Malaria in Pregnancy

From Research to Practice: Postgraduate Training in Reproductive Health/Chronic Disease

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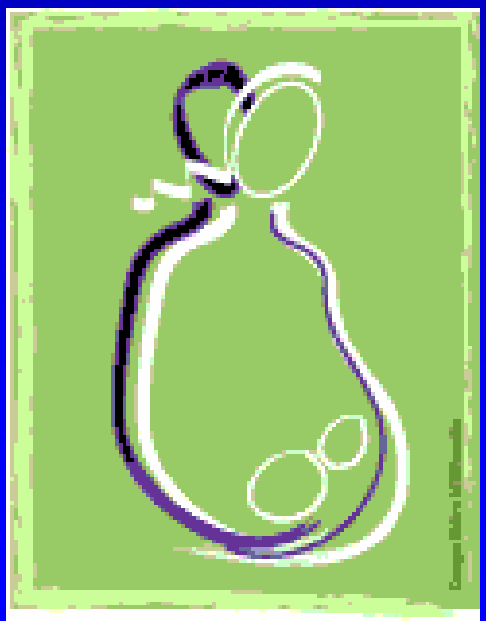
Making pregnancy safer
RHR/WHO
April 4,2003



Malaria in Pregnancy

- What type of problem is it?
- How big a problem is it?
- Who is most affected?
- What can be done about it?
  - ITNs
  - Antimalarial drugs
    - case management
    - prevention

Human Malaria

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*

Malaria in Pregnancy

Malaria

Pregnant Women

- parasitemia
- spleen rates
- morbidity
  - anemia
  - fever illness
  - cerebral malaria
  - hypoglycemia
  - puerperal sepsis
- mortality
  - severe disease
  - hemorrhage

Fetus

- abortions
- stillbirths
- congenital infection

Newborn

- low birthweight
  - prematurity
  - IUGR
- malaria illness
- mortality

What type of problem is it?

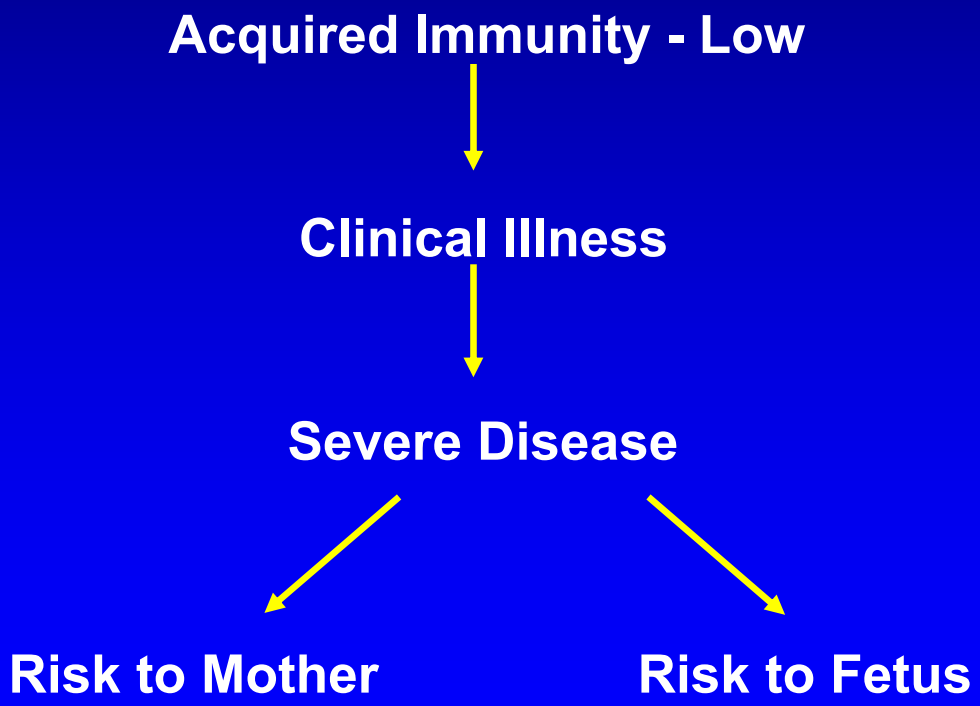
Low, unstable transmission:

- Maternal death
- Foetal death

High, stable transmission:

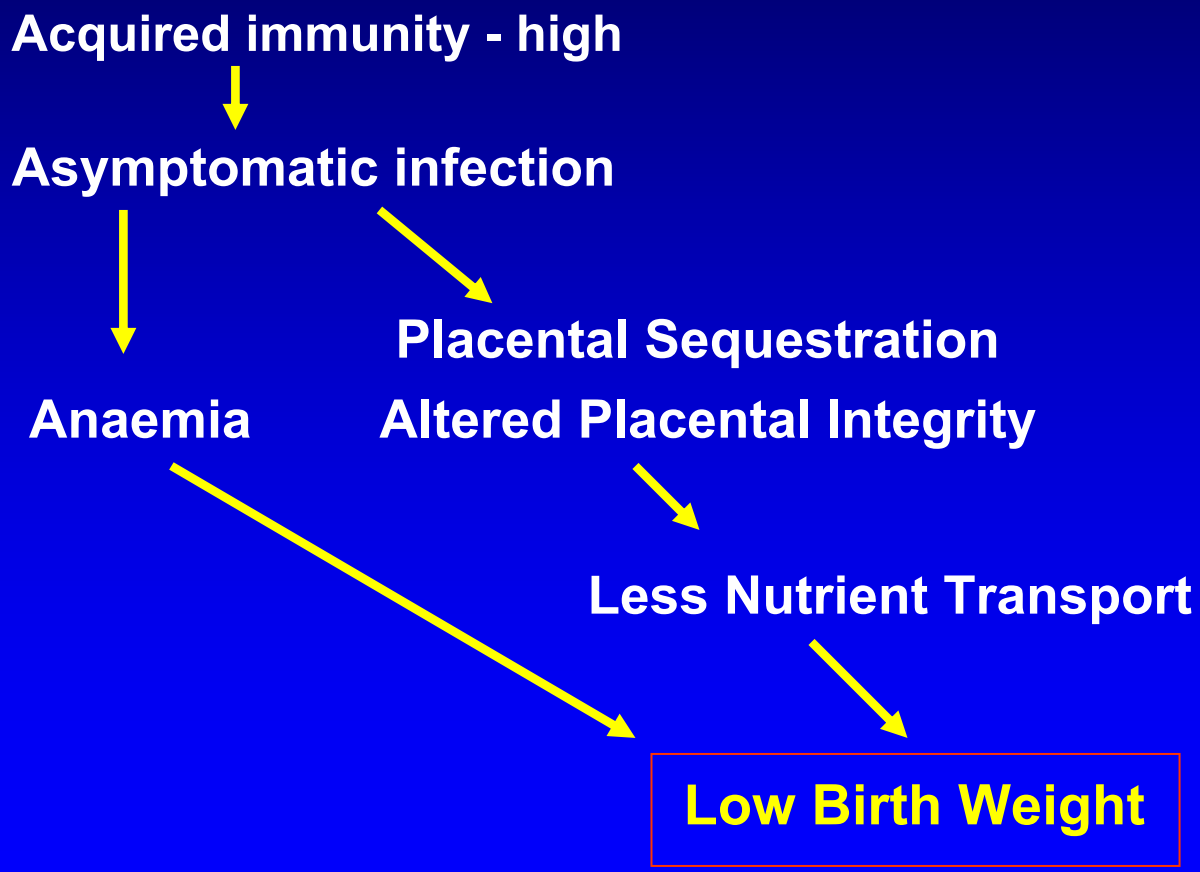
- Anaemia in the mother
- LBW infant

Malaria in Pregnancy
Low Transmission Areas

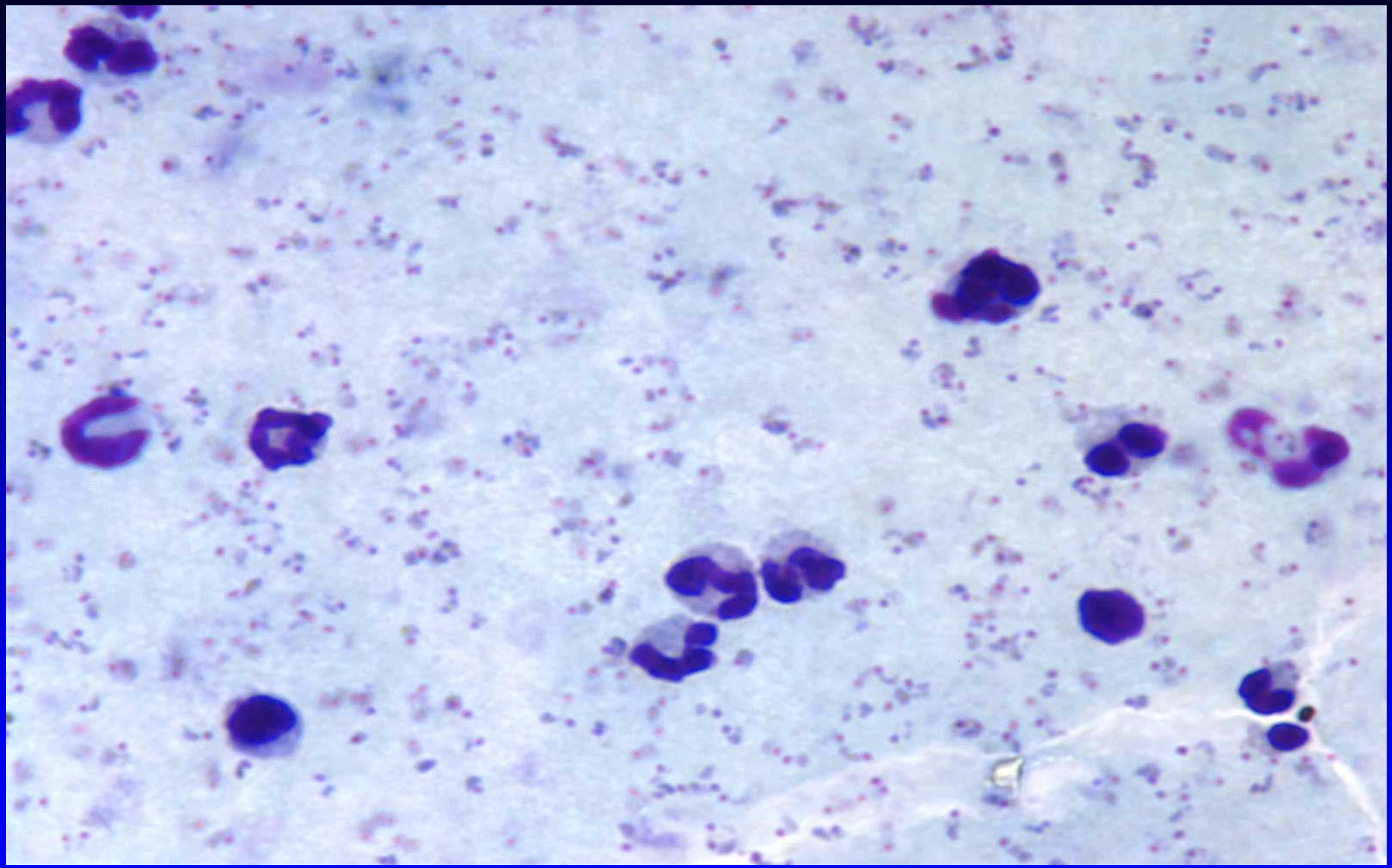


- All pregnancies
- Recognition and case management

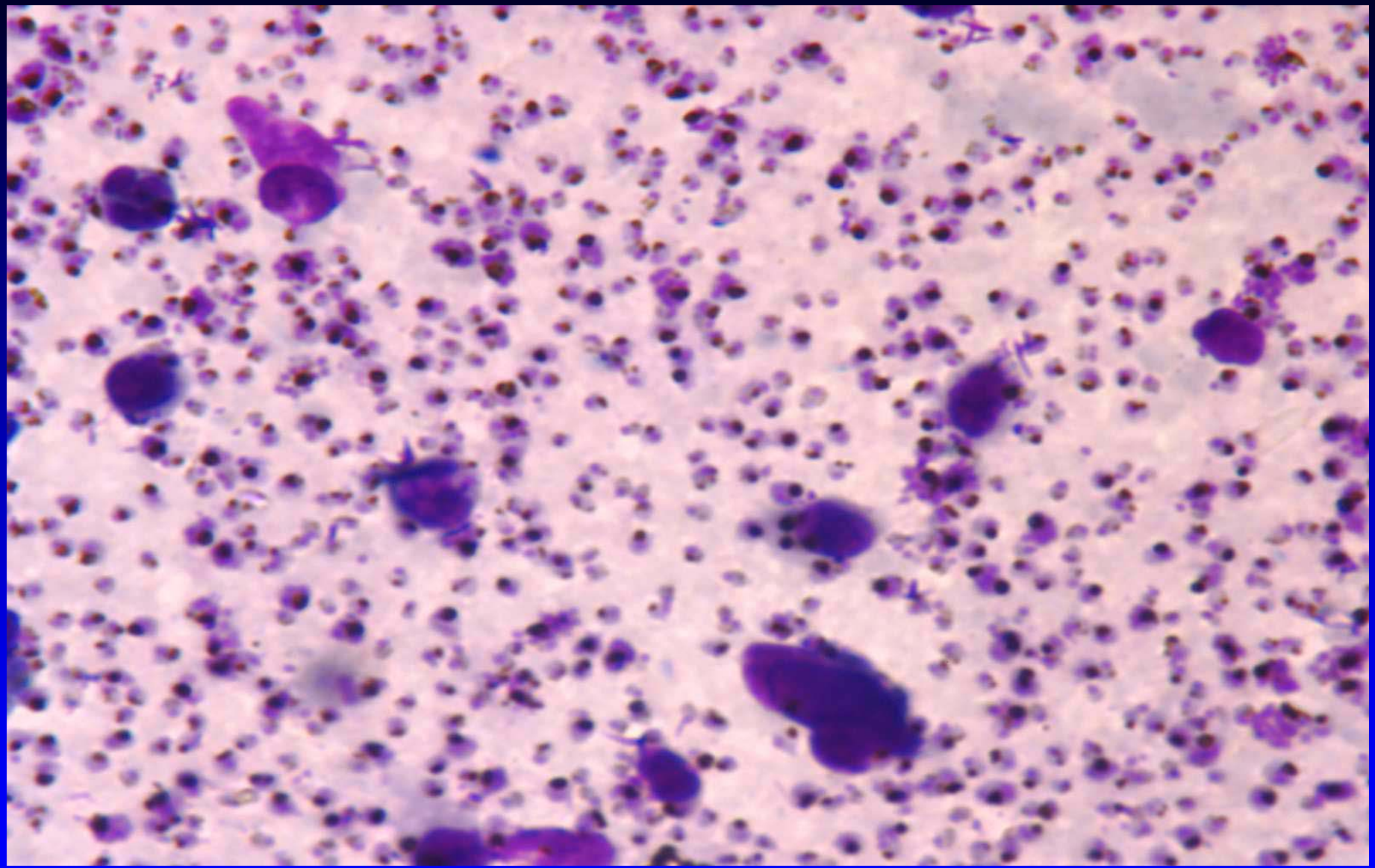
Malaria in Pregnancy
High Transmission Areas



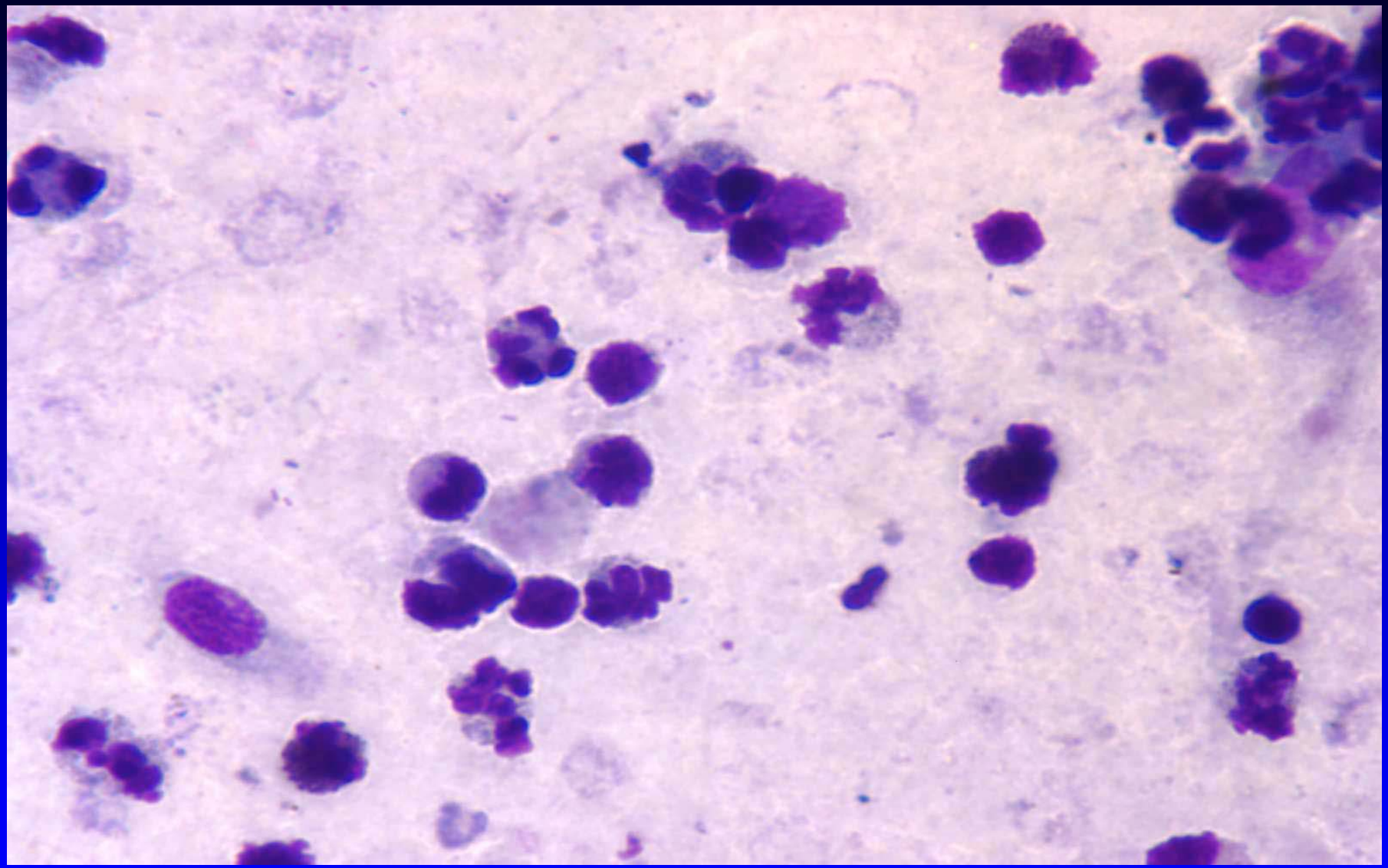
- 1st & 2nd pregnancies
- HIV infection extends this to all pregnancies, and makes it worse



Maternal Peripheral Blood

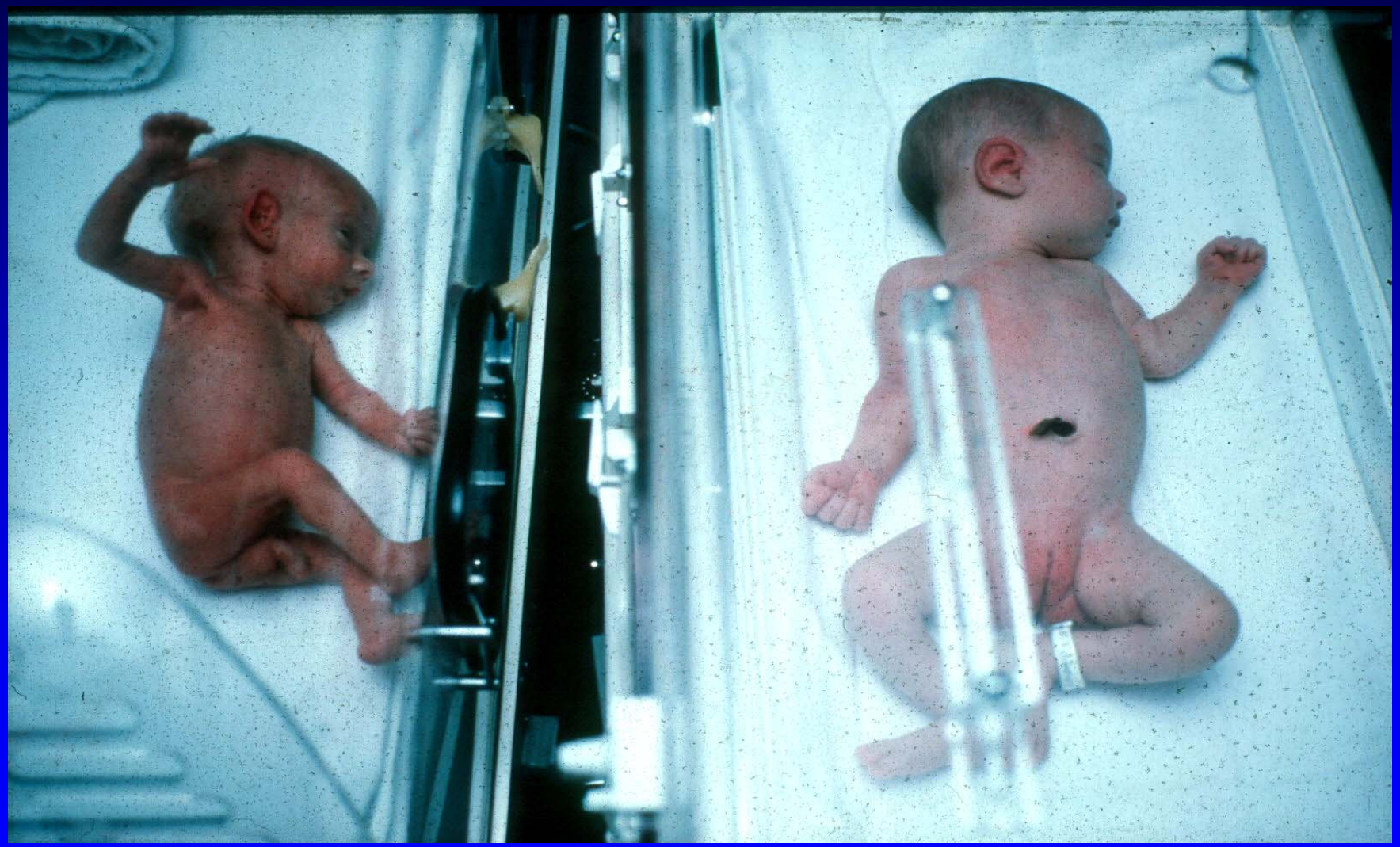


Placental Blood

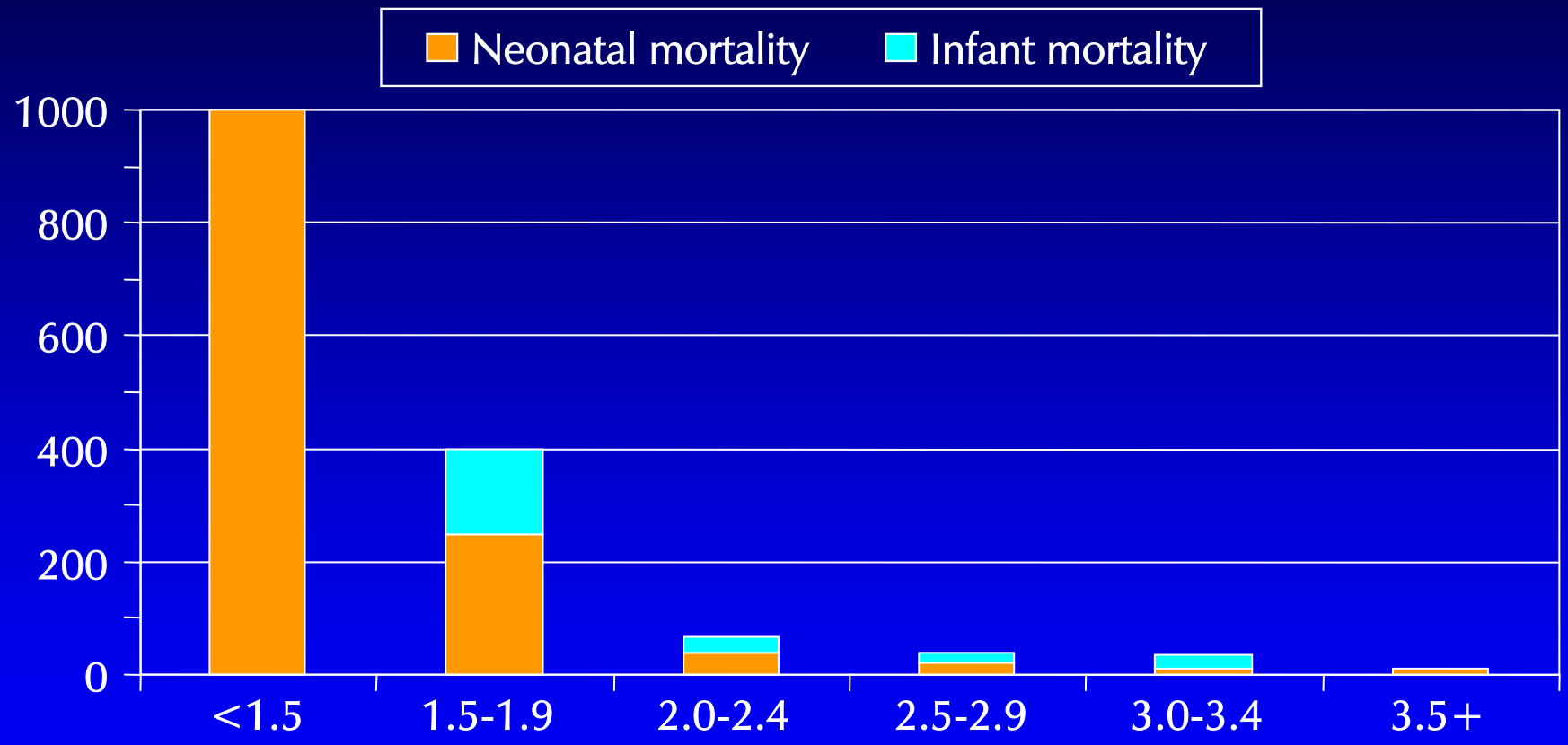


Cord Blood

Low birth weight

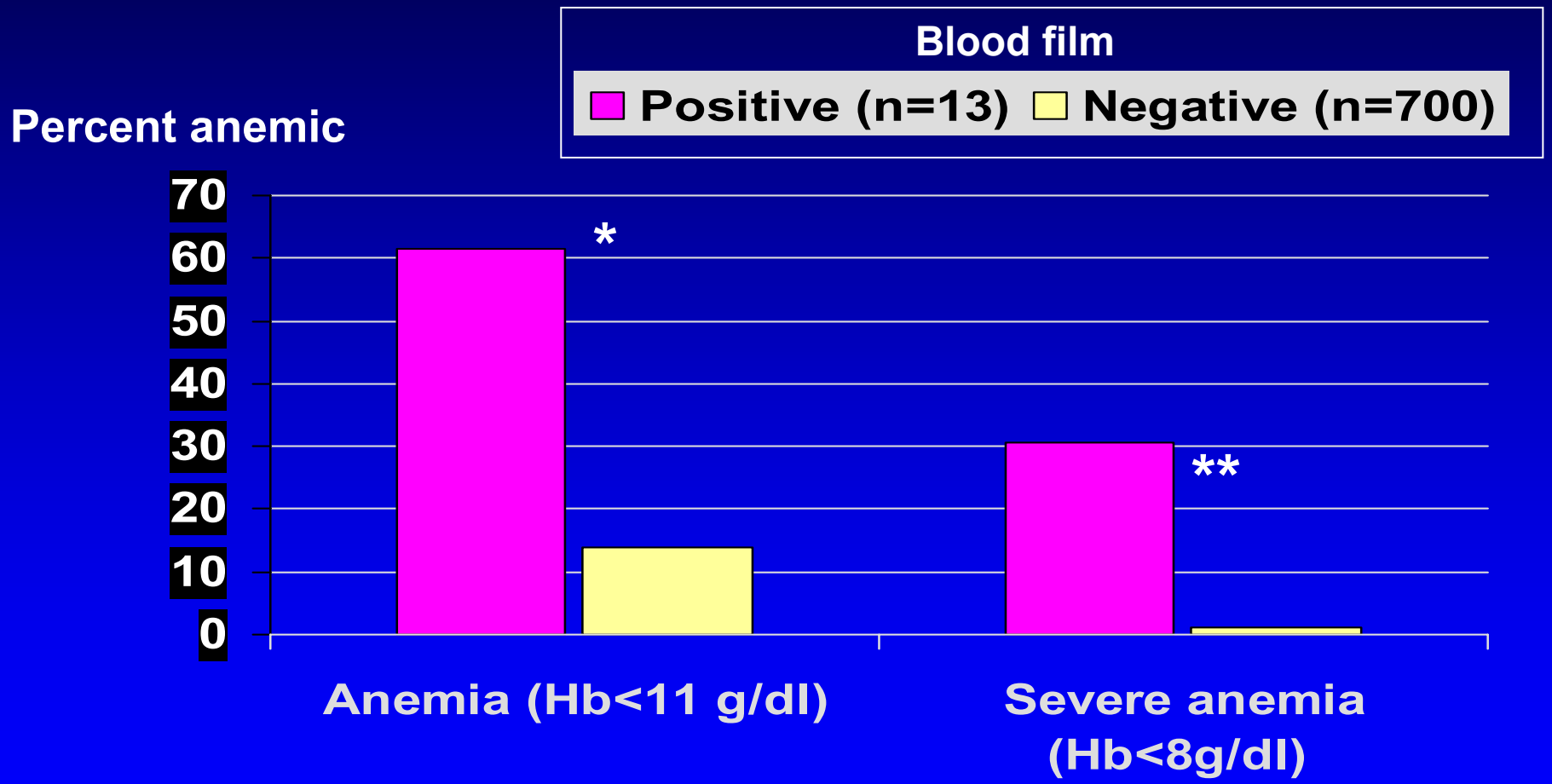


Low Birth Weight and Infant Mortality



Adapted from Greenwood et al, Trans Roy Soc Trop Med Hyg (1992) 86:483-485.

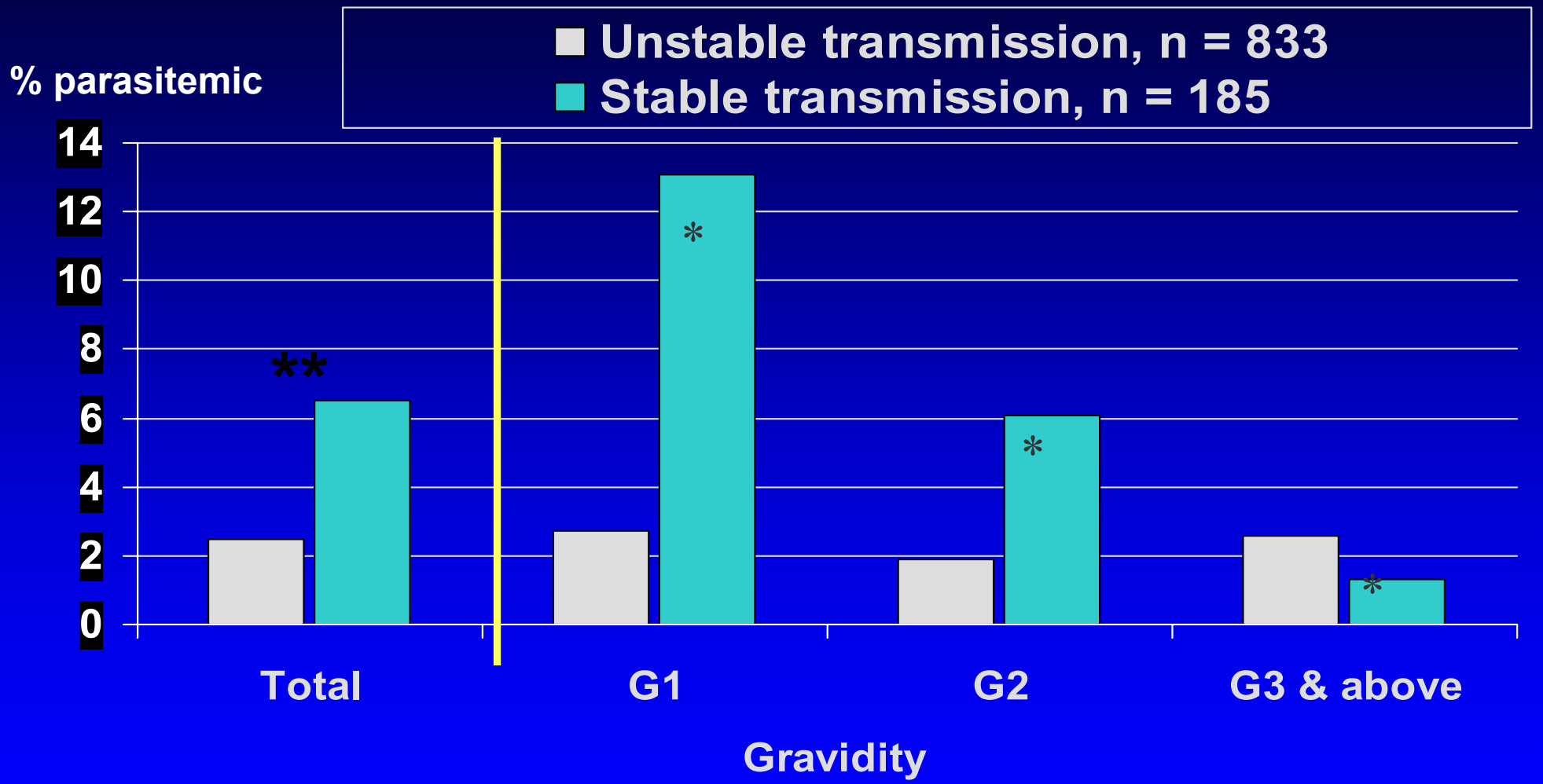
Peripheral parasitemia as a risk factor for anemia in unstable areas (n=713)



* $P < 0.001$
RR = 4.4

** $P < 0.001$
RR = 31

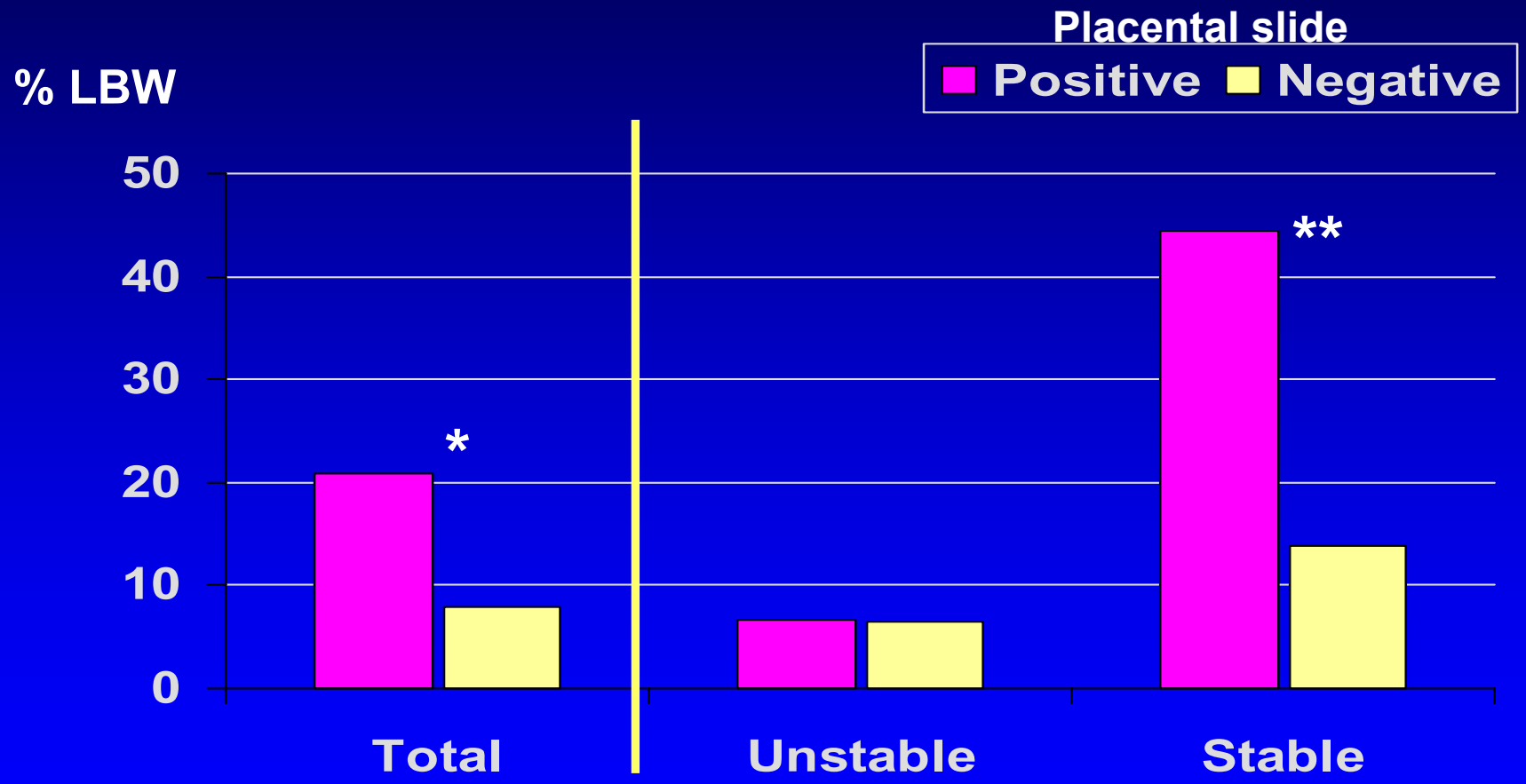
Placental parasitemia at delivery



** *P* = 0.006 difference between stable & unstable

*chi-square trend, *P* = 0.006

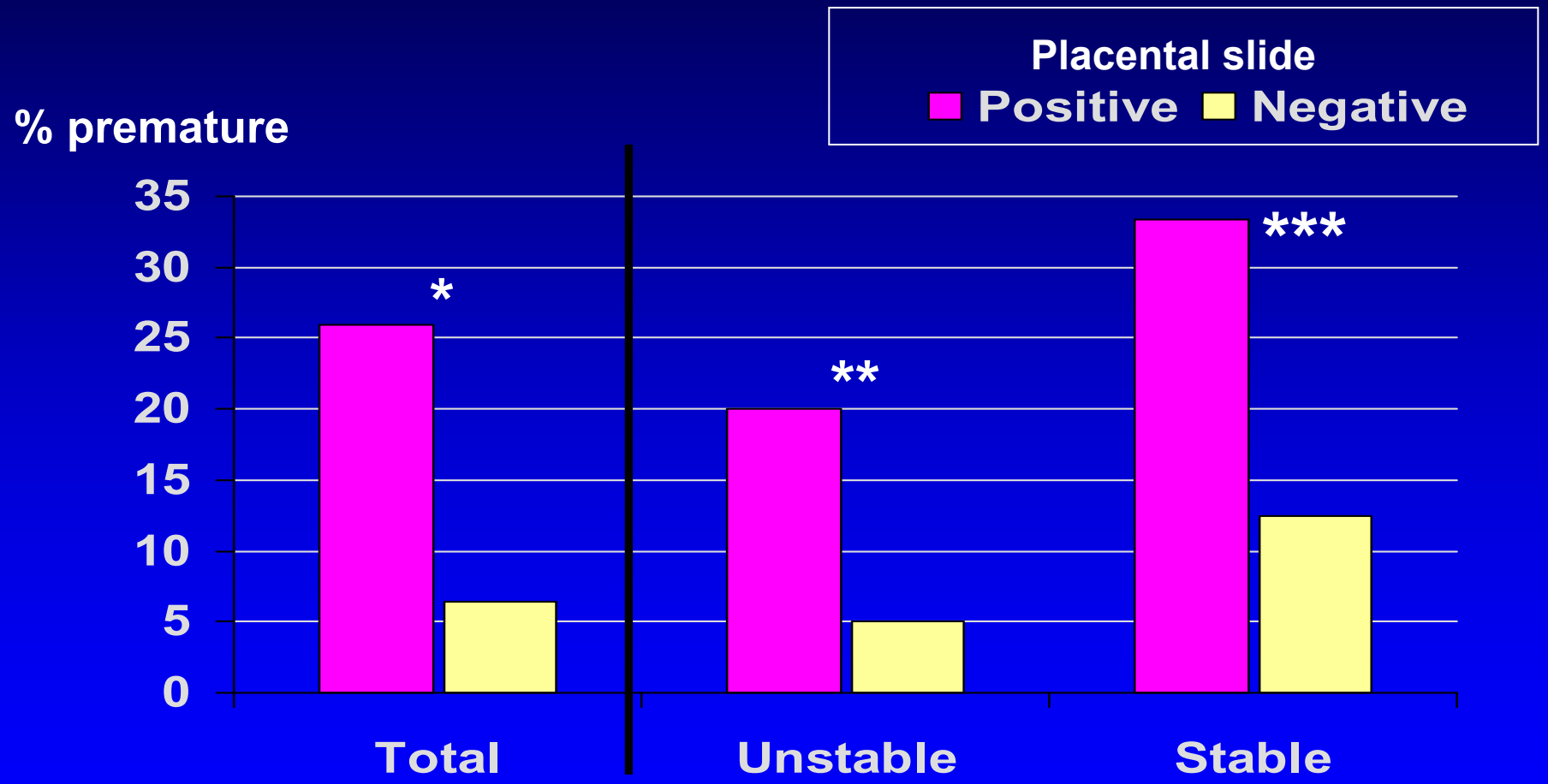
Association between placental parasitemia and low birth weight (<2,500 grams)



* *P* = 0.02
RR = 2.7

** *P* = 0.01
RR = 3.2

Association between placental parasitemia and prematurity (< 37 weeks)



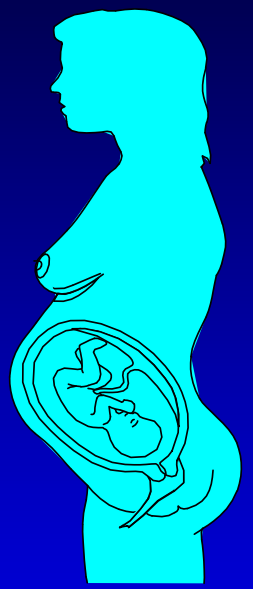
* $P < 0.001$ RR = 4.0

** $P = 0.01$ RR = 3.9

*** $P = 0.04$ RR = 2.7

How big a problem is it?

Malaria in Pregnancy



- 40% of world population is at risk of malaria.
- 90% of global burden of malaria and deaths occur in Sub Saharan Africa.
- 45 million pregnant women live in malarious areas

- 23 million in sub-Saharan Africa.

- Frequency and severity of malaria is increased during pregnancy.
- Pregnant women are likely to have2-10 times higher mortality than non pregnant women

Who is most affected?

- Low, unstable transmission
  - all pregnancies
- High, stable
  - primigravidae, secundigravidae
  - HIV-infected women

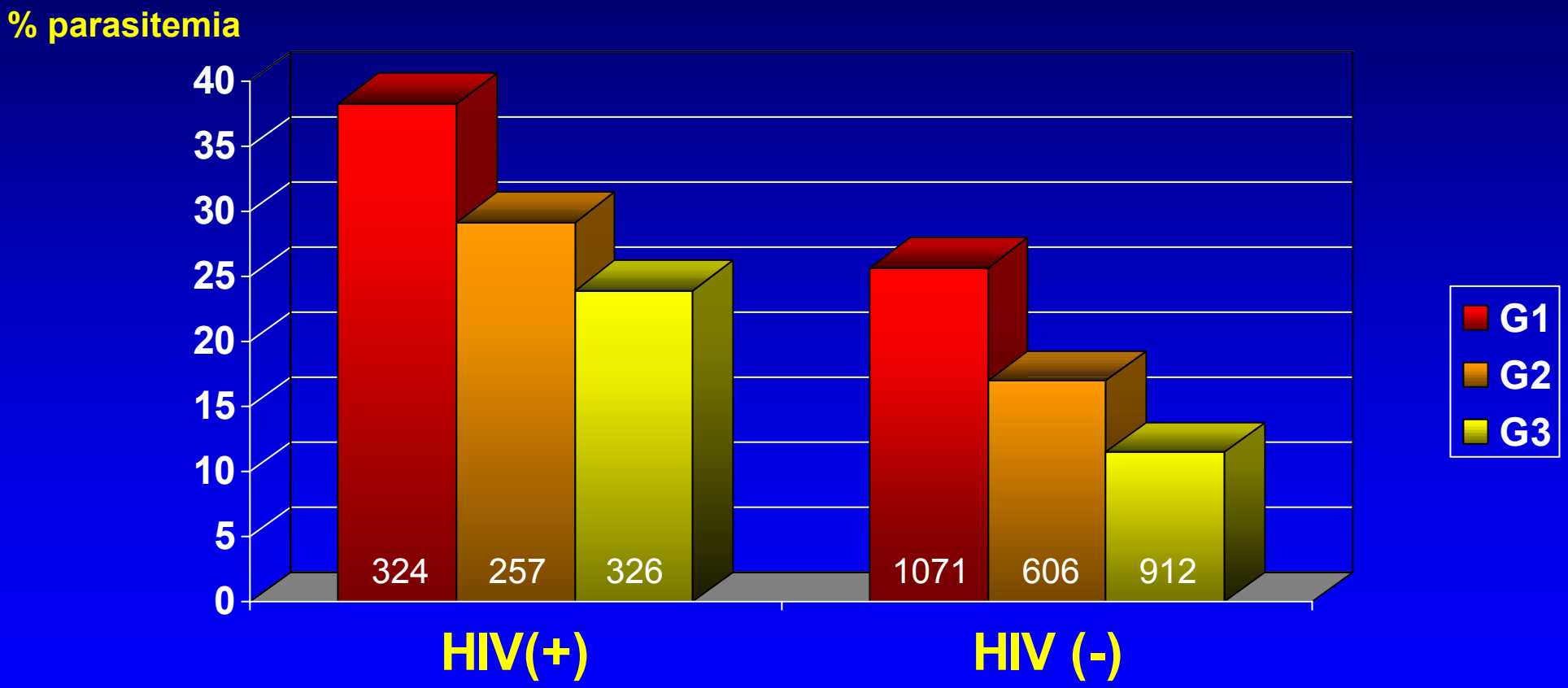
Malaria in Pregnancy

- Pregnant women have higher densities and prevalences of parasitemia
- Stable transmission:
  - Women in 1st & 2nd pregnancies most affected
  - Biologic mechanism for parity-specific differences not understood
  - Parasitemia prevalence highest 20-36 weeks
  - Clinical malaria higher in 2nd and 3rd trimesters

HIV and Malaria in Pregnant Women

- HIV-positive women have higher prevalences and densities of peripheral and placental parasitemia
- Effect seen in HIV-positive women of all gravidities

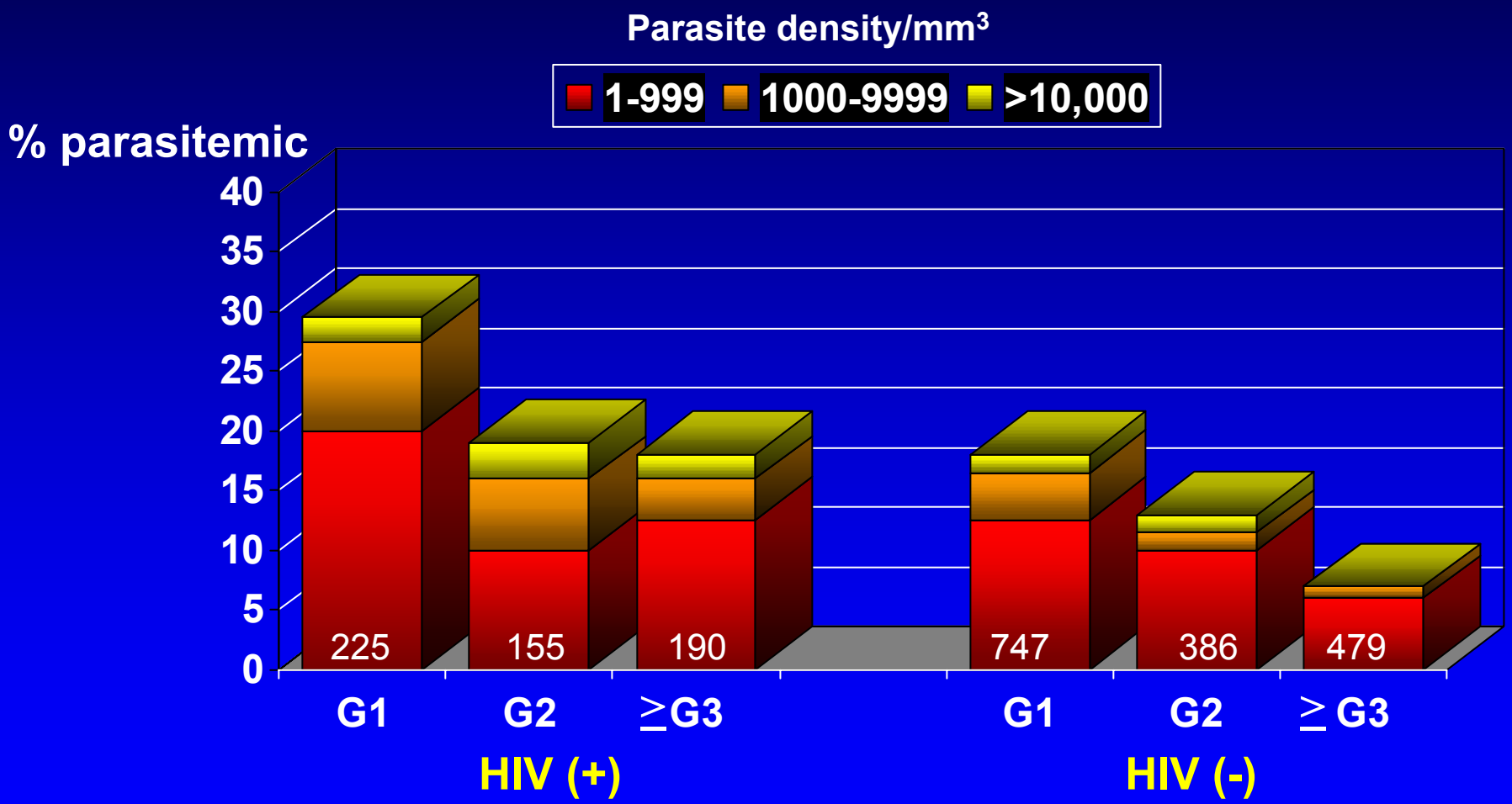
Antenatal clinic parasitemia by HIV status and pregnancy number, Kisumu, Kenya, 1996-98



N = 3496

Summary RR = 1.58 (1.41-1.78) p>0.001)

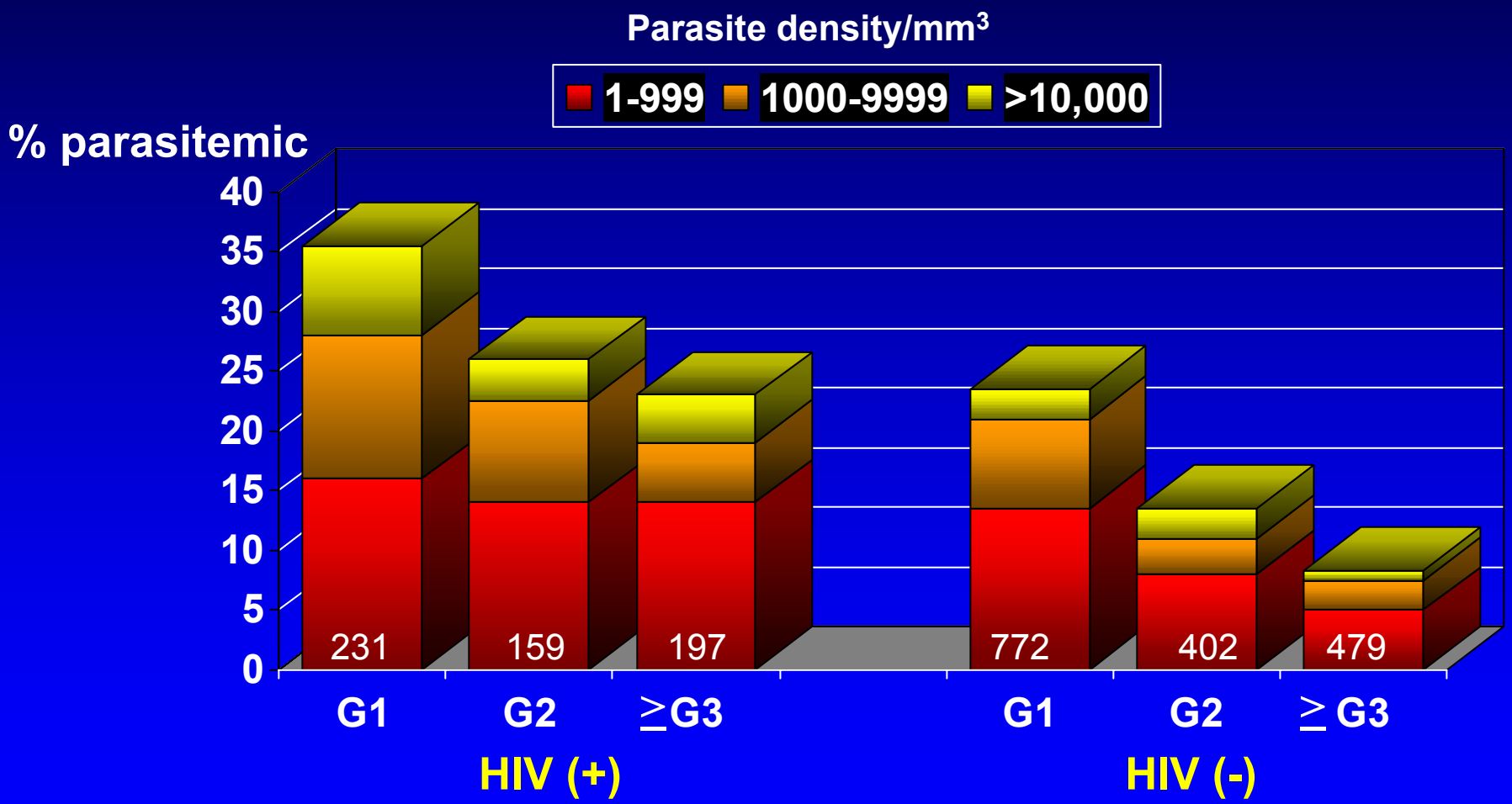
Delivery peripheral parasitemia by HIV status and pregnancy number, Kisumu, Kenya, 1996-98*



N = 2182

Summary RR = 1.58 (1.35-1.85), p<0.001

Placental parasitemia by HIV status and pregnancy number, Kisumu, Kenya, 1996-98*



N = 2263

Summary RR = 1.63 (1.41-1.89), p<0.001

What can be done about it?

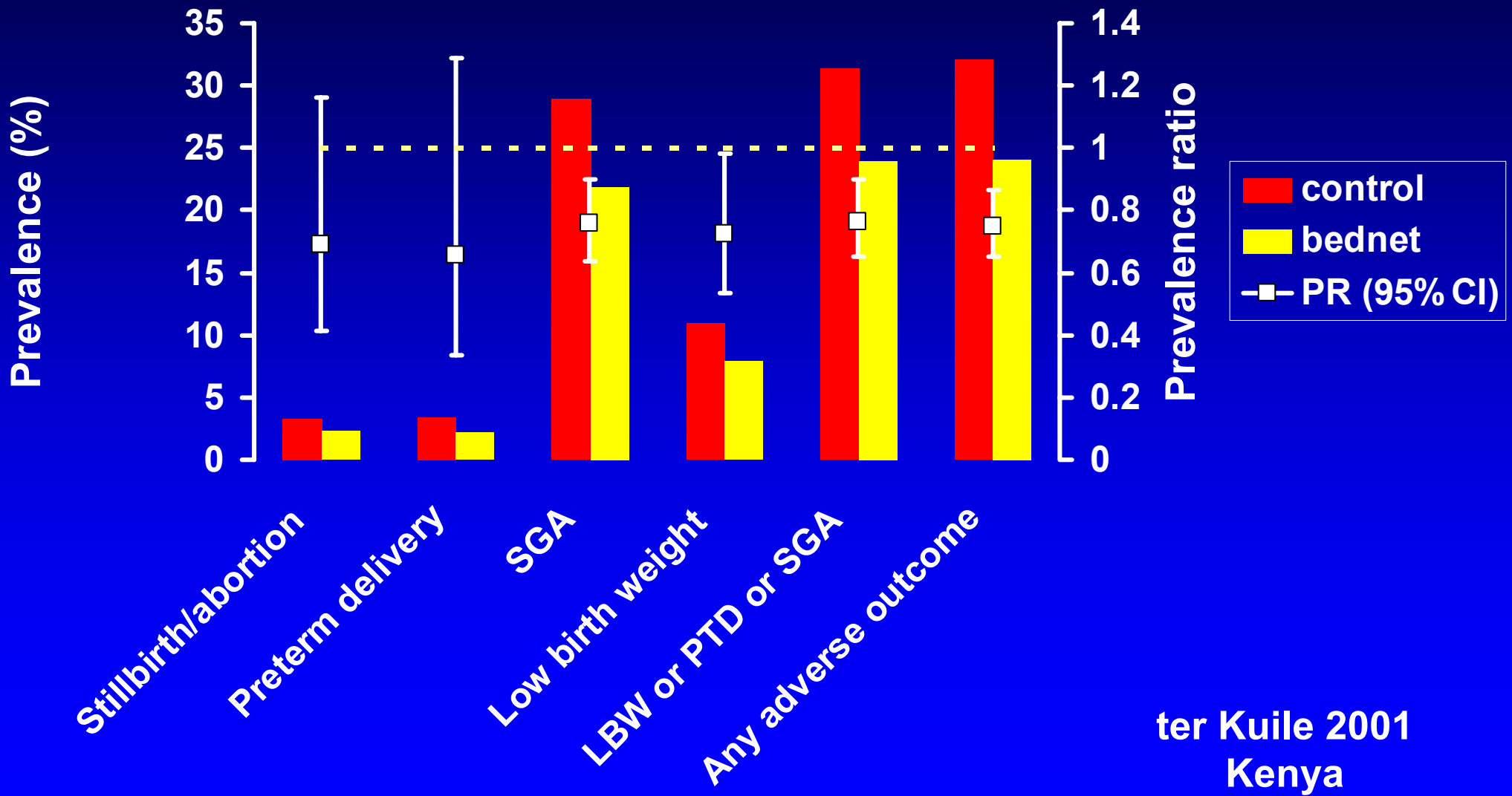
Cost-effective tools to fight malaria during pregnancy

- **Treatment**
  - *Case management*
- **Prevention**
  - *Intermittent preventive treatment (IPT)*
  - Insecticide-treated nets

Insecticide-treated nets protect pregnant women against malaria

Bednets: Birth Outcome

Gravidae 1-4



ter Kuile 2001
Kenya

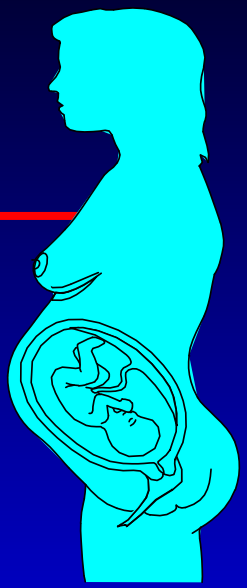
Summary

Among Gravidae 1-4 bednets associated with:

- **During pregnancy**
  - 38% (17-54) reduction in peripheral parasitemia
  - 21% (4-35) reduction in all cause anemia (Hb < 11 g/dl)
  - 47% (6-71) reduction in severe malarial anemia
- **At delivery**
  - 23% (6-37) reduction in placental malaria
  - 28% (2-47) reduction in LBW
  - 25% (13-35) reduction in any adverse birth outcome`

ter Kuile 2001
Kenya

Uses of antimalarial drugs during pregnancy



- Febrile case management
- Chemoprophylaxis
- Intermittent preventive treatment (IPT)

Treatment During Pregnancy

- Drugs of choice depend on drug sensitivity patterns
- CQ safe - use for sensitive parasites
- CRPF - SP or quinine+SP
- Quinine/quinidine safe at therapeutic doses
- Theoretical concerns about sulfa drugs displacing bilirubin in newborn - benefits outweigh theoretical risks

Malaria in Pregnancy

WHO - Expert Committee on Malaria

- **1986** On initial visit a curative dose of an antimalarial drug, followed by chemoprophylaxis

Chemoprophylaxis

- Refers to use of drug at < therapeutic dosage
- Weekly chemoprophylaxis previously the method of choice but program effectiveness compromised by:
  - Increasing parasite resistance to chloroquine and
  - Lack of patient compliance with frequent dosing schedule
- Estimates of program effectiveness < 10%

The move away from chemoprophylaxis is not about a specific drug but about an ineffective program strategy

Malaria in Pregnancy

WHO - Expert Committee on Malaria

- 1986 On initial visit a curative dose of an antimalarial drug, followed by chemoprophylaxis

- **2000 In highly endemic areas, intermittent treatment with an effective antimalarial drug**
  - **Preferably one-dose**
  - **For primi- and secundigravidae**
  - **From 2nd trimester onwards at intervals greater than one month**

Intermittent preventive treatment (IPT)

IPT involves the administration of full, curative treatment doses of an effective antimalarial drug at predefined intervals during pregnancy

Intermittent Preventive Treatment - possible regimens -

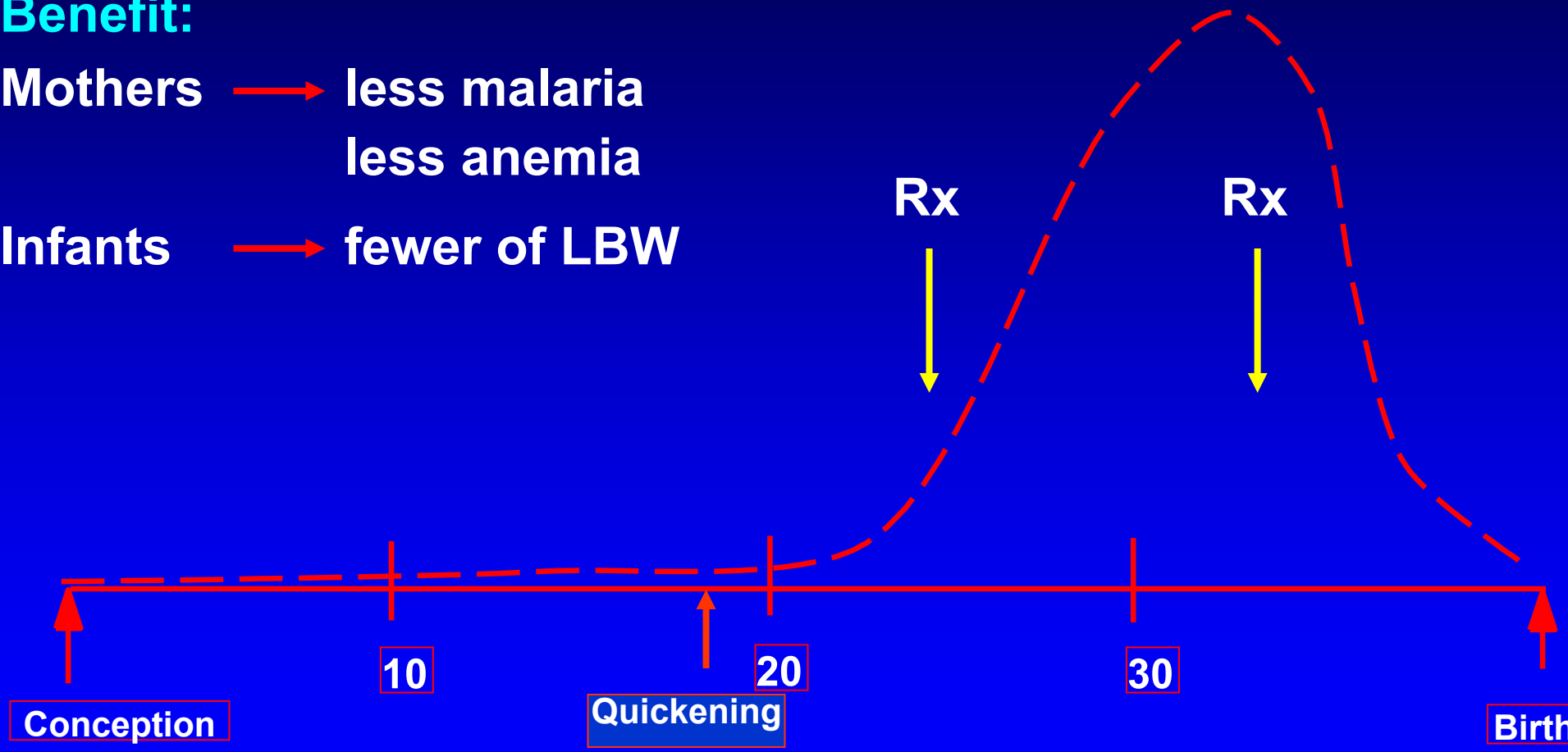
- **Sulfadoxine-pyrimethamine (S-P)**: at least two treatment doses at monthly visits beginning after quickening
  - ✓ for areas with CQ-resistant *P. falciparum*
  - ✓ only drug for which there is adequate safety, efficacy and effectiveness data at this time
- **Chloroquine (CQ)**: at least two treatment doses at monthly visits beginning after quickening
  - ✓ for areas with CQ-sensitive *P. falciparum* and/or other malaria species
  - ✓ Initial analysis of study from Mali indicates adequate safety and efficacy?
  - ✓ Effectiveness likely to be undermined by need for optimal compliance with 3-day regimen
- **Other drugs** (e.g. artemisinin derivatives, LAPDAP, CT)?
  - ✓ Need for research on safety and effficacy

Intermittent Preventive Therapy

Benefit:

Mothers → **less malaria**
less anemia

Infants → **fewer of LBW**



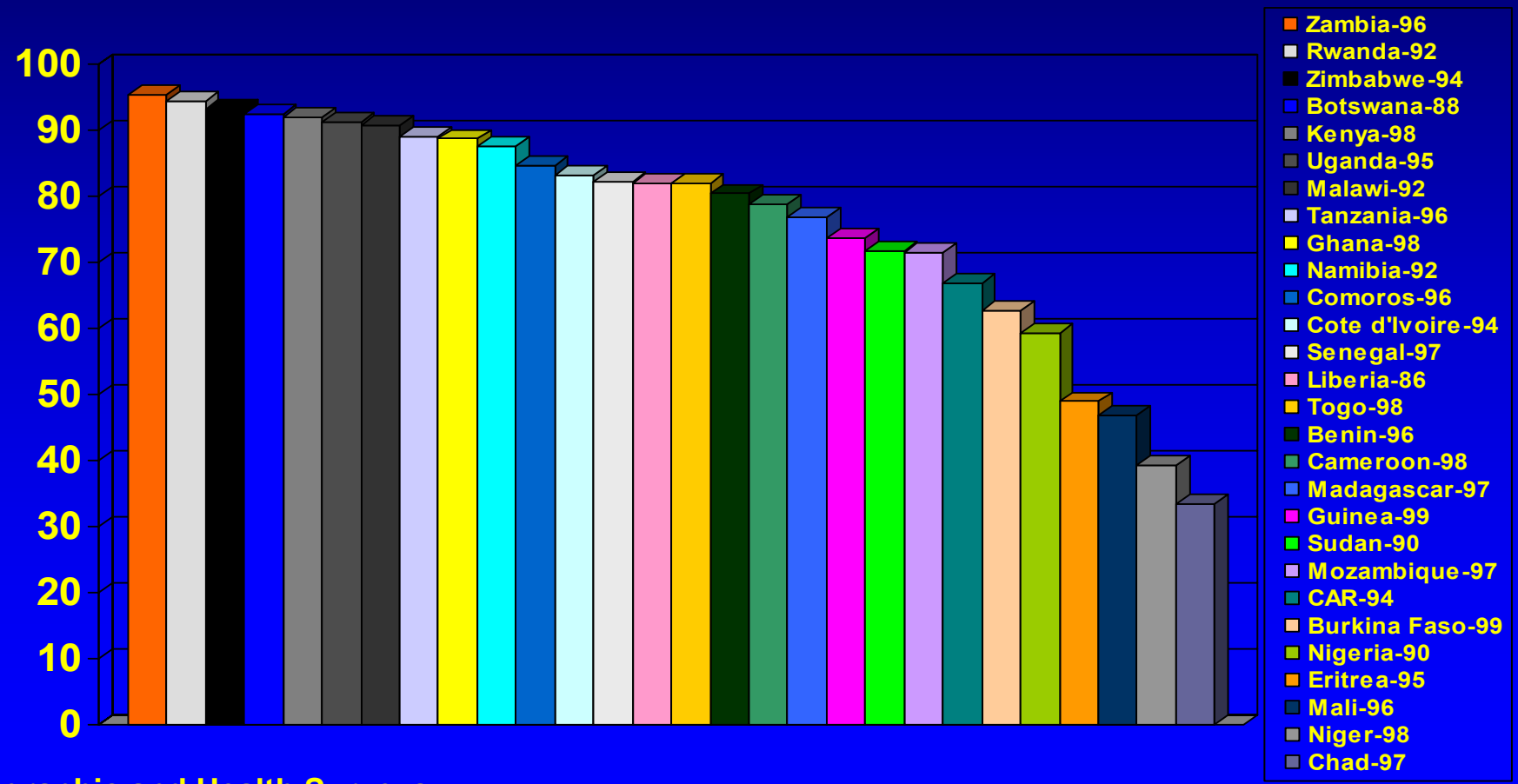
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Countries which have adopted IPT and ITNs as policy for pregnant women

- Kenya
- Malawi
- Nigeria
- Tanzania
- Uganda
- Zambia

Program opportunity

In most countries of Africa >70% of pregnant women attend antenatal clinics



Demographic and Health Surveys

Safety of antimalarials for use in pregnancy

Difficult to unequivocally prove safety

Widely varying amounts of information allow us to consider drugs as:

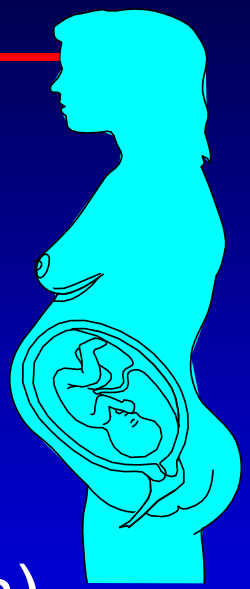
- drug useful for a pregnant woman
- possibly useful for pregnant woman, but more data are needed
- not useful for a pregnant woman because of known adverse events associated with their use in pregnancy, and safe and efficacious alternatives exist

Two major issues for use of antimalarials during pregnancy:

Is the drug toxic to the woman or the foetus during pregnancy, or to the infant during lactation?

Is the drug use strategy and its implementation likely to have its desired effect--to reduce the burden of malaria during pregnancy?

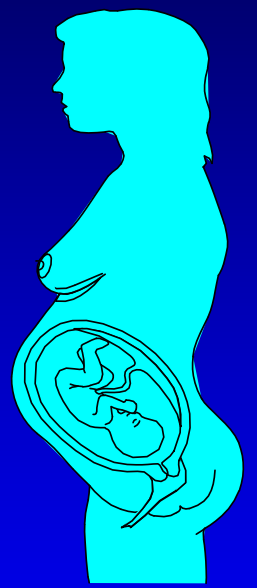
Drugs Believed to be Safe



- Chloroquine
- Quinine/quinidine
- Proguanil
- Pyrimethamine
- Sulfadoxine-pyrimethamine (2nd & 3rd trimesters)
- Dapsone-pyrimethamine (Maloprim)
- Chlorproguanil-dapsone (Lapdap)
- Clindamycin

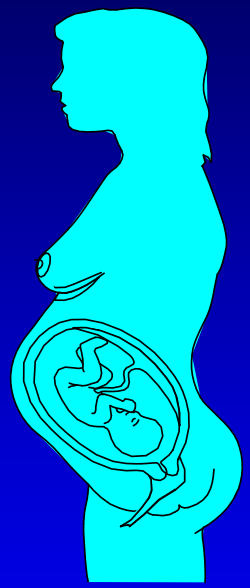
Drugs with questionable safety or with insufficient data

- Amodiaquine
- Mefloquine
- Artemisinins
- Atovaquone (component of Malarone)
- Azithromycin
- Lumefantrine (usually combined with artemether--Coartem, Riamet)
- Combination therapy



Contraindicated* Drugs

- Tetracycline
- Doxycycline
- Primaquine
- Tafenoquine
- Halofantrine

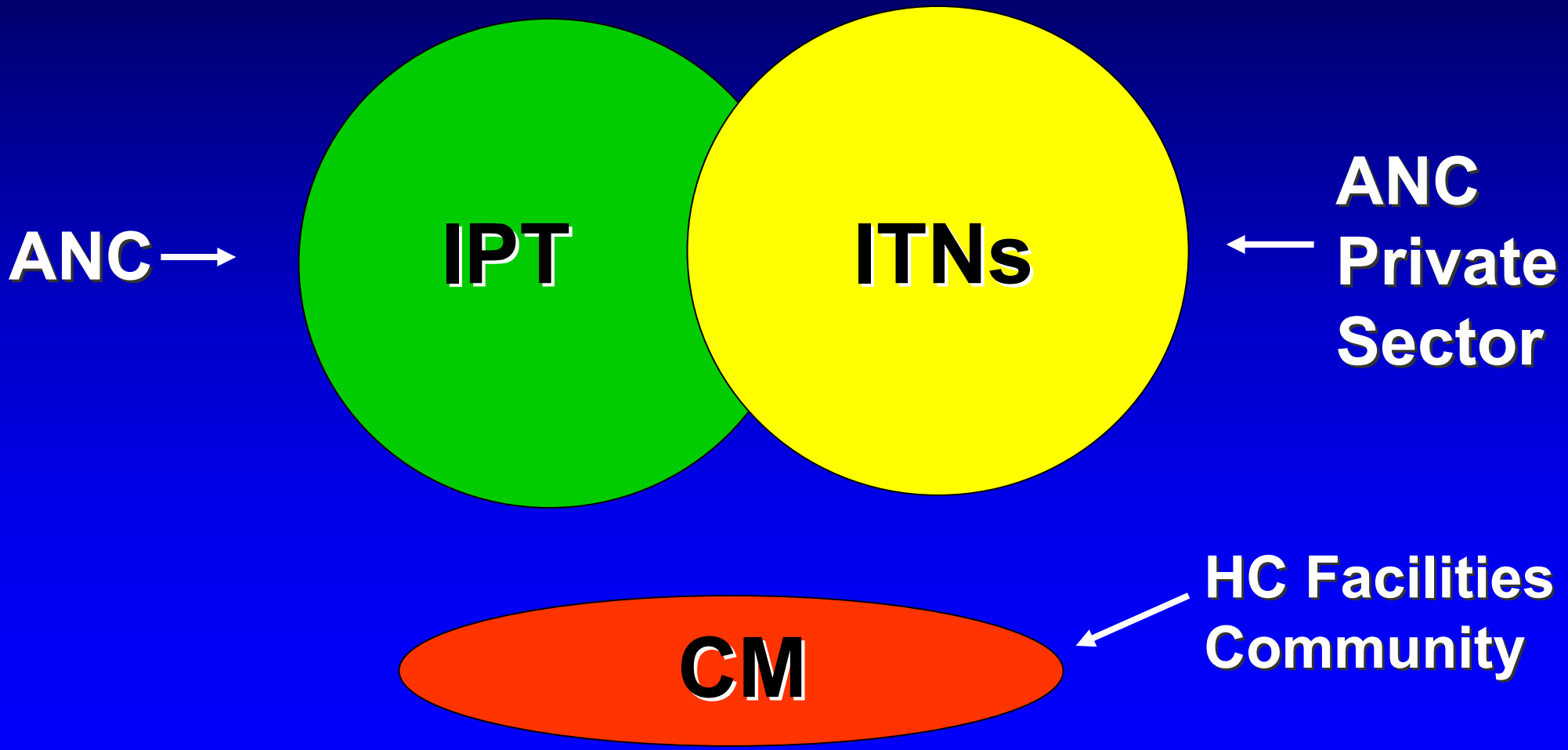


*** Note: if serious illness, and where limited number of drugs are available, it is necessary to balance risk of life of the mother with hypothetical risks to the infant**

Cochrane Library : 2002

- Drugs given routinely for malaria during pregnancy reduces severe anaemia in the mother, and are associated with higher birthweight and probably reduced perinatal mortality. (low parity women)

Malaria Control during Pregnancy
Implementation Packages



Malaria-Pg Program Partners

- Roll Back Malaria partners: USAID,DFID
- UN Agencies: WHO, UNFPA, UNICEF
- Technical: LSTMH/Gates, Columbia Univ., PREMA-EU, CDC, JHPIEGO, TDR/MIM, CISM (Univ. Barcelona), Wellcome Trust, Medical Research Council
- Africa-based: KEMRI, NIMR/Dar-es-Saalam, Blantyre Integrated Malaria Initiative, DCM Univ. Addis Ababa

Research opportunities (1)

- Improved understanding of the burden of malaria in pregnancy on maternal and child health
- Develop methods to improve implementation and compliance with control strategies :
  - innovative drug delivery
  - reaching adolescent girls
  - using anaemia to focus on the problem
  - emphasis on reproductive health

Research Opportunities (2)

- Find alternative drugs to SP for IPT
  - LAPDAP
  - CT
  - Artemesinins
  - Mefloquine
  - Malarone???
- Assess interactions between ITNs and IPT
- Define impact of IPT and ITNs on maternal immunity and on offspring.

Research opportunities (3)

- Interactions between malaria and HIV on maternal and infant health
- Social science issues
  - ANC use
  - perceptions of pregnant women of intervention tools
  - cost-effectiveness studies

….women are not dying because of diseases we cannot treat. They are dying because societies have yet to make the decision that their lives are worth saving.

Dr. M. Fathalla