

TNF- α , IL-10, IFN- γ and TGF- β gene
polymorphism analysis in children exposed
to malaria and/or helminth infections in
Zimbabwe

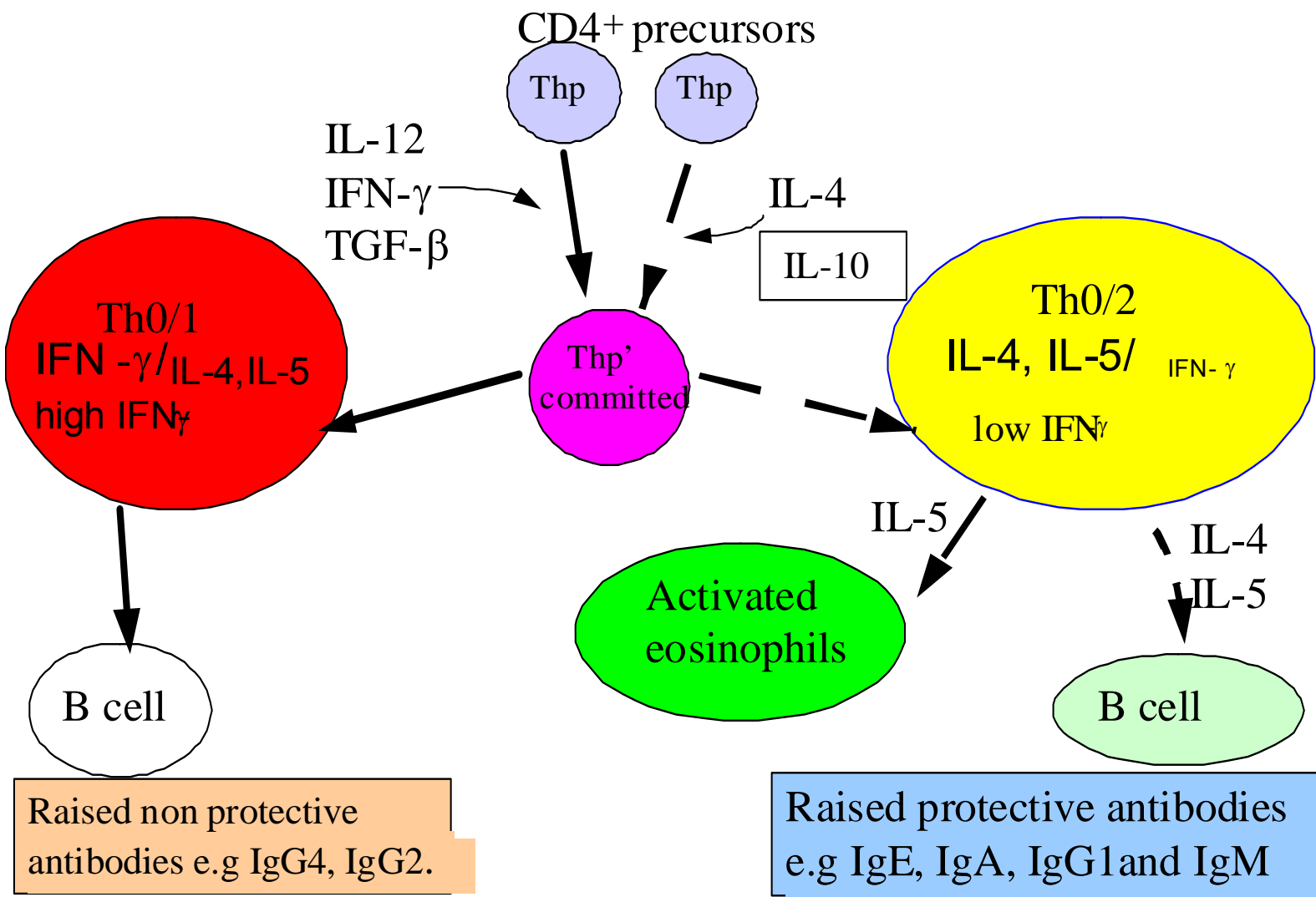
Background

- Consequences of infectious diseases due to Immune response
- Cytokine balances essential to controlling immunopathology
- Enormous pressure of different environmental effects on the genomic selection sculpture differences, which together with other factors shape the modern epidemiology of human disease.

Resistance and susceptibility to *P.falciparum* infection in humans

- TNF- α & IFN- γ associated with susceptibility, active disease and immunopathology.
- IL-10, IL-4 & TGF- β 1 associated with resistance and protection.
- Th1/Th2 balances important for immunopathology and immune suppression.

