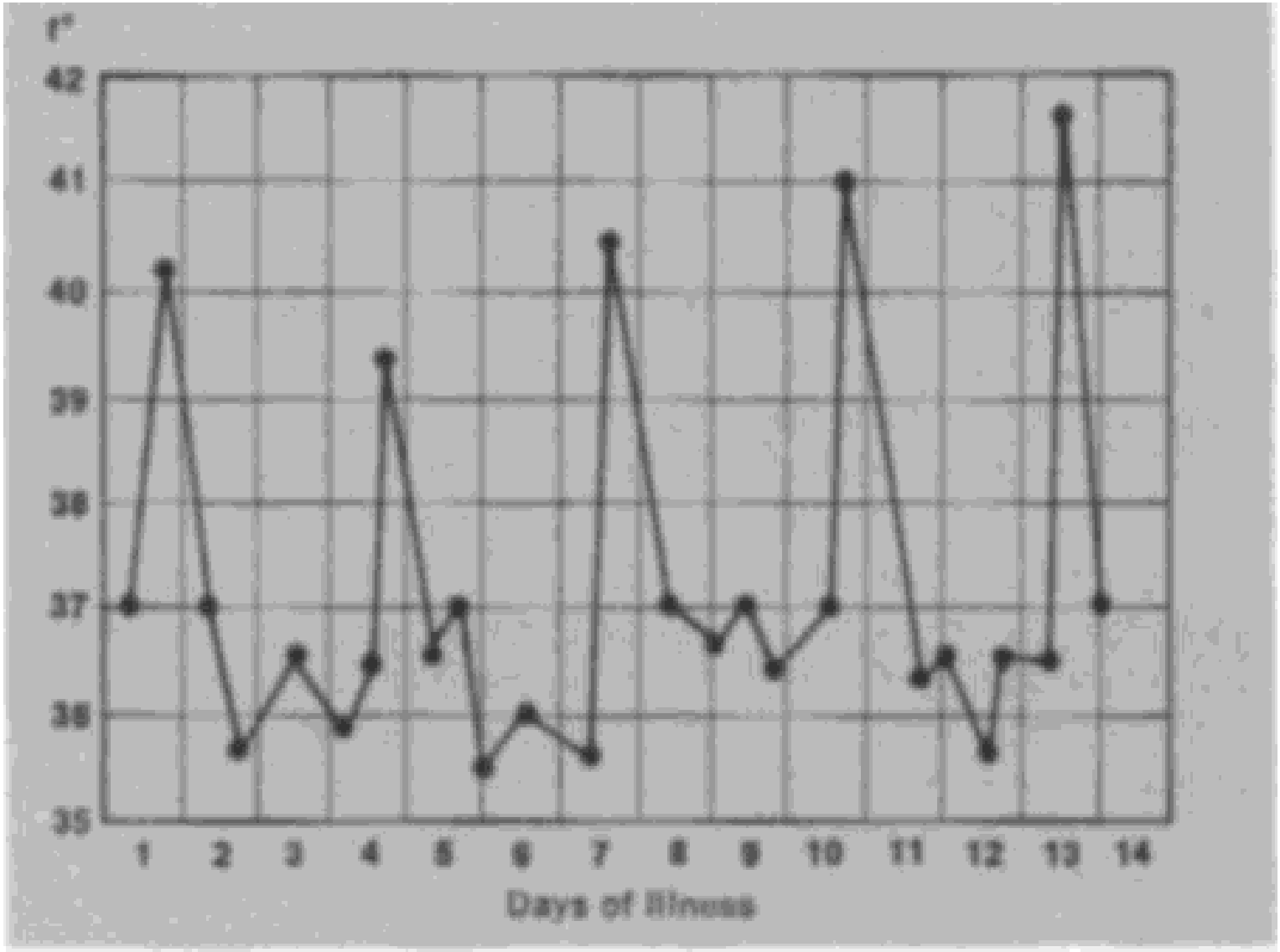
MALARIA - 2

32 YEARS OLD MALE FROM DEHIWALA, ADMITTED TO MEDICAL CASUALTY UNIT OF COLOMBO NORTH TEACHING HOSPITAL WITH A HISTORY OF FEVER FOR 8 DAYS AND ABDOMINAL PAIN. ON EXAMINATION, HE WAS FOUND TO HAVE HEPATOMEGALLY.


