CASE
CASE WESTERN RESERVE UNIVERSITY

# Malaria and other Parasitic Infections During Pregnancy and Infancy

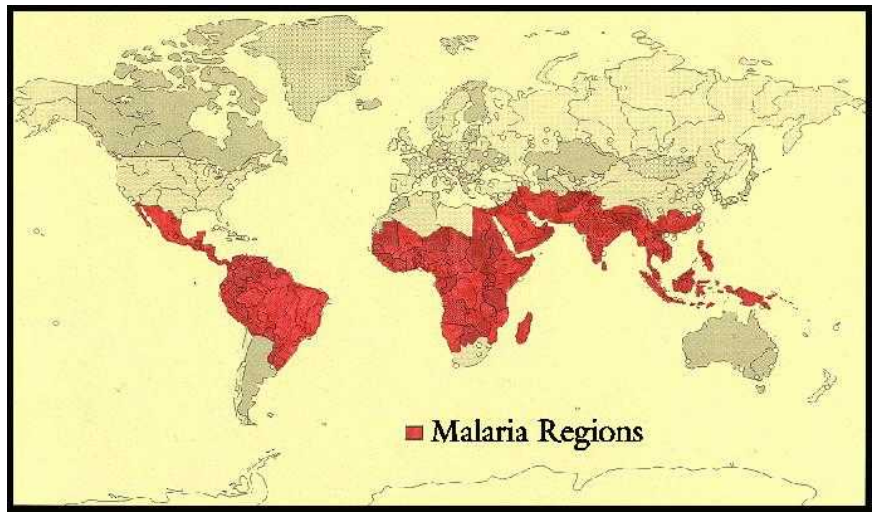
Christopher L. King, MD, PhD
*Center for Global Health and Diseases*

# Overview

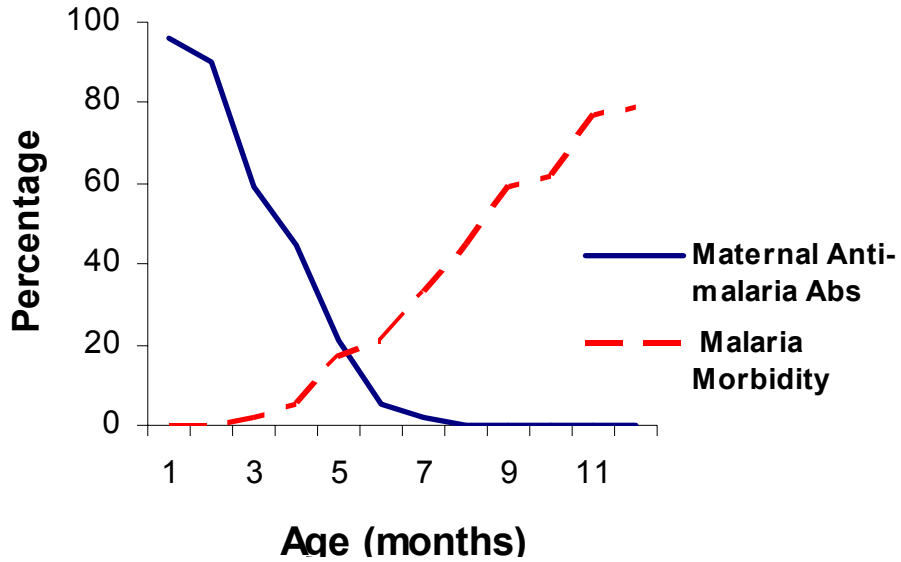
- Burden of parasitic diseases in infants
- Status of vaccines against parasitic infections
- Impact of prenatal exposure to parasites on the fetal immune response
- How does this prenatal exposure affect
  - Subsequent immune response to potential vaccine candidates
  - Efficacy to other vaccines

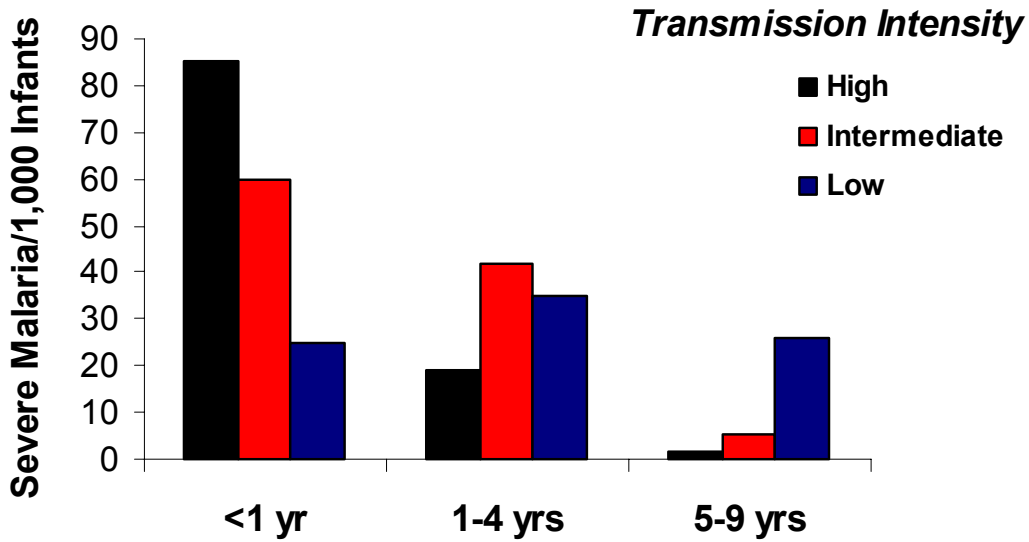
# Parasitic Diseases in Infants

- Malaria
  - 300-500 million infection/yr
  - 100 million clinical cases/yr
  - ~2.7 million deaths/yr
  - >75% are in children <5 years of age
  - ~40% of world population lives in malaria endemic parts of the world



# Burden of Malaria is in Infancy



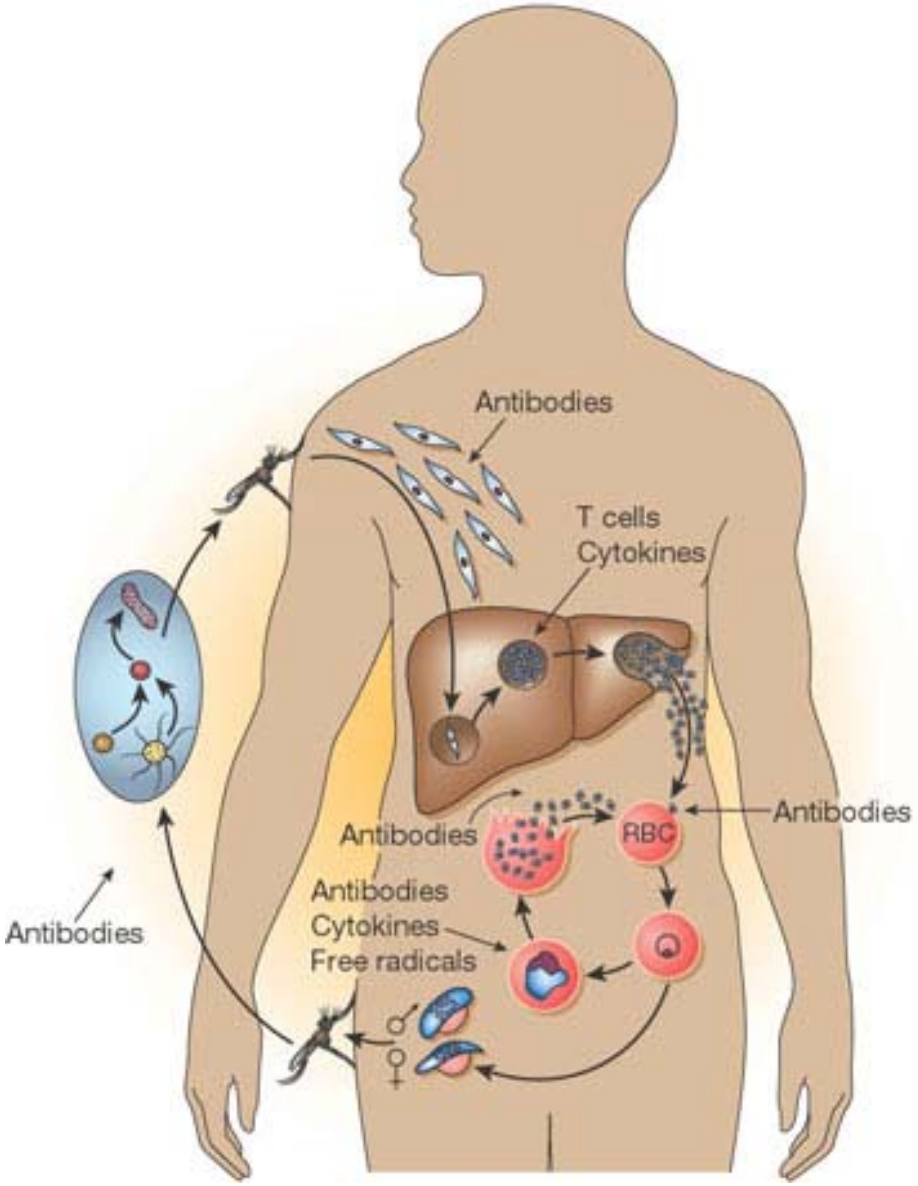




Snow, et al Lancet, 1997

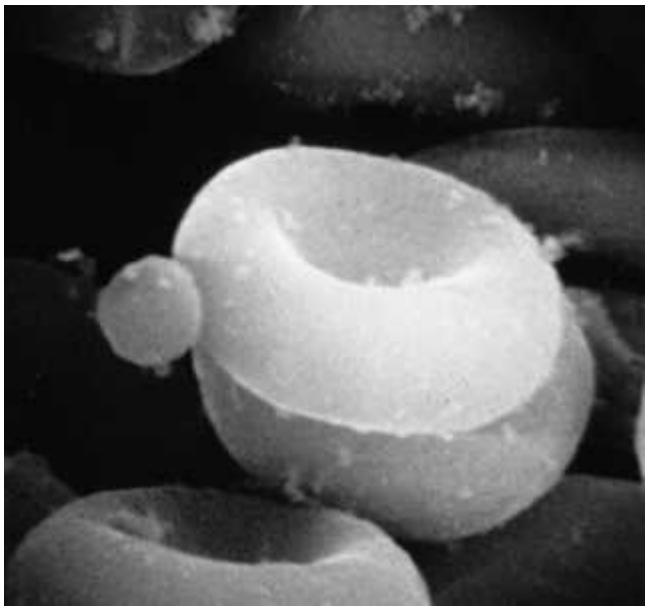
# Burden of other Parasitic Infections

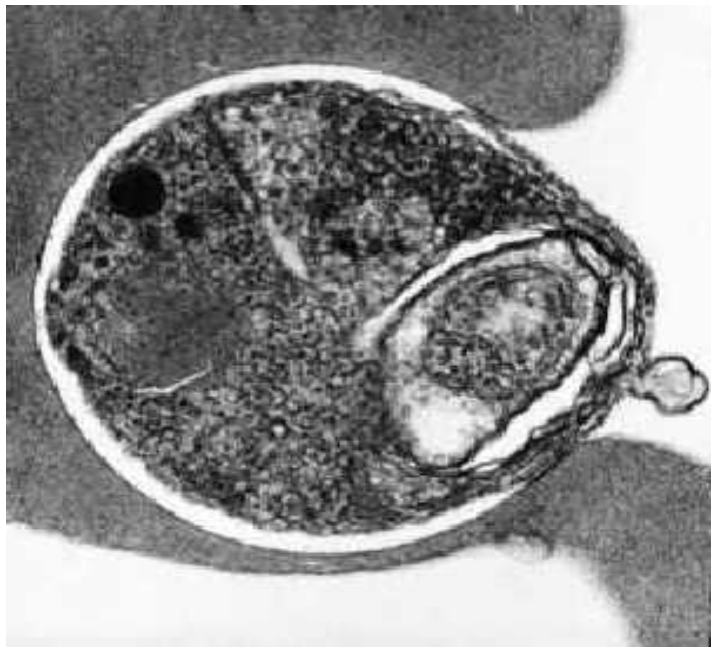
- *Helminthic Infections (Intestinal [hookworm],schistosomiasis, LF)*
  - >1.3 billion infected worldwide/chronic
  - Peak prevalence/morbidity during adolescence
  - Anemia, impaired growth and development, infrequently fatal
- *Others – burden comparatively small in children*
  - Trypanosomiasis
  - Leishmaniasis
  - Toxocariasis

# Malaria Vaccines

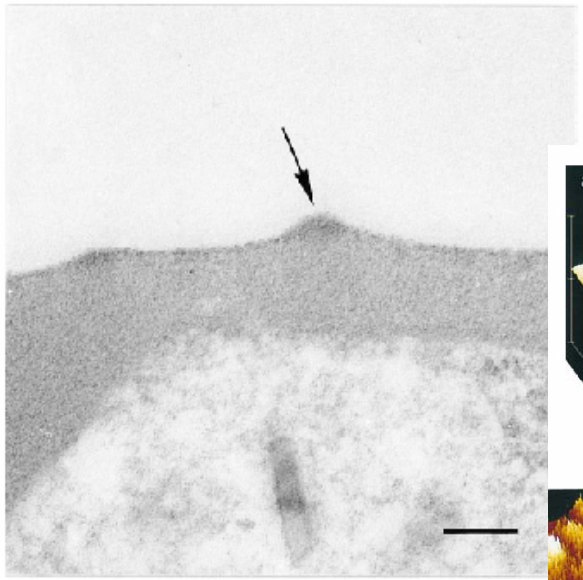


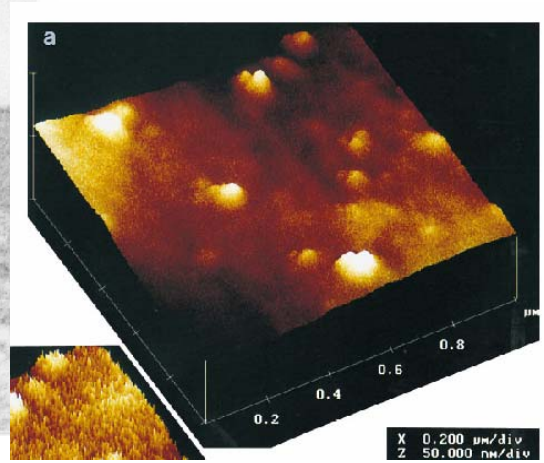

- *Pre-erythrocytic*
  - CSP
  - LSA1
- *Blood Stage*
  - MSP1-42
  - AMA1
  - EBA-175
- *Transmission blocking*
  - Pf25
  - Pf28

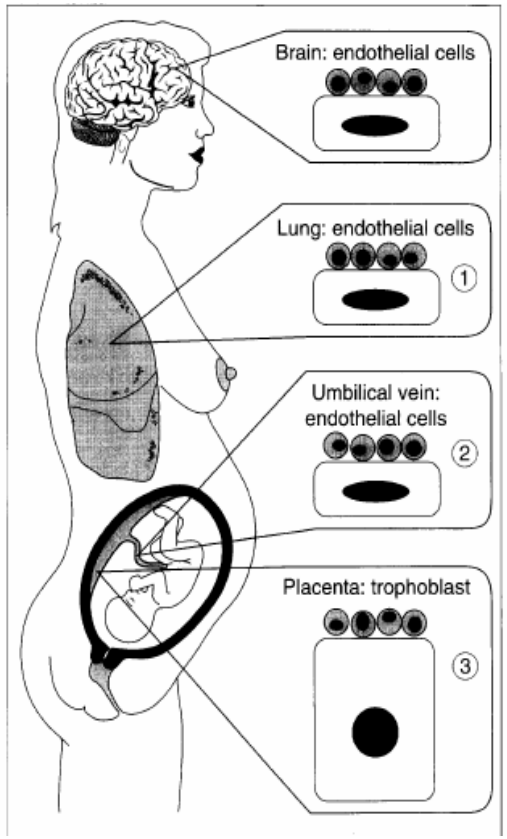




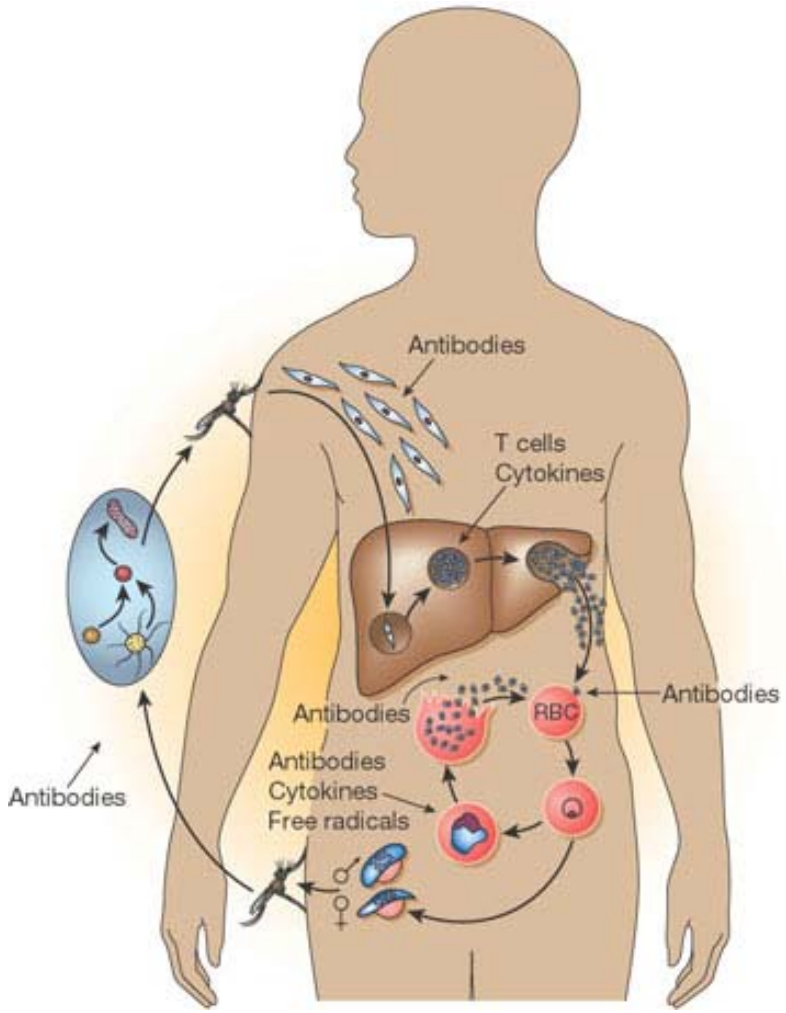
# PfEMP1




a
0.2
0.4
0.6
0.8
X 0.200 µm/div
Z 50.000 nm/div


Brain: endothelial cells
Lung: endothelial cells
1
Umbilical vein:
endothelial cells
2
Placenta: trophoblast
3

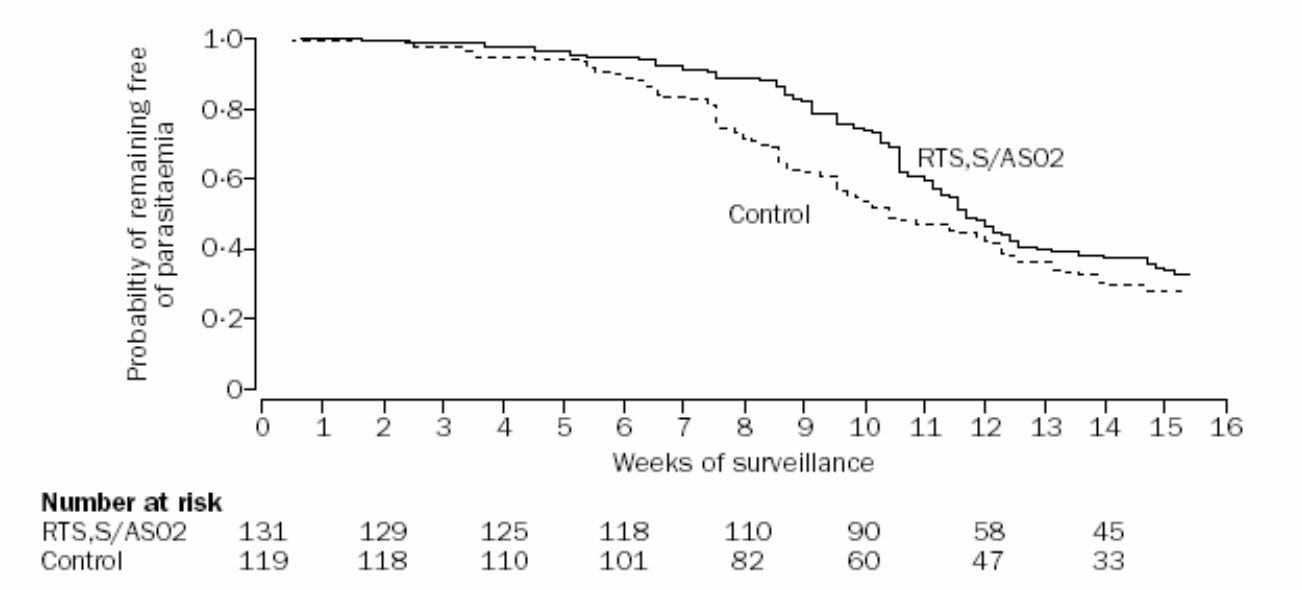
# Malaria Vaccines




- *Pre-erythrocytic*
  - CSP
  - LSA1
- *Blood Stage*
  - MSP1-42
  - AMA1
  - EBA-175
- *Transmission blocking*
  - Pf25
  - Pf28

# Partial Protection to Pre-erythrocytic Stage Malaria Vaccine (CSP)

- Efficacy 34-47% in adults in an endemic area
- Transient protection



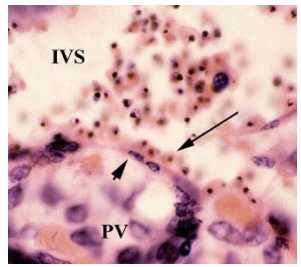

Bojang, et al Lancet 358:1927, 2001

# Helminth Vaccines

- *Hookworm vaccine*
  - irradiated larvae
  - ASP-1,2
  - Partial protection in dogs – no studies in humans
- *Schistosomiasis*
  - Irradiated infective larvae protective in non-human primates
  - No subunit vaccine available
- *Leishmaniasis*
  - Killed - partially effective in humans
  - Subunit protective in animal models, not tested in humans

# Intravascular Parasitic Infections and the Fetus

| *Parasite* | *Congenital Infection* | *Circulating Ag in Cord Blood* |
|---|---|---|
| **Malaria** | + | + |
| **Schistosomiasis** | - | + |
| **LF** | - | + |
| Hookworm | - | - |
| *T. cruzi* | + | + |
| Toxoplasmosis | + | + |



- How often do parasites or their soluble products cross the placenta?
- Does antigen exposure of the fetus stimulate an immune response or generate tolerance?
- Does prenatal antigen exposure affect maturation of fetal immune response? Does this alter immune responses to other antigens?
- Does fetal exposure affects subsequent susceptibility to infection and disease later in childhood?

# Birth Cohort Study

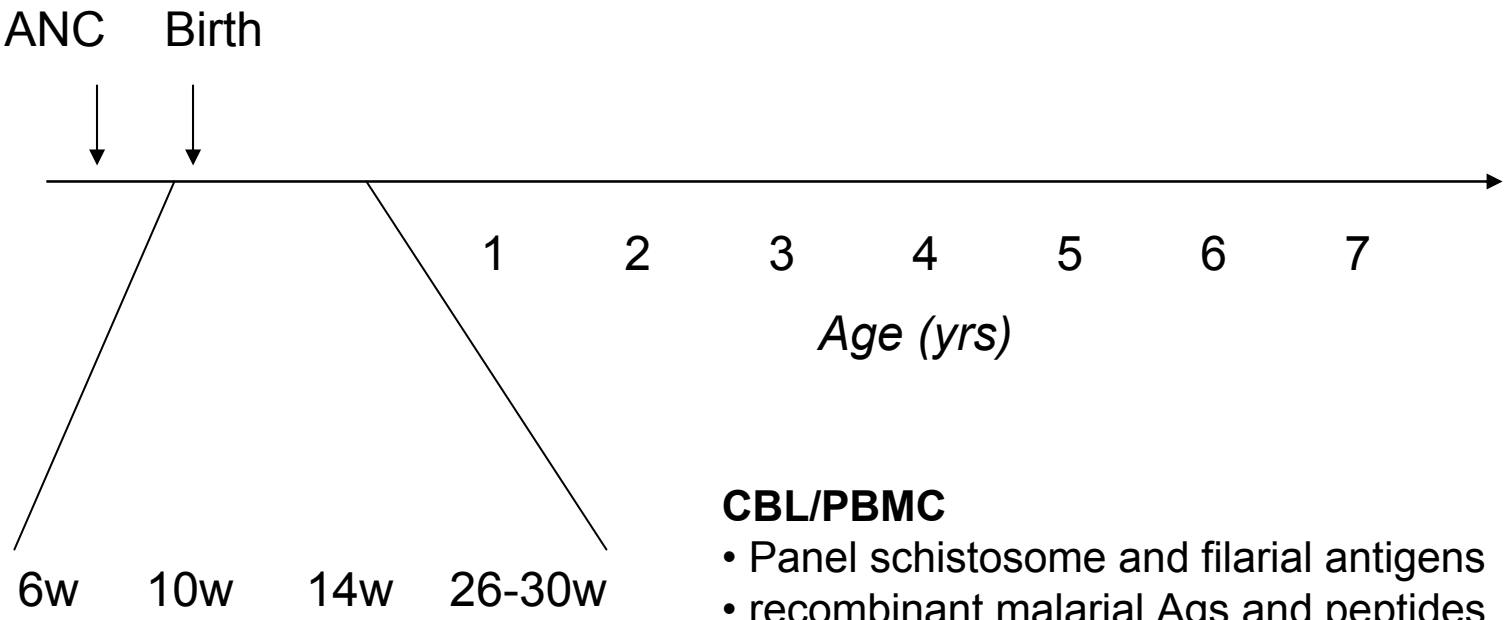
***Prospective cohort study*** **comparing newborns of parasite infected verses uninfected mothers stratified by whether the fetus acquires an immune response *in utero to* parasite antigens**

***Setting:*** **Women and their offspring born at the Msambweni District Hospital, Kwale District, Coast Province, Kenya.**

***Enrollment Criteria*****: healthy, term, vaginal deliveries**

**Parasite Infections**

- malaria blood smears, cir Ag and PCR
- Filariasis cir Ag
- Schistosomiasis – egg in urine
- Intestinal helminths - stools




PRP-specific titers
following Hib vaccination

**CBL/PBMC**

- Panel schistosome and filarial antigens
- recombinant malarial Ags and peptides
- PPD,TT
- Measure cytokine response by ELISPOT and ELISA
- antibodies to PRP

*Controls*: CBL/PBMC from non-endemic individuals

# What Proportion of Newborns Develop an Immune to Parasite Antigens in Cord Blood?

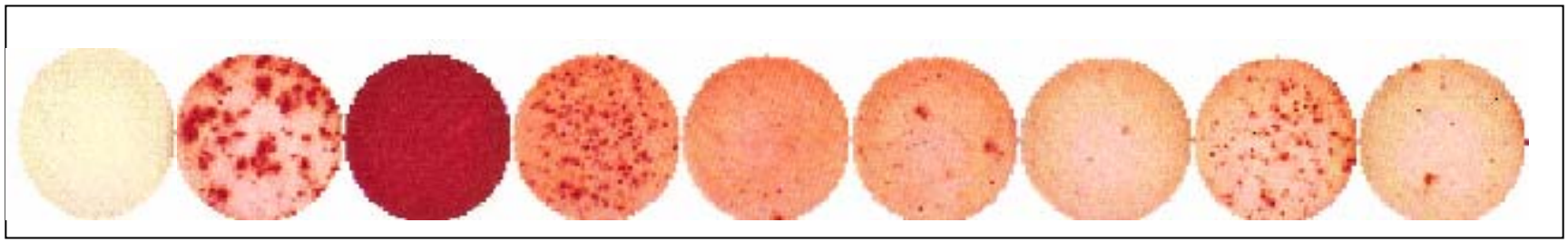
# Neonatal Immune Response to Parasites

| Parasite | % CBL Sensitized* | Type of Ag-specific Immune response |
|---|---|---|
| *Malaria* | 5-62% | Th1/Th2 (CD4/8+) |
| *Lymphatic filariasis* | 26-57% | Th1/Th2 (CD4+) |
| *Schistosomiasis* | 10-30% | Th1/Th2 (CD4+) |
| Onchocerciasis | 5-10%? | Th1/Th2 |
| *T. cruzi* | 23-35%? | Th1 (CD8+) |

**Newborns of infected women during pregnancy*

# IFN-γ Production to Malaria Antigens in Cord Blood

Elispot - IFNγ secreting cells in 4 x$10^5$ CBL



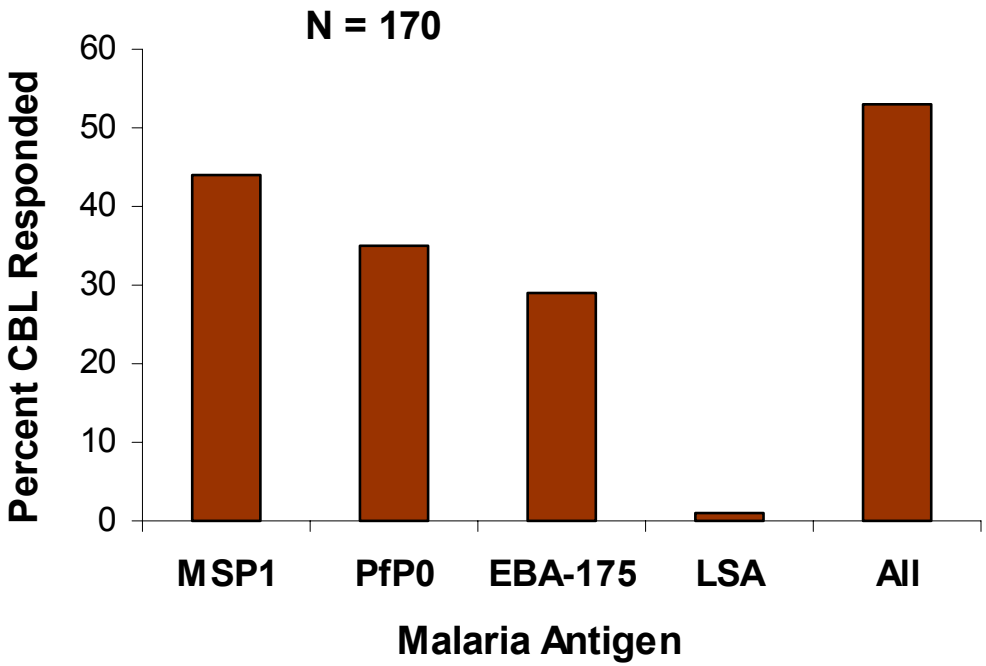

*Malaria blood stage vaccine candidate associated with erythrocytes invasion*

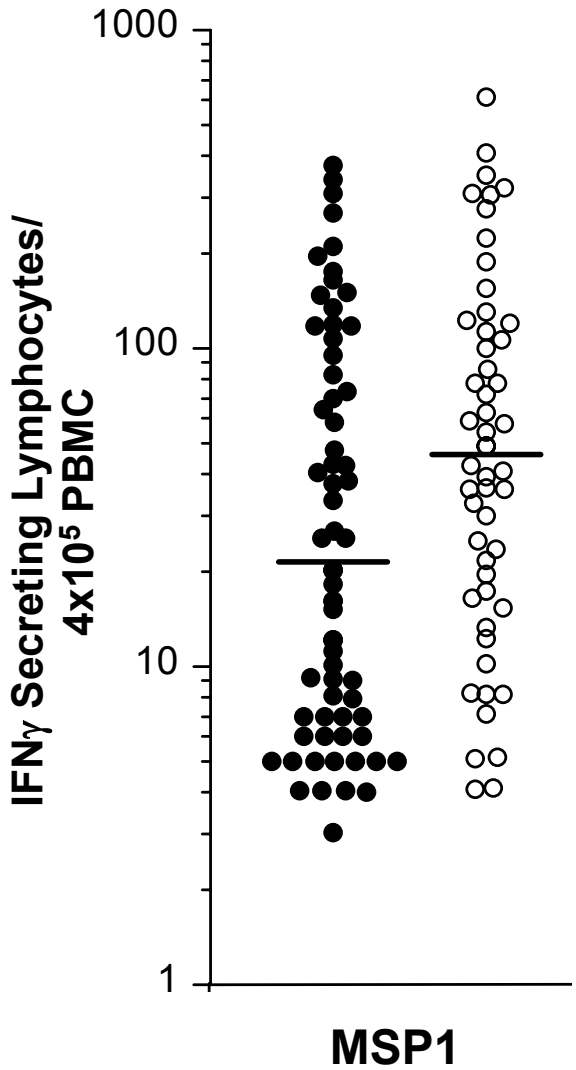
- EBA-175 RII
- MSP1
- PfP0

*Malaria-pre-erythrocyte stage antigen*

-LSA (liver stage antigen)

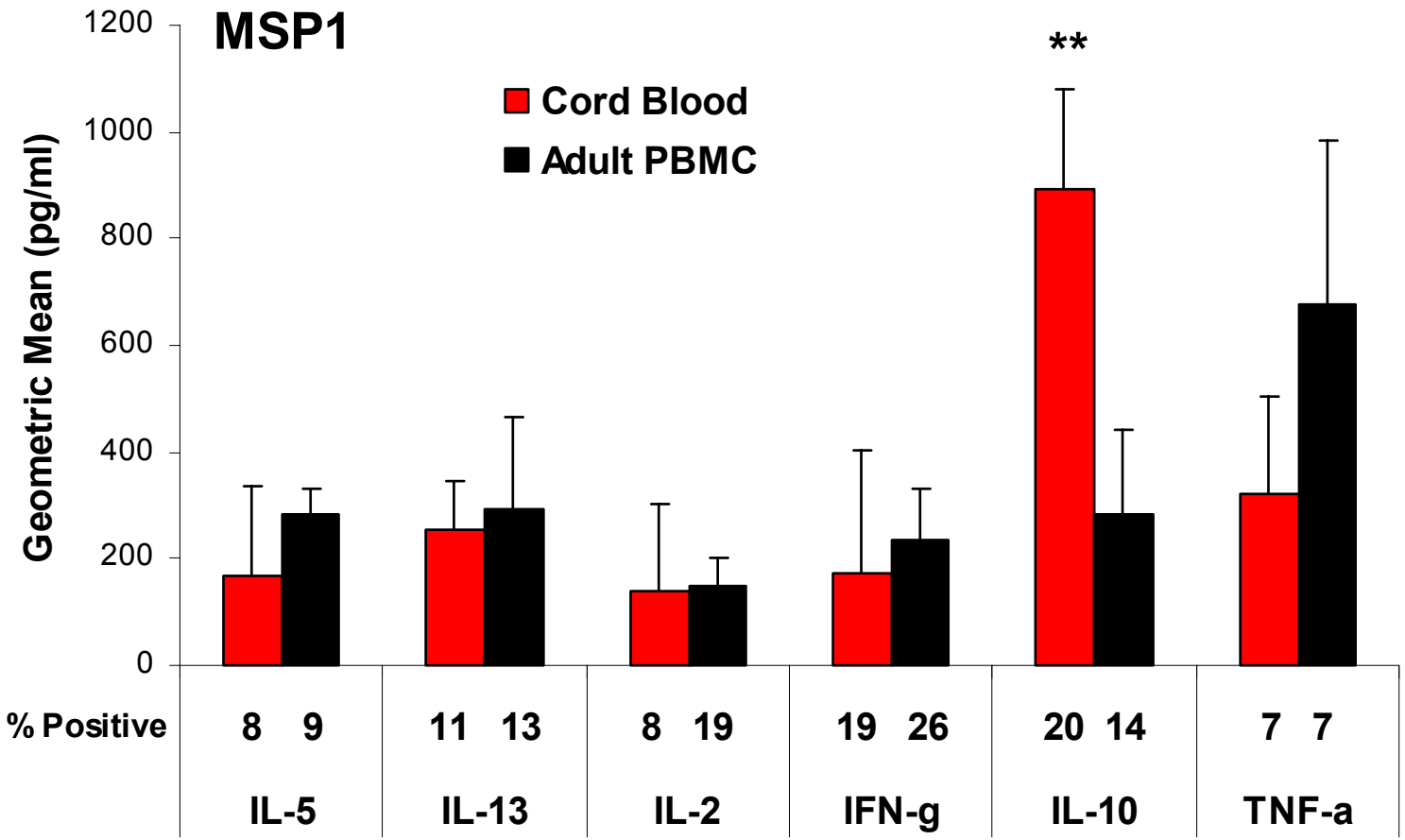
# Malaria-specific Tc responses in Cord Blood



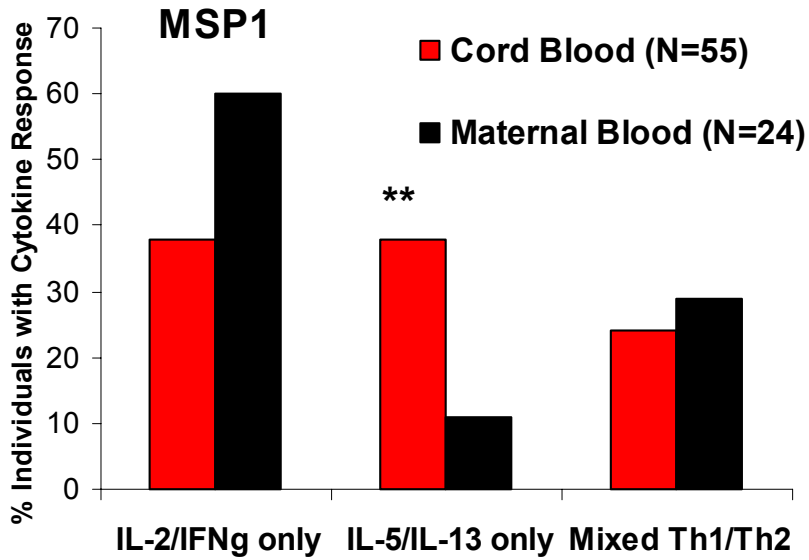
Do the type of cytokine responses differ between cord blood and adults to malaria antigens?

# Cord blood Tc have Increased Malaria Ag-specific IL-10 Production

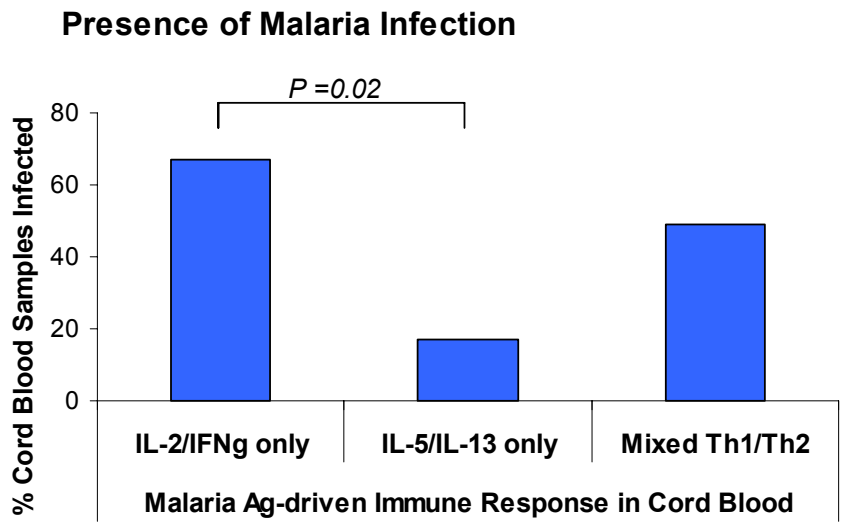


# Th2 bias develops in some neonates to malaria blood stage antigens

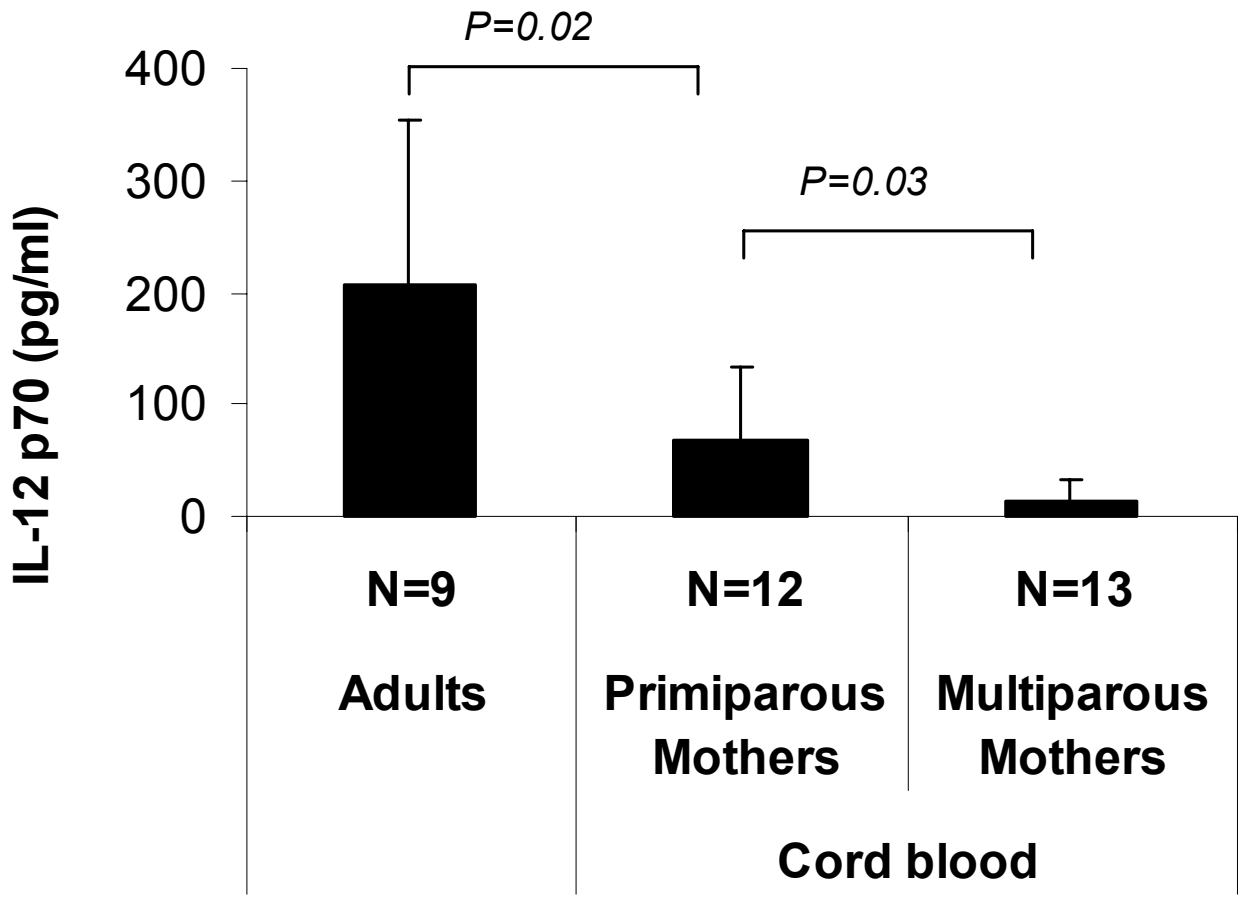
*Cord blood Lymphocyte Response*




*Presence of Malaria Infection In Cord Blood*



# Presence of Malaria Infection or Parity Associated with Enhanced anti-CD40-driven IL-12



# Does Tolerance Develop to Malaria Blood Stage Antigens?

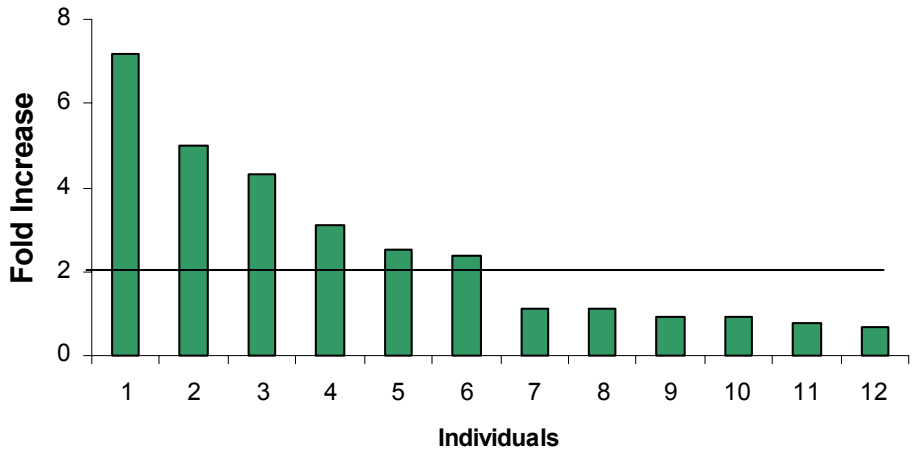
| | At Birth | | During Infancy | |
|---|---|---|---|---|
| *Presumed Immune Response* | *Maternal Infection* | *Tc Response cord* | *Tc Response* | *Susceptibility infection* |
| 'Tolerant' | + | - | ↓ | ↑↑ |
| 'Sensitized' | + | + | ↑↑ | ↓ |
| 'Unexposed' | - | - | | |

# Evidence for Tc Anergy to Malaria Antigens in Cord Blood

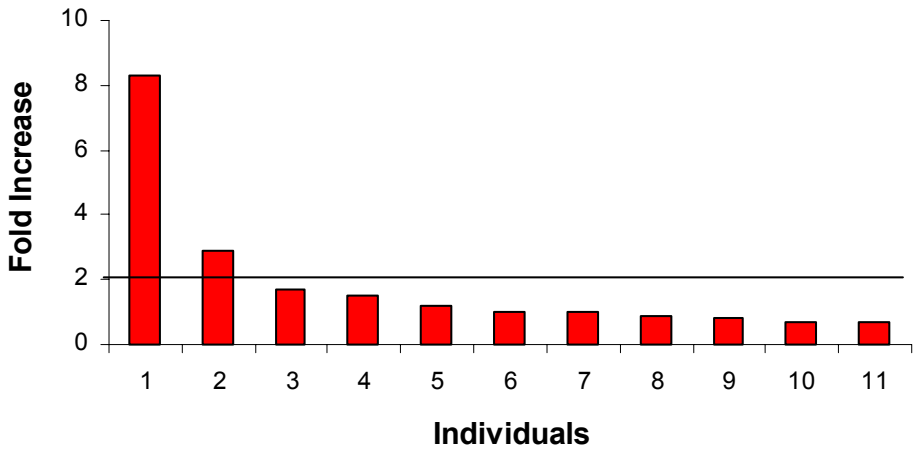
| *Culture conditions* | *Fetal Lymphocyte Response (pg/ml)* | | |
|---|---|---|---|
| | *Cpm* *X 1000* | *IL-10* *(pg/ml)* | *IFNγ* *(pg/ml)* |
| Media alone | 88±21[c] | 103±36 | 0 |
| MSP1 | 116±33 | 97±25 | 0 |
| MSP1 + rhuIL-2 (10U/mL) | **984±180** | **381±50** | **129±45** |
| rhuIL-2 (10U/mL) | 269±38 | 123±19 | 0 |

# Presence of Anergy to Malaria Antigens is More Common in Putatively Tolerant Newborns

Putatively Tolerant

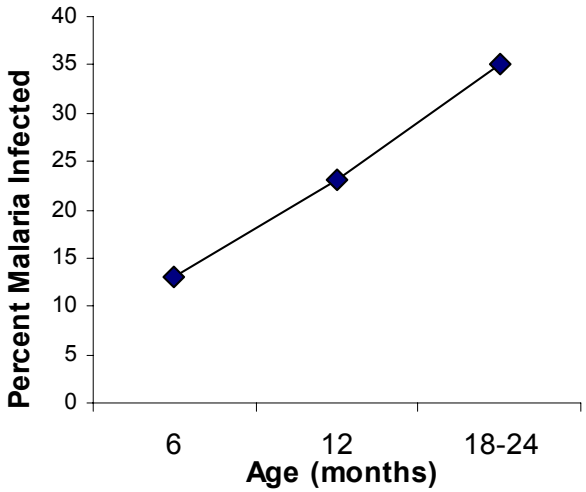



Unsensitized

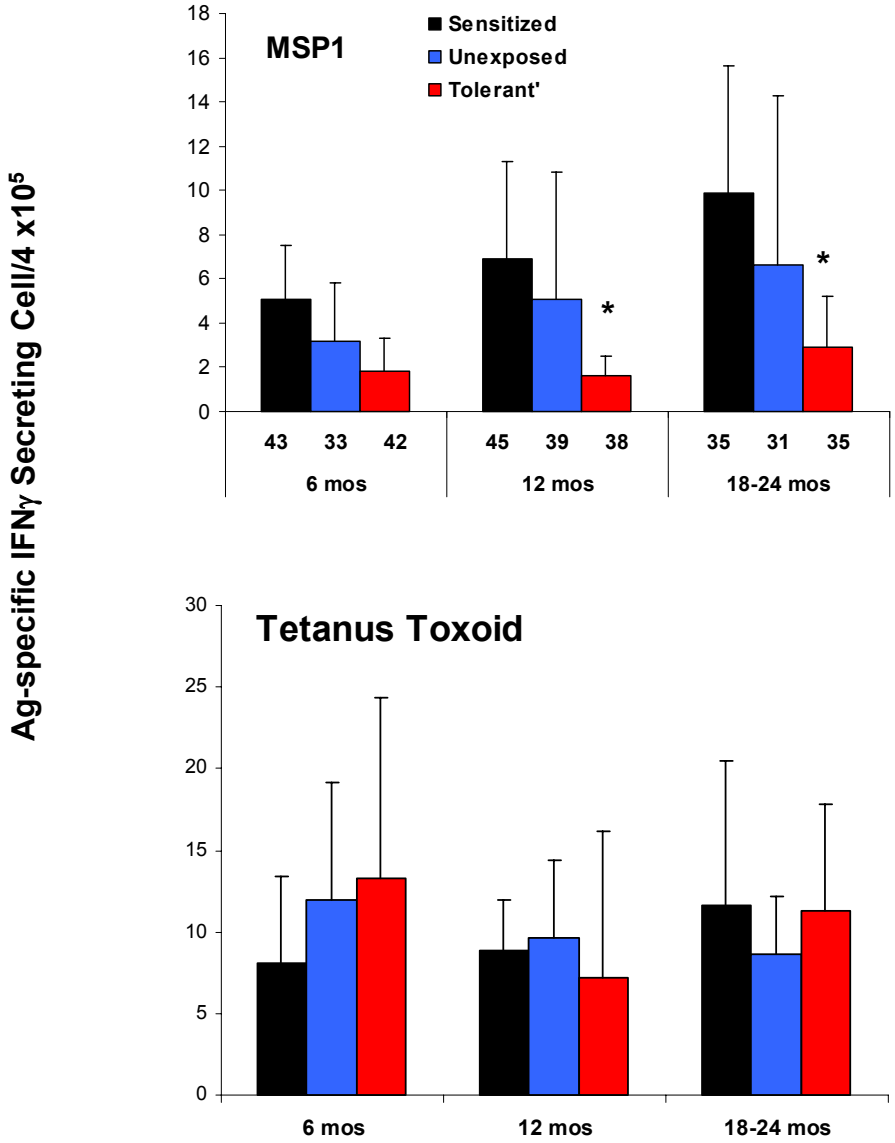



Fold increase in lymphocyte proliferation response with IL-2+Ag/IL-2 alone

# *In utero* exposure to malaria modifies immune responses to subsequent malaria exposure during infancy




| | *Malaria Infection* | *CBL Tc Response* |
|---|---|---|
| **Sensitized** | Pos | Pos |
| **Unexposed** | Neg | Neg |
| **"Tolerant"** | Pos | Neg |

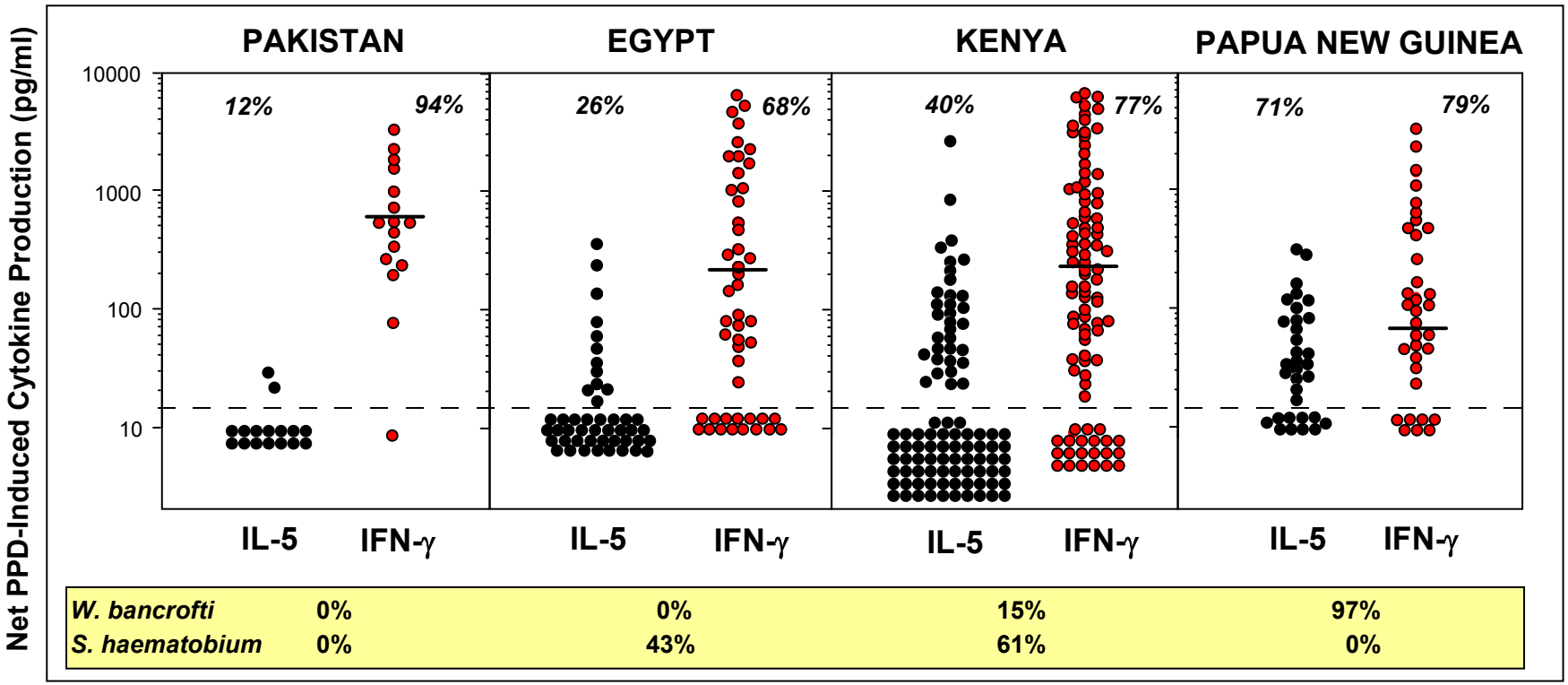


# Does pre-natal antigen exposure affect subsequent immune responses to heterologous antigens during infancy?

BCG immunization at birth

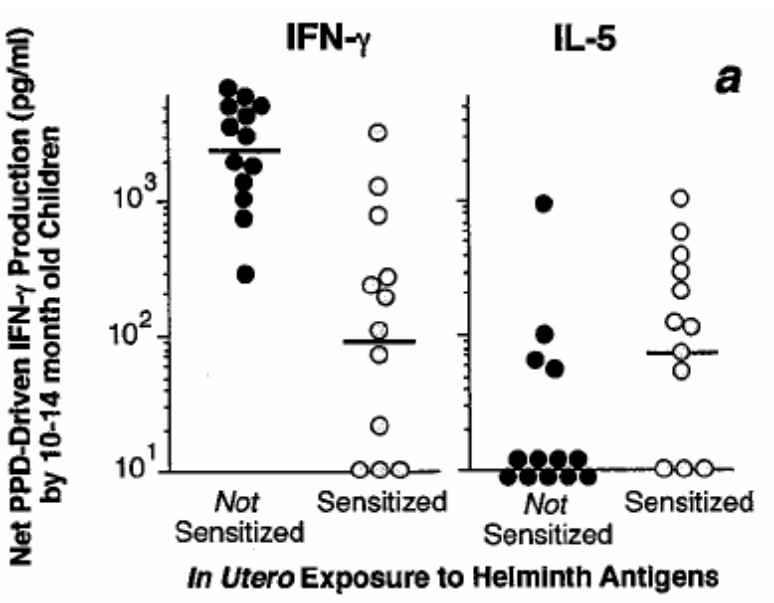
Hib immunization

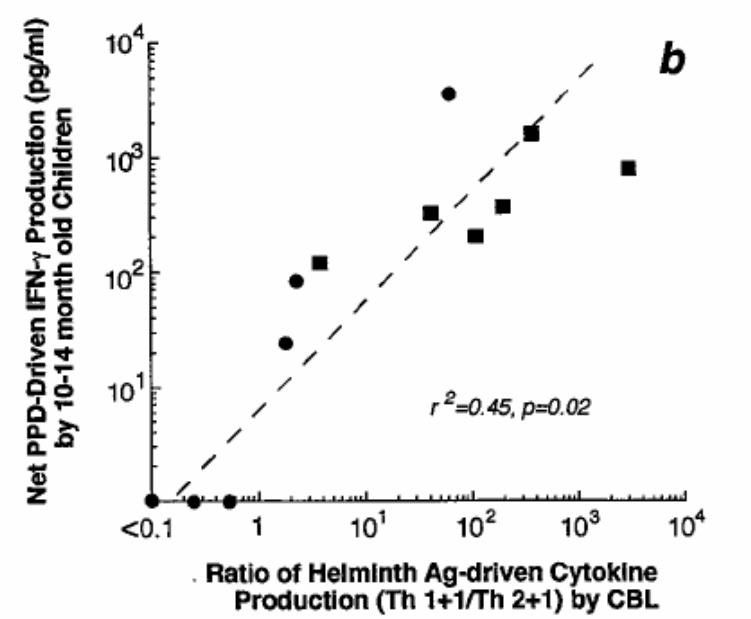
# PPD-driven IFN-γ production is Reduced in Communities with Helminth Co-infections



# Prenatal Sensitization to helminth Ags biases Tc Immunity in Induced by BCG vaccination away from a

# Th1-type IFN-γ responses associated with protection




Malhotra, et al J. Immunol. 162:6863, 1999

# Summary

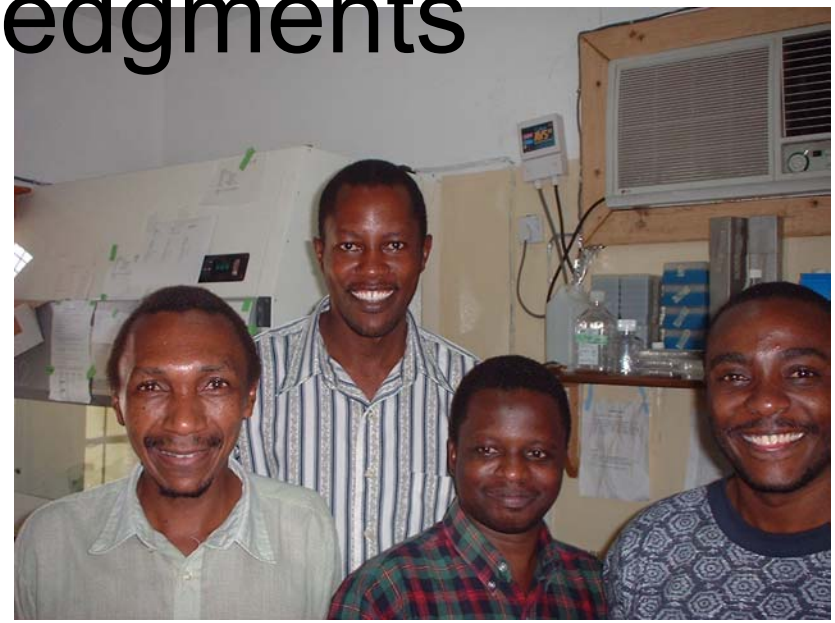
- Malaria is a major cause of morbidity during infancy, but typically not within the first 4-6 months of life.
- At present there are no good immunologic correlates for protective immunity.
- Prenatal exposure to parasite antigens is common and can prime neonatal immune responses or induce tolerance.
- Prenatal antigenic experience may affect vaccine efficacy to homologous or heterologous antigens.

# Conclusions

- The frequency of malaria chemoprophylaxis during pregnancy should be increased to further reduce the risk of malaria since even light perinatal antigen exposure may induce tolerance.
- Reproductive age women in endemic areas should be targeted for eradication of helminthic infection.

# Acknowledgments

Alex Wamachi



**CWRU**

Chris King
Jim Kazura
Pete Zimmerman
Jen Cole-Tobian
Sigi Pedraza
Jia Xainli
Rajeev Melhotra
Dave McNamara

Peter Mungai
John Ouma

John Kioko
Kasuka
Masungu
Adams Omollo

Maternity Nurses At Msambweni District Hospital