The "see-saw" system in the cytokine balance and immune response control



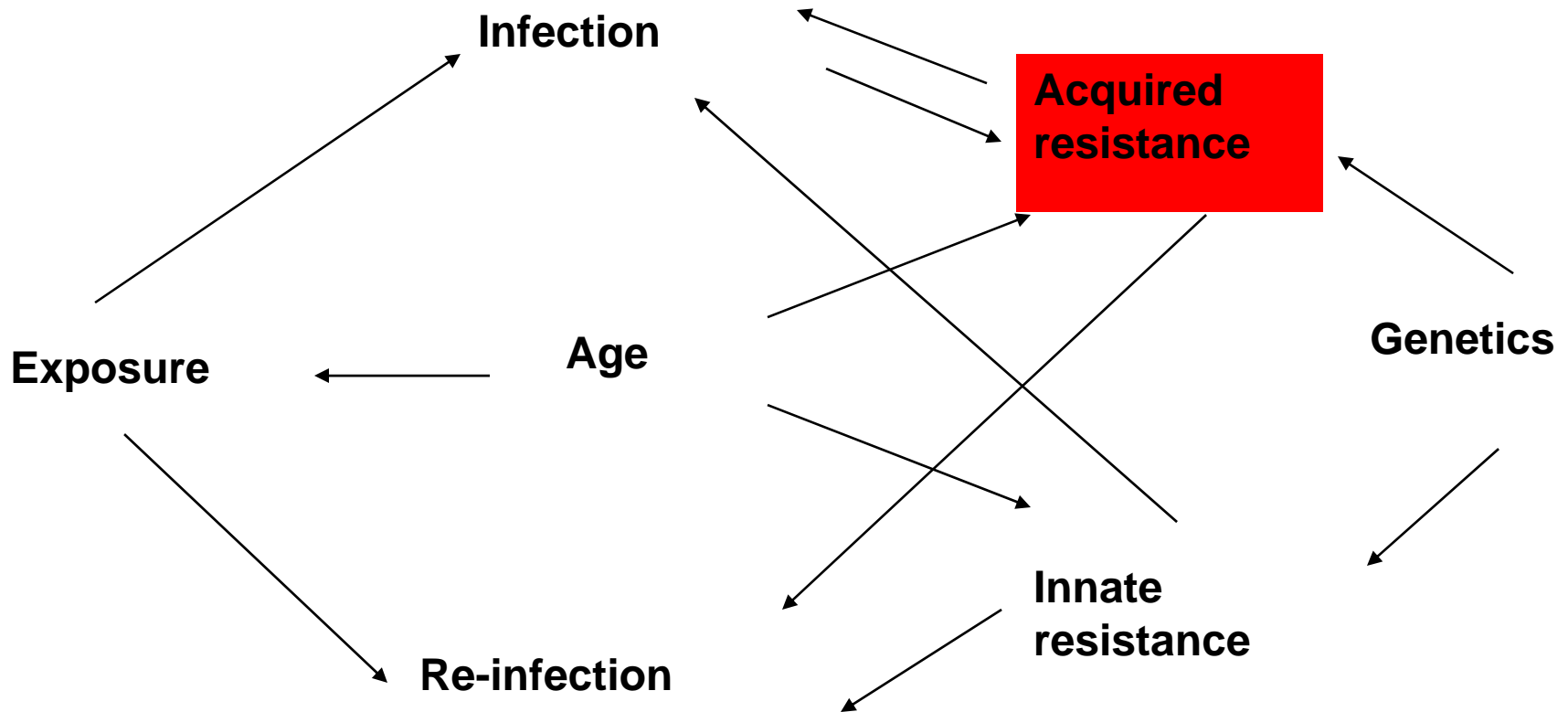
Hypothesis

➤➤ Pro- and anti-inflammatory cytokine gene polymorphism confers susceptibility or protection to malaria and helminth infections.

Cytokine gene polymorphisms loci investigated

cytokine	<i>nt</i>	mutation
TNF- α	- 308	A \rightarrow G
IFN- γ	+ 874	T \rightarrow A
IL-10	- 1082	A \rightarrow G
IL-10	- 819	C \rightarrow T
TGF- β 1	codon 10	T \rightarrow C
TGF- β 1	codon 25	G \rightarrow C

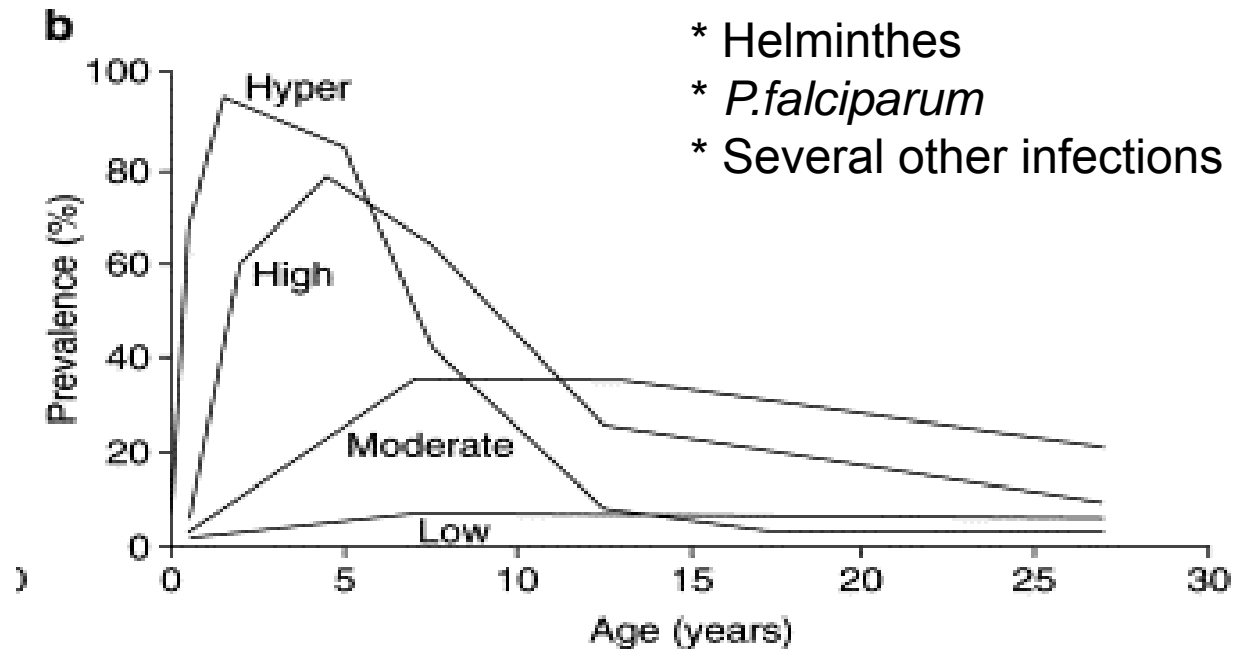
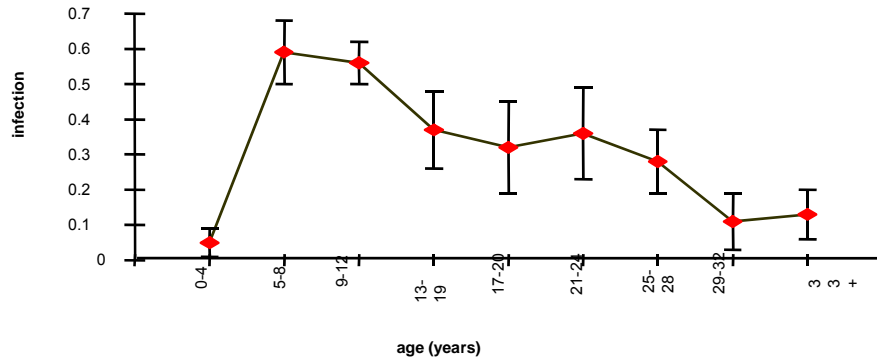
Functional relationships



Ghost of past infection/Trickle infections

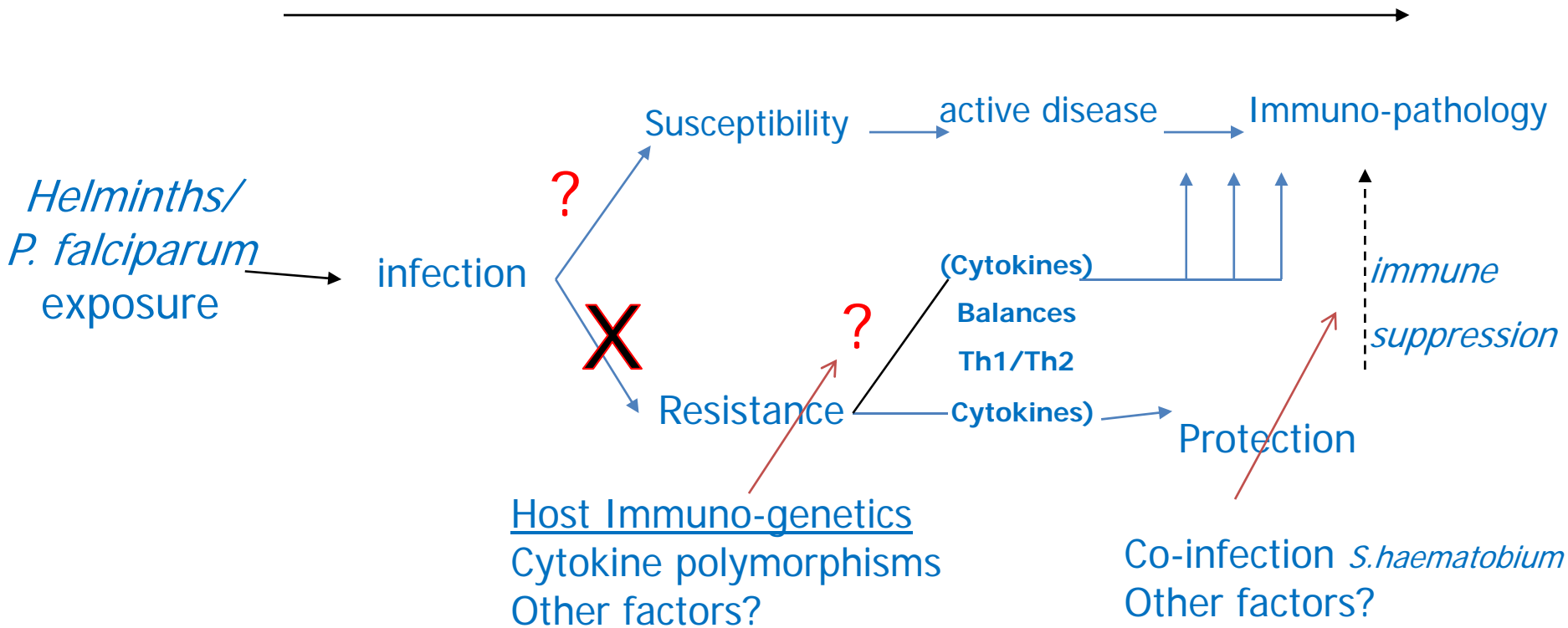
Epidemiological Patterns

Age-infection curve

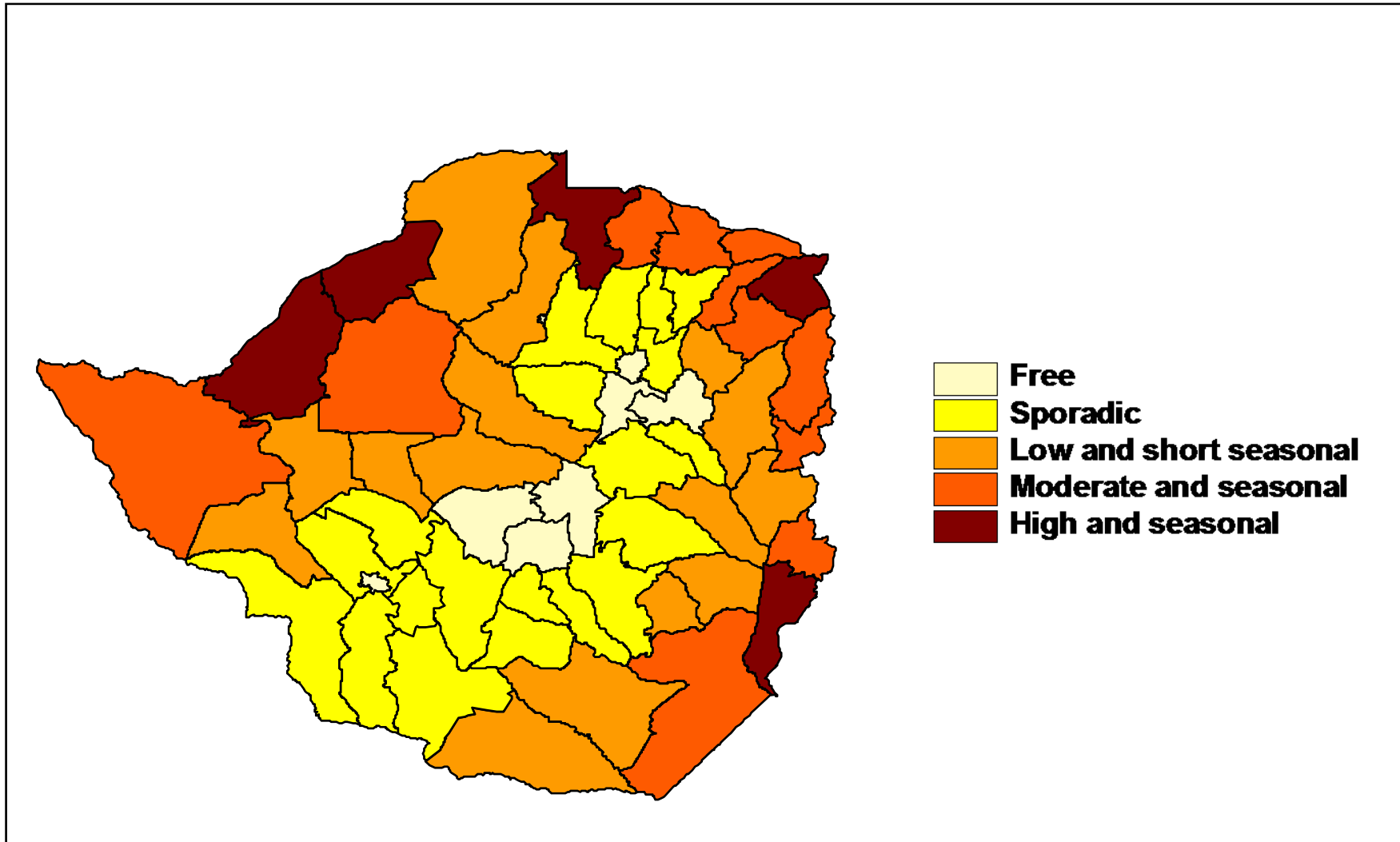


Helminthes/*P. falciparum* infection resistance and susceptibility in humans

Progression- immunological markers of resistance and susceptibility



Study area



Objectives

- **Main aim**
 - To investigate the influence of cytokine genetic polymorphism on resistance or susceptibility to malaria
- To determine plasma cytokine profiles.
- To understand the effect of *P.falciparum* co-infection with helminth
 - i.e. *S.haematobium*, *S.mansoni* and soil transmitted helminths.

Methodology

Qualitative Parasitological Diagnosis

Quantitative Parasitology

DNA Extraction

Full Blood Counts

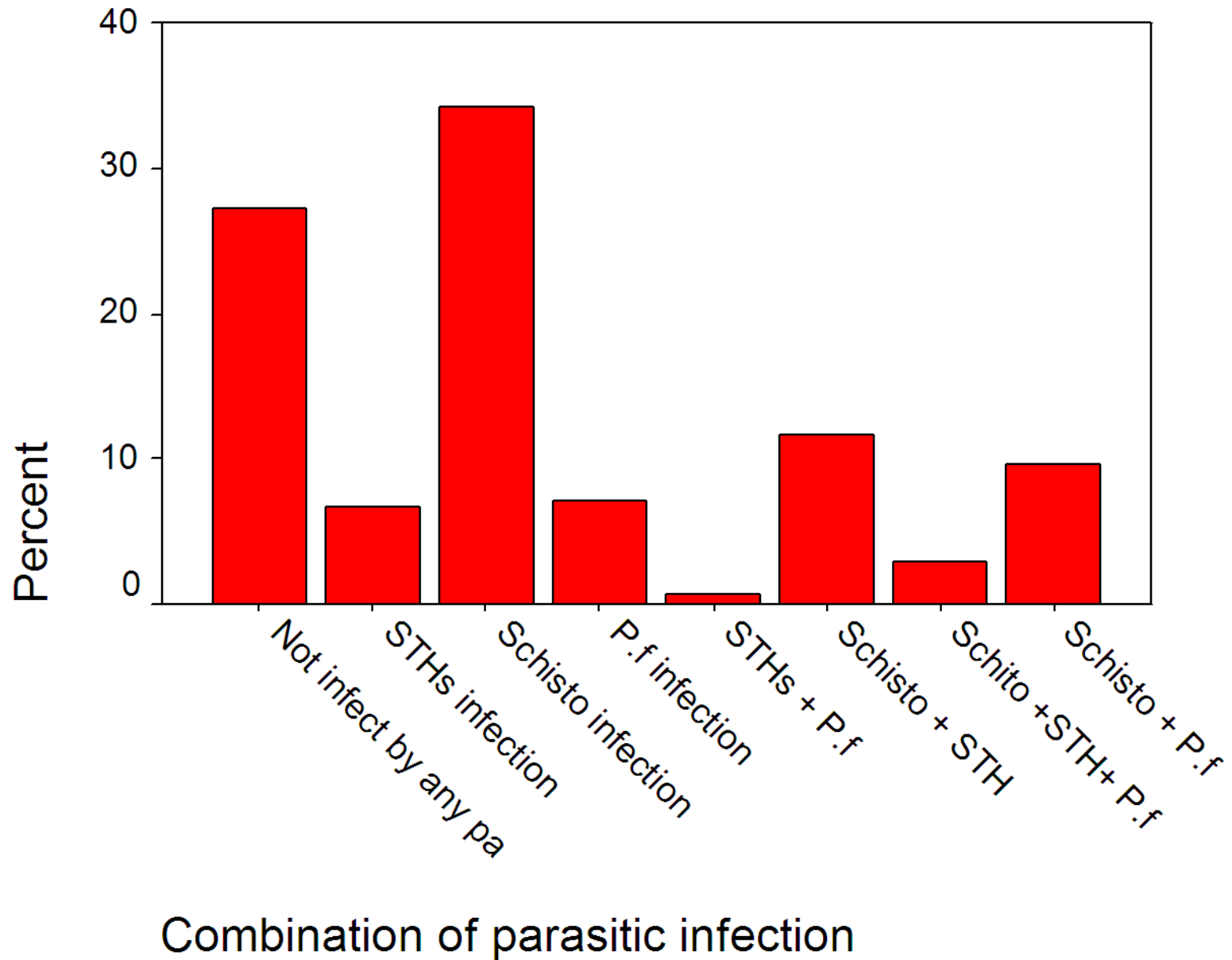
Cytokine Assays

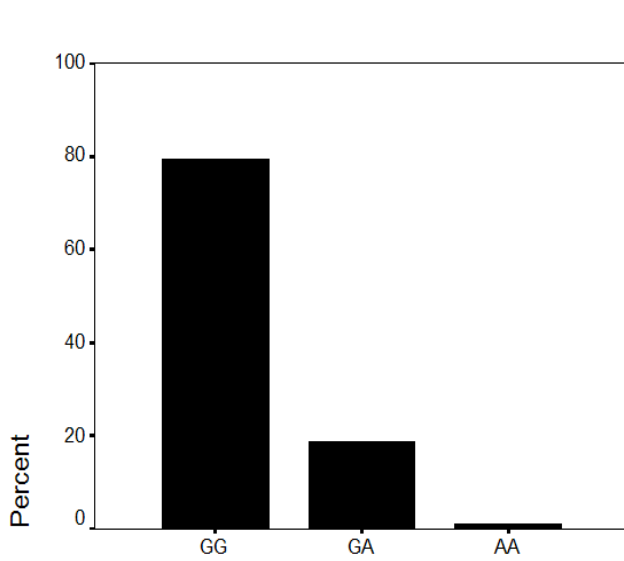
ARMS PCR

IL-10
-1082

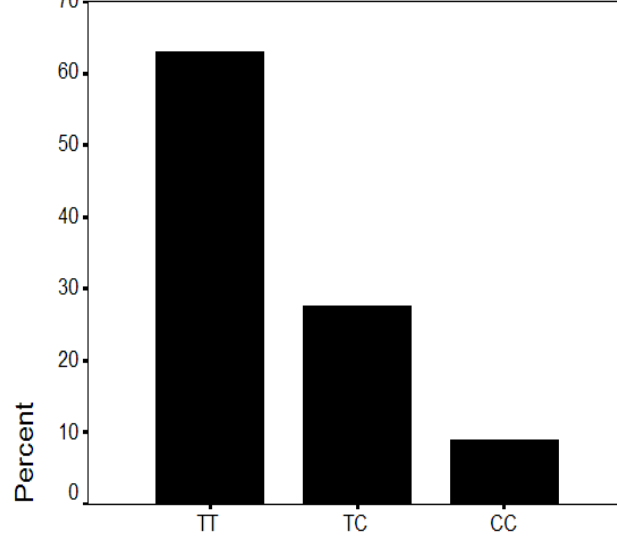
TNF- α
-308

Polyparasitism in Zimbabwe

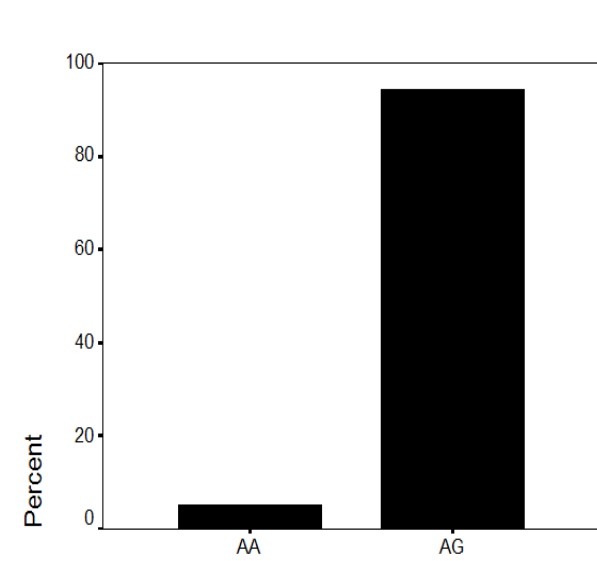




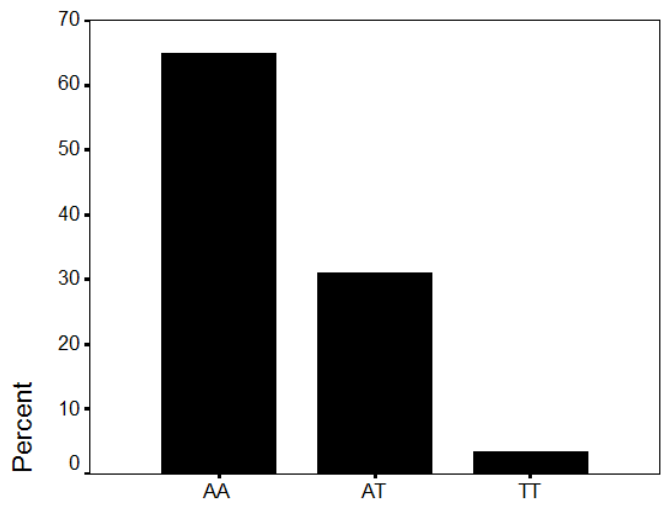
TNF alpha G/A (-308)



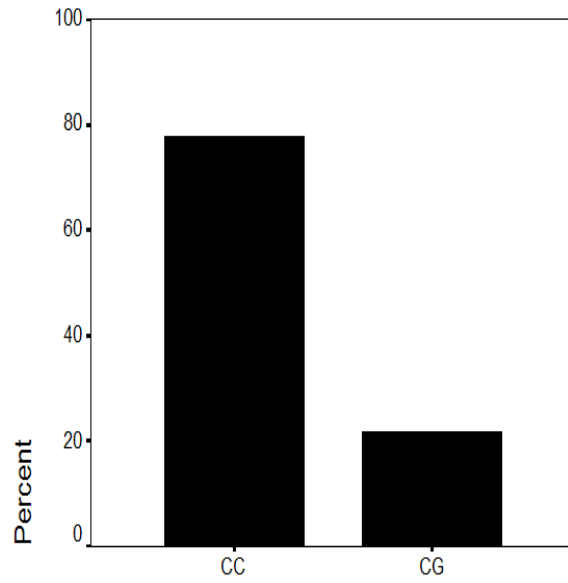
IL-10 T/C (-819/-592)



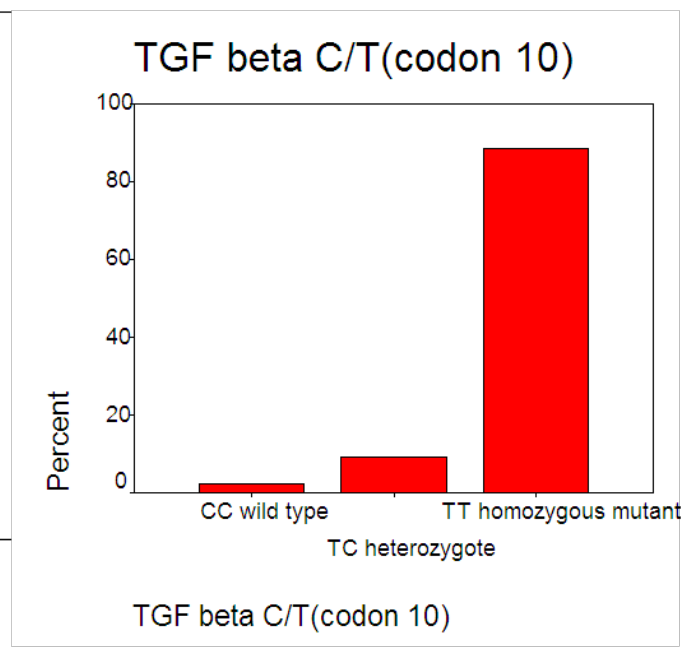
IL-10 A/G (-1082)



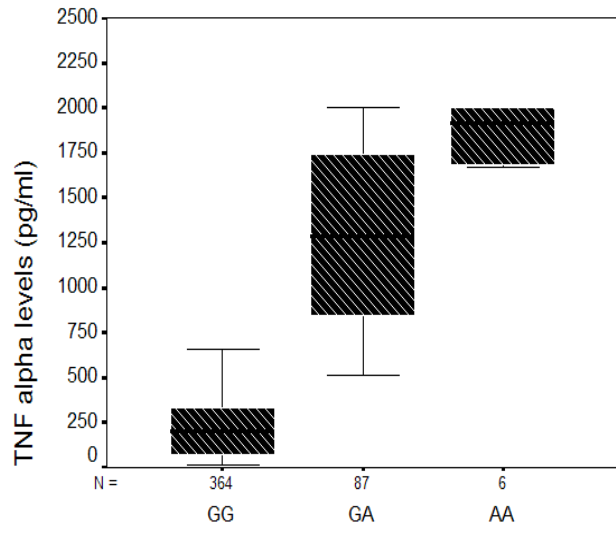
IFNg A/T (+874)



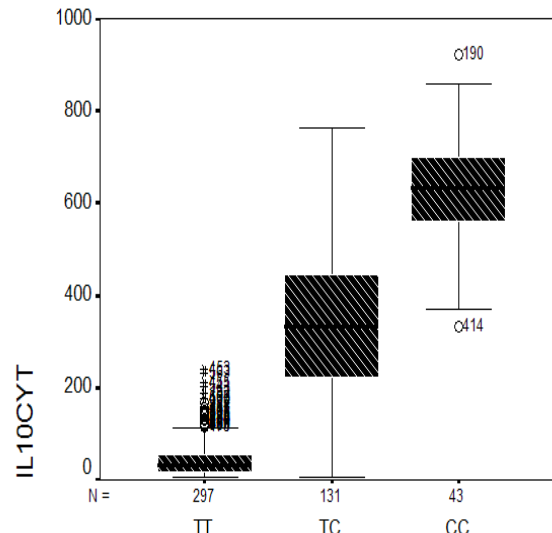
TGF beta G/C (+915 codon 25)



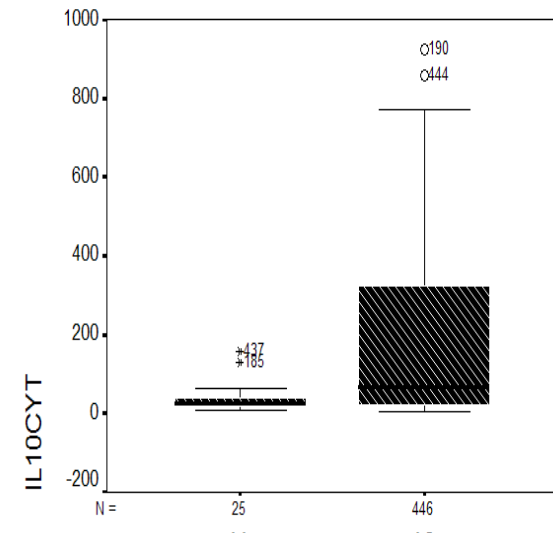
TGF beta C/T (codon 10)



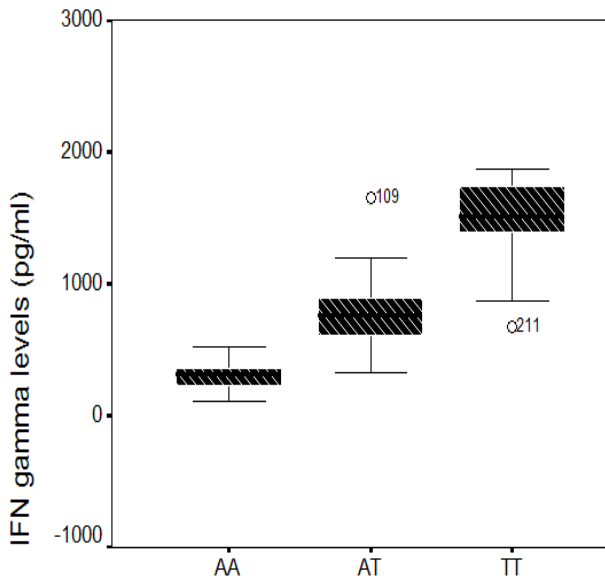
TNF alpha G/A (-308)



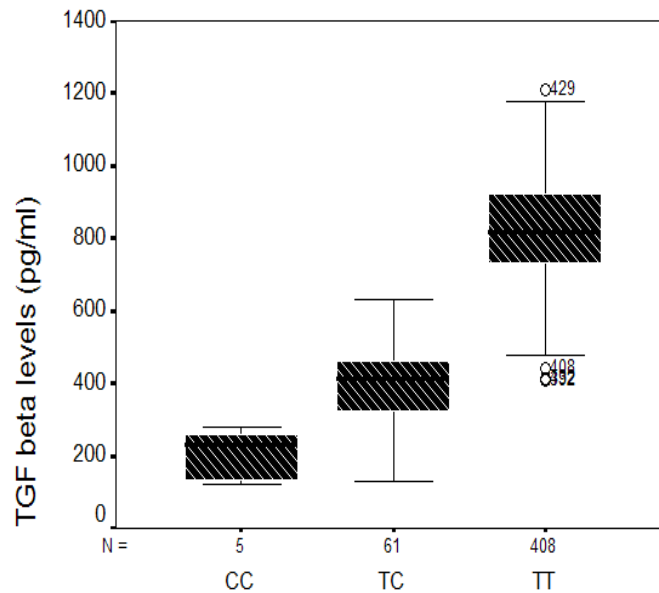
IL-10 T/C (-819/-592)



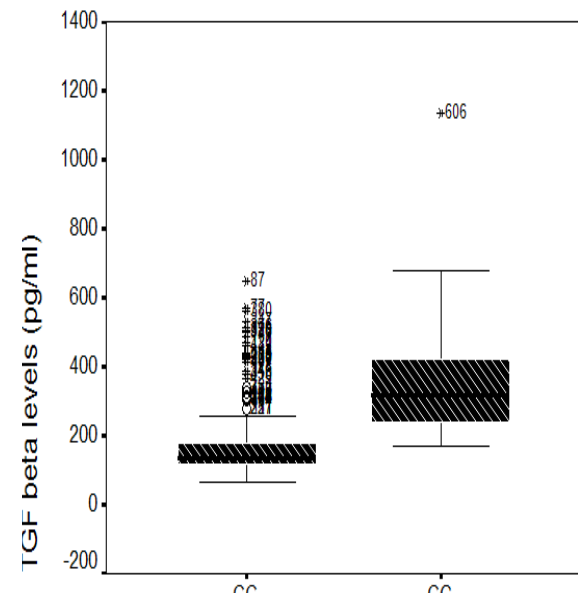
IL-10 A/G (-1082)



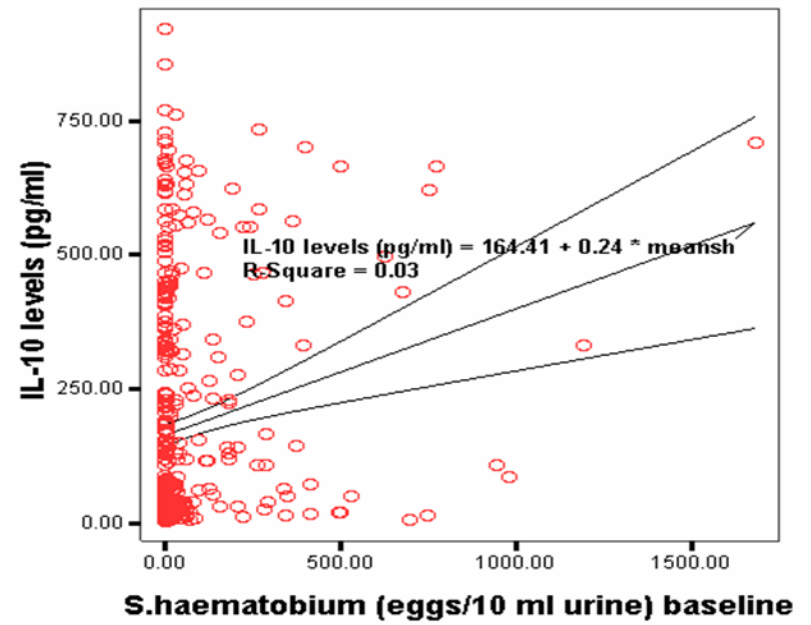
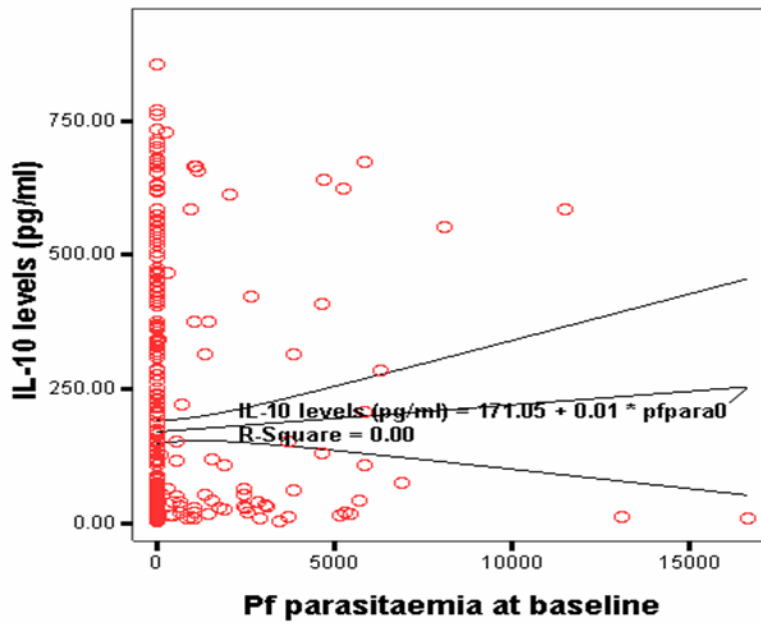
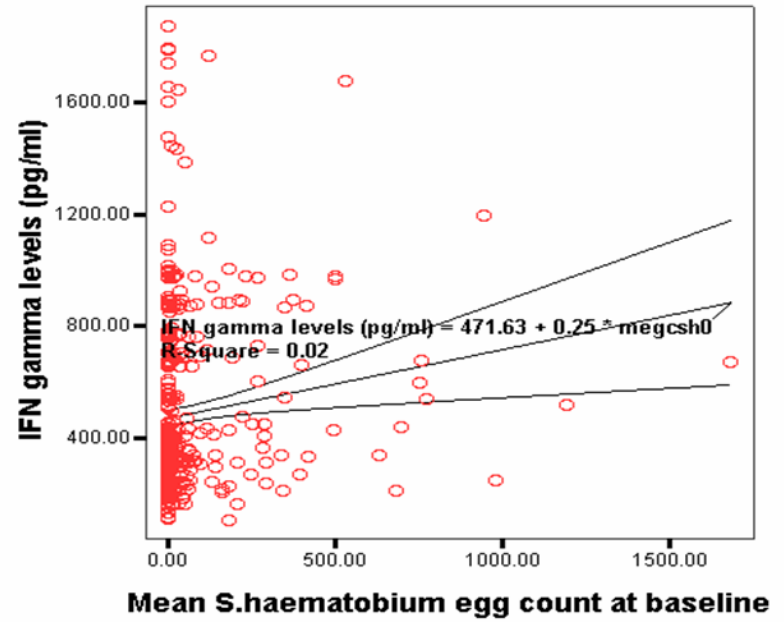
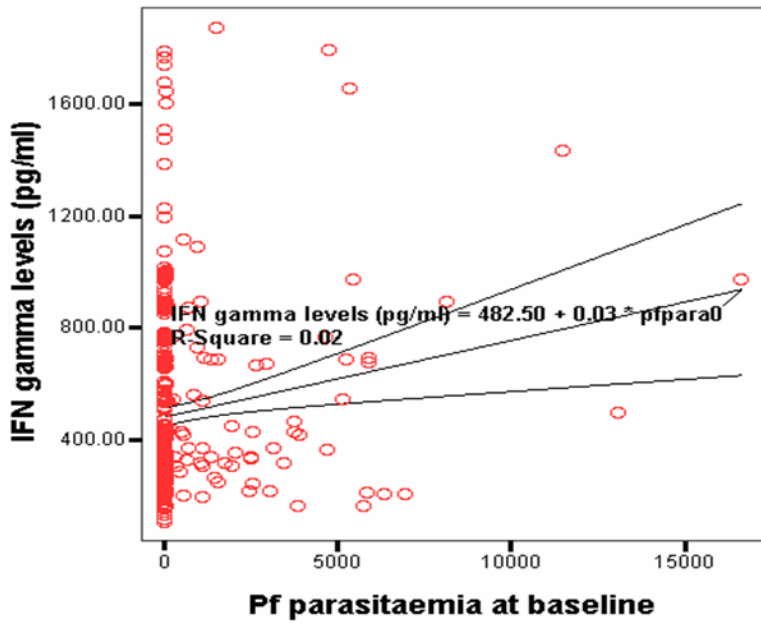
IFN γ A/T (+874)

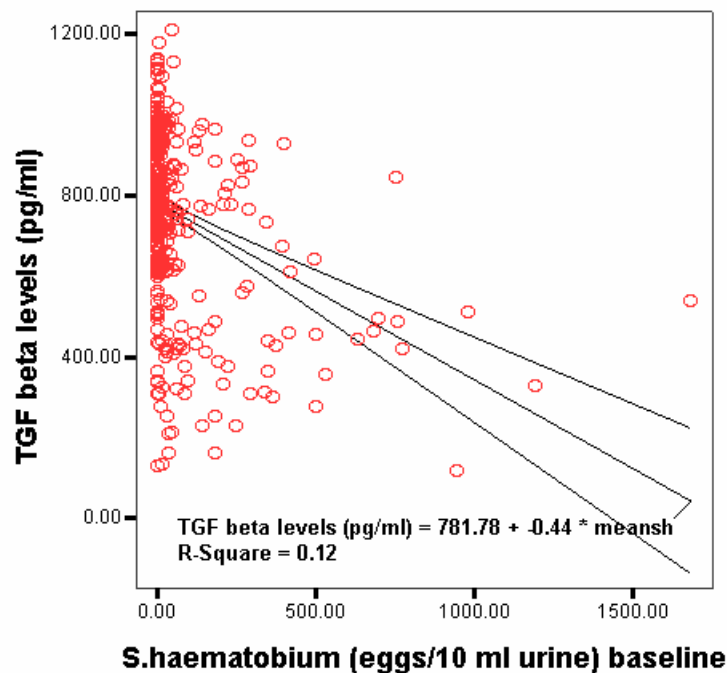