f°
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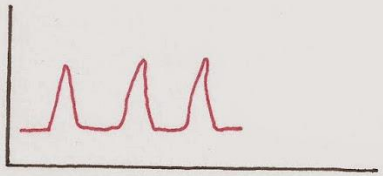
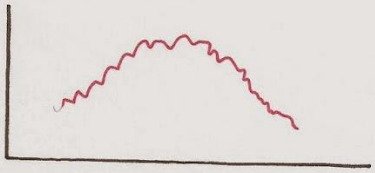
Days of Illness

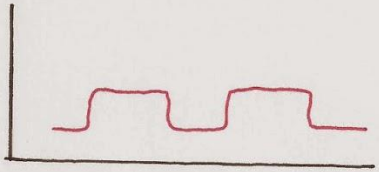


TERTIAN
SPIKES EVERY 3 DAYS
e.g. P. virax or P. ovale
types of malaria

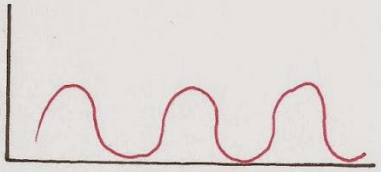
QUARTAN
SPIKES EVERY 4 DAYS
e.g. P. malaria
type of malaria.



Typhoid fever



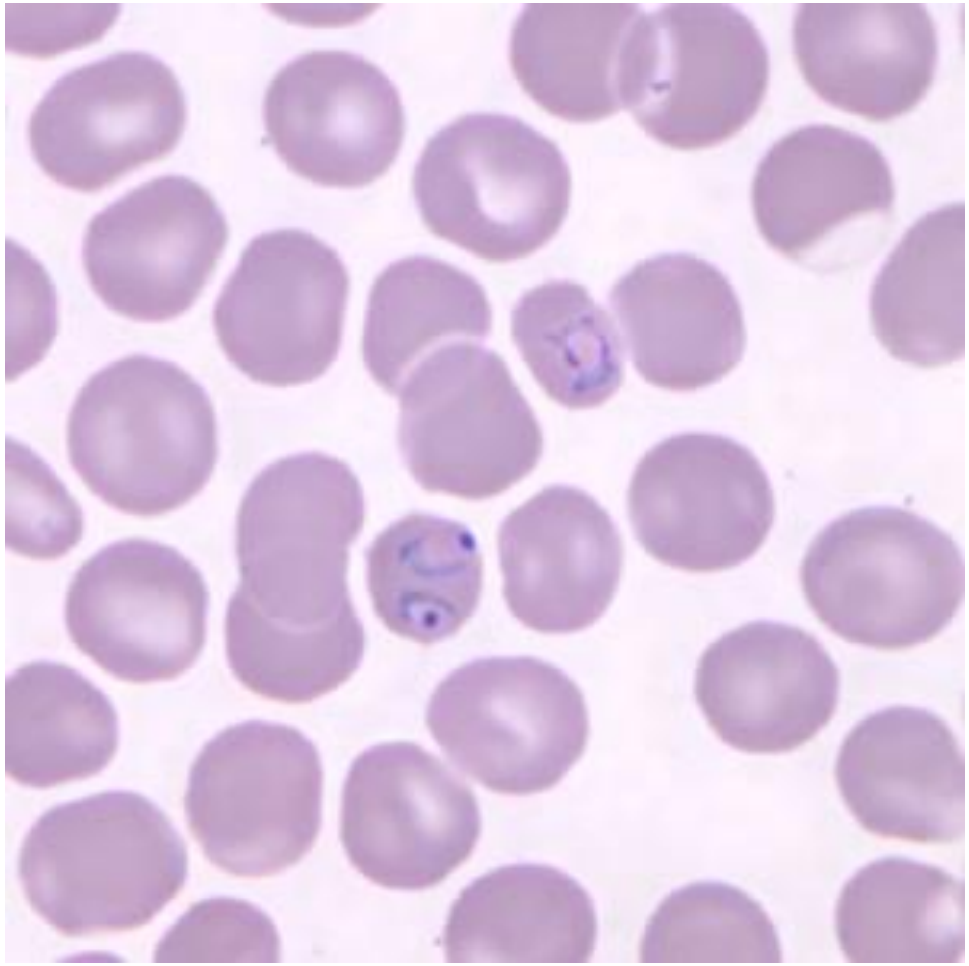
Intermittent
e.g. abscess



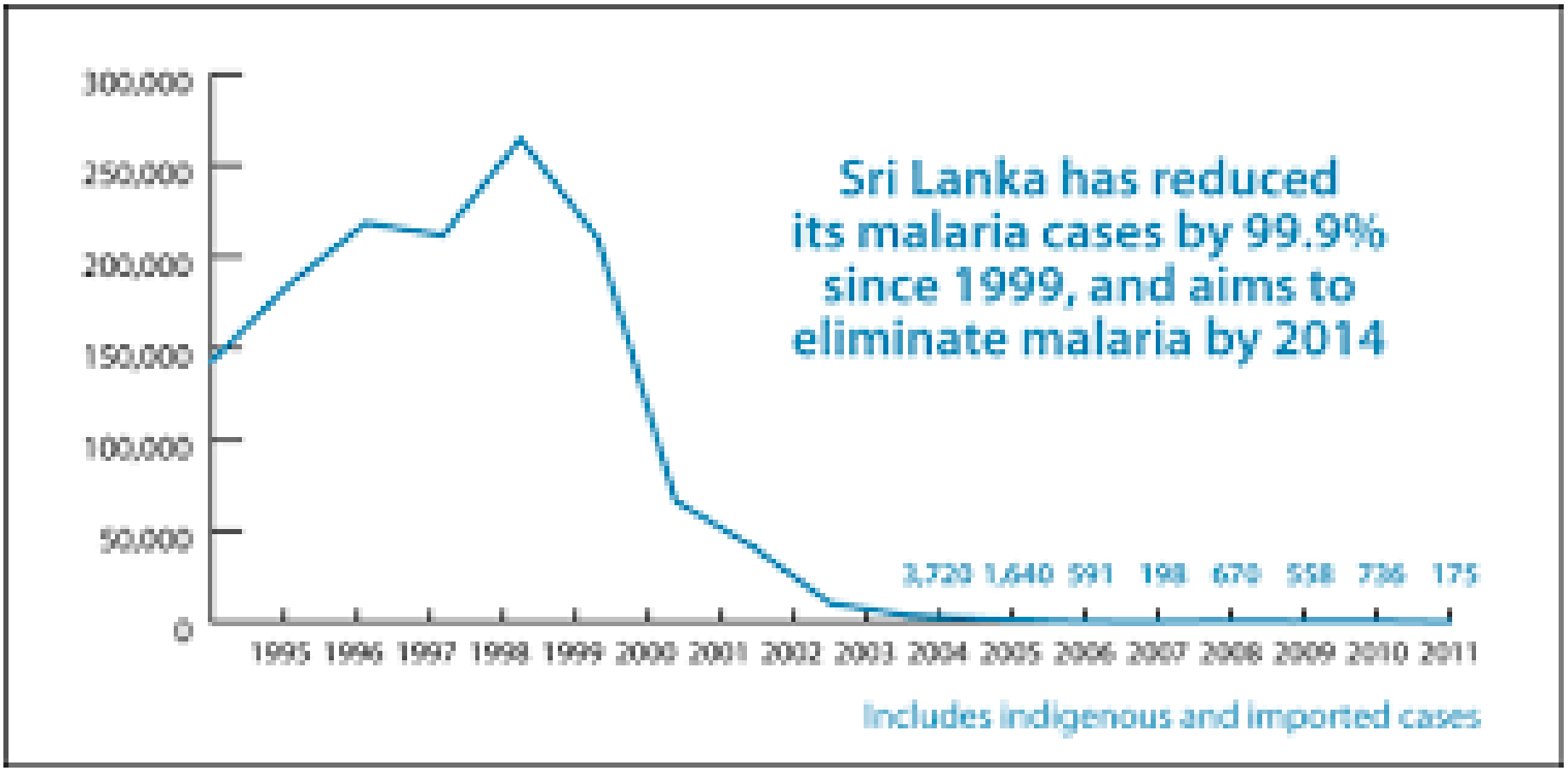
UNDULENT FEVER
e.g. Brucellosis

What are the investigations you want to carried out on this patient?

Blood for Malaria Parasite



What **IS THE QUESTION** you want to ask from this patient?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200,000
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1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011
3,720 1,640 591 198 670 558 736 175
Sri Lanka has reduced its malaria cases by 99.9% since 1999, and aims to eliminate malaria by 2014
Includes indigenous and imported cases

Treatment of malaria

Objectives :

i. Describe anti malarial drugs used in the treatment

ii. Describe the guideline available to manage patients with malaria

iii. Resistance to anti malarial drugs

Several drugs are used to treat and prevent malaria

- Quinine
  - First antimalarial to be discovered (16th century)
  - Extracted from the bark of the cinchona tree
  - Many side effects
- Chloroquine
  - Artificial compound developed during World War II
  - Used extensively for many years; still used for *P. vivax*
  - Drug resistance in *P. falciparum* is now widespread
- Artemisinin – based compounds developed in the 1990's now used in combination with other drugs

Guidelines for treatment of malaria in Sri Lanka

- New circular issued in May 2008 by Anti-Malaria Campaign

- Mono-infection with *P. vivax*
  - Chloroquine 25 mg / kg body wt over 3 days
  - Primaquine 0.25 mg / kg daily for 14 days (to eliminate hypnozoites)

- Uncomplicated *P. falciparum* mono-infection
  - Treat in a medical institution
  - Age appropriate course of Artemisinin Combination Therapy (Artemether + lumefantrine, Coartem) over 3 days
  - Primaquine 0.75 mg / kg bwt on Day 3, before discharge (to eliminate gametocytes)

- Uncomplicated mixed Pv / Pf infections

  - Treat in ward for at least 3 days

  - Age appropriate course of Artemisinin Combination Therapy (Artemether + lumefantrine) over 3 days

  - Primaquine 0.25 mg / kg daily for 14 days (to eliminate hypnozoites of Pv and gametocytes of Pf)

Complicated *P falciparum* infections :

- If patient is unable to take oral medication
  - Start on quinine iv, 10 mg /kg bwt, in a slow infusion with 5% dextrose, repeat every 8 h until patient is able to take oral medication
  - Monitor blood glucose levels frequently; also cardiac monitoring
  - When patient is able to take orally, give full age appropriate course of Coartem + single dose of primaquine
- If patient is able to take oral drugs
  - Give full course of Coartem + single dose of primaquine

Resistance to antimalarials

- Major problem in many parts of the world, including Sri Lanka
- Chloroquine resistance first emerged in 1960's in SE Asia and S America
- Resistance to many other antimalarials since then
  - Antifolates
  - Sulfadoxime-pyrimethamine
  - Mefloquine

Situation in Sri Lanka

- Chloroquine resistance in *P. falciparum* first reported in 1984
- Second line treatment with sulfadoxime-pyrimethamine (Fansidar) for uncomplicated cases or quinine for severe and complicated cases
- Resistance to SP emerged in the late 1990s.
- Use of ACTs recommended by AMC in 2008

Global extent of antimalarial resistance

- Resistance to antimalarials has been a particular problem with *P. falciparum*, in which widespread resistance to chloroquine, sulfadoxine-pyrimethamine and mefloquine has been observed
- Antifolate and chloroquine resistance has developed in *P. vivax* in several areas
- Chloroquine resistance in *P. malariae* has also recently been reported
- No significant resistance has yet been observed to artemisinin and its derivatives

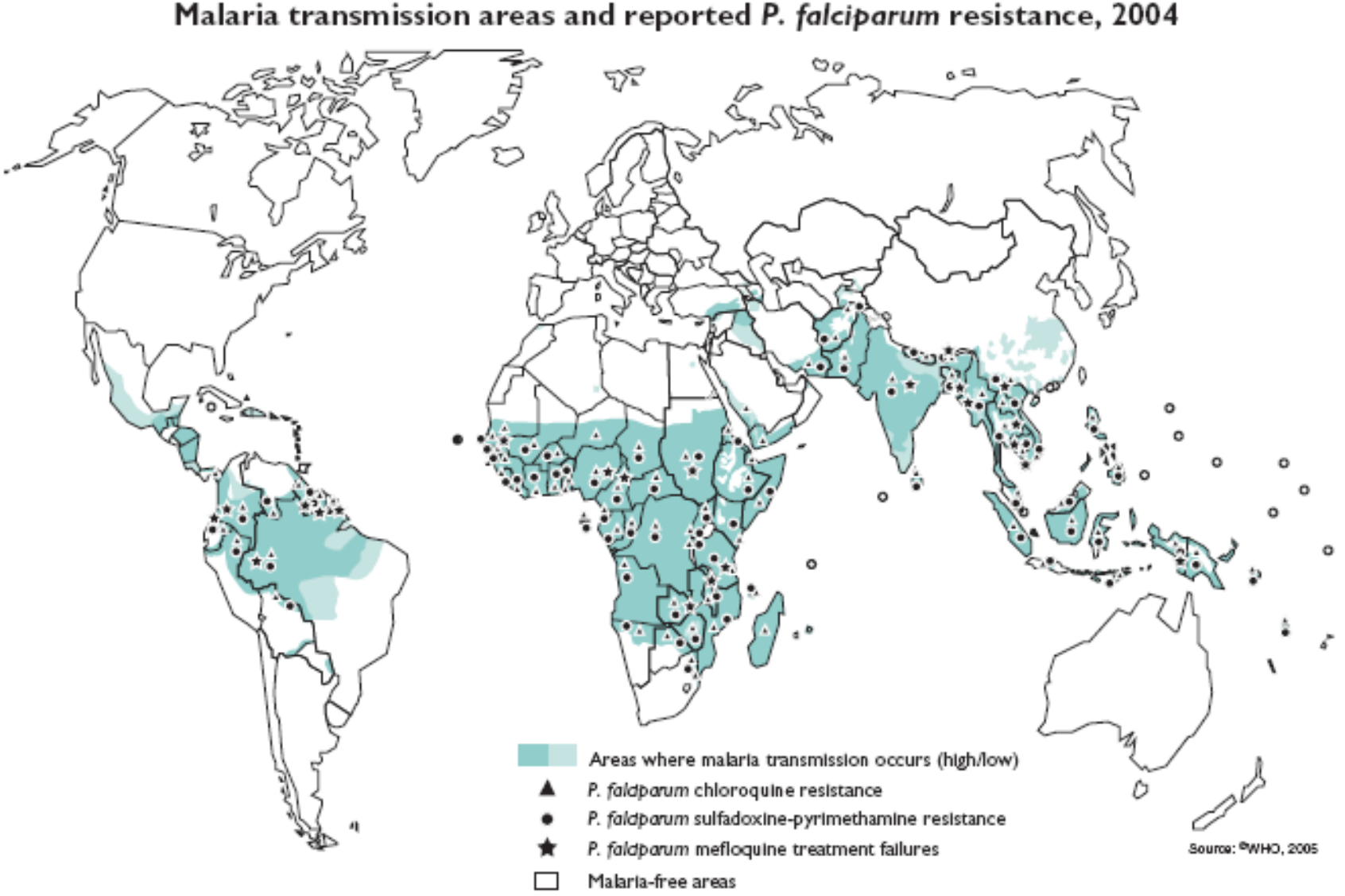


Figure A6.3 Malaria transmission areas and the distribution of reported resistance or treatment failures with selected antimalarial drugs,

Definition

- **Antimalarial drug resistance** is defined as the ability of a parasite strain to survive and/or multiply despite the proper administration and absorption of an antimalarial drug in the dose normally recommended.

- Antimalarial drug resistance is not necessarily the same as malaria "**treatment failure**", which is a failure to clear malarial parasitaemia and/or resolve clinical symptoms despite the administration of an antimalarial.

- Drug resistance may lead to treatment failure, but not all treatment failures are caused by drug resistance.

- Treatment failure can also be the result of
  - incorrect dosing,
  - problems of treatment adherence (compliance),
  - poor drug quality,
  - interactions with other drugs,
  - compromised drug absorption,
  - misdiagnosis of the patient.

Development of resistance has 2 stages

1. Initial genetic mutation
2. Subsequent selection of resistant mutants and spread of resistance

- Resistance to one drug may select for resistance to another where the mechanisms of resistance are similar (cross-resistance).

- Immunity to malaria has a central role in preventing the emergence and spread of resistance in high transmission areas

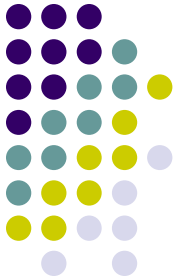
Mechanisms of resistance

- **Chloroquine** acts by interfering with the ability of the parasite to detoxify the haem molecule (i.e., make malaria pigment).

- Chloroquine resistance in *P. falciparum* results from mutations in a gene that encodes a transporter (PfCRT) which pumps chloroquine out from the food vacuole.

- Resistant parasites are able to pump out CQ very rapidly from the food vacuole.

Resistance to antifolate antimalarials



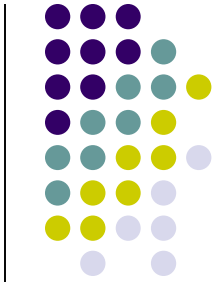
- With **pyrimethamine** and **proguanil**, resistance in *P. falciparum* and *P. vivax* results from the sequential acquisition of mutations in the gene *(dhfr)* that encodes dihydrofolate reductase (DHFR).

- In *P. falciparum*, **sulfonamide** and **sulfone** resistance also develops by progressive acquisition of mutations in the gene encoding the target enzyme PfDHPS

Monitoring of antimalarial resistance

- Standard protocol developed by WHO for testing therapeutic efficacy (*in vivo* testing)
- Involves the repeated assessment of clinical and parasitological outcomes of treatment, during a fixed period of follow up (28 days)
- Other methods include *in vitro* studies of parasite susceptibility to drugs in culture, and studies of point mutations or duplications in parasite resistance genes with molecular methods (PCR)

Possible outcomes in efficacy studies



- Four categories of outcomes:
  - Early treatment failure,
  - Late clinical failure,
  - Late parasitological failure, and
  - Adequate clinical and parasitological response.

- **Early treatment failure**: the patient develops clinical symptoms with parasitaemia during the first 3 days of follow-up

- **Late Clinical Failure**: symptoms develop during the follow-up period (from day 4 to day 28), without previously meeting the criteria for early treatment failure

- **Late Parasitological Failure**: only parasitaemia reappears without any symptoms, in the period from day 7 to day 28

- **Adequate clinical and parasitological response** is defined as the absence of symptoms and of parasitaemia on day 28, without any of the criteria for the other three categories having been met previously.

Prevention of resistance by combination therapy

- Rationale:
  - If two drugs with different modes of action, and therefore different resistance mechanisms, are used in combination, then the per-parasite probability of developing resistance to both drugs is the product of their individual per-parasite probabilities.
  - the lower the *de novo* per-parasite probability of developing resistance, the greater the delay in the emergence of resistance.

- Artemisinin derivatives are particularly effective in combinations because of their very high killing rates, lack of adverse effects, and absence of significant resistance

- Combinations of artemisinin derivatives (which are eliminated very rapidly) given for 3 days, with a slowly eliminated drug such as lumefantrine (artemisinin combination treatment, **ACT**) provide complete protection for the artemisinin derivatives from selection of a de novo resistant mutant if adherence is good (i.e., no parasite is exposed to artemisinin during one asexual cycle without lumefantrine being present)

AMC Guidelines specifically mention that artemisinin derivatives should not be used as monotherapies, in order to prevent development of resistance

Summary :

- Treat malarial patients according to the guidelines issued by AMC

- Notification of patients

Thank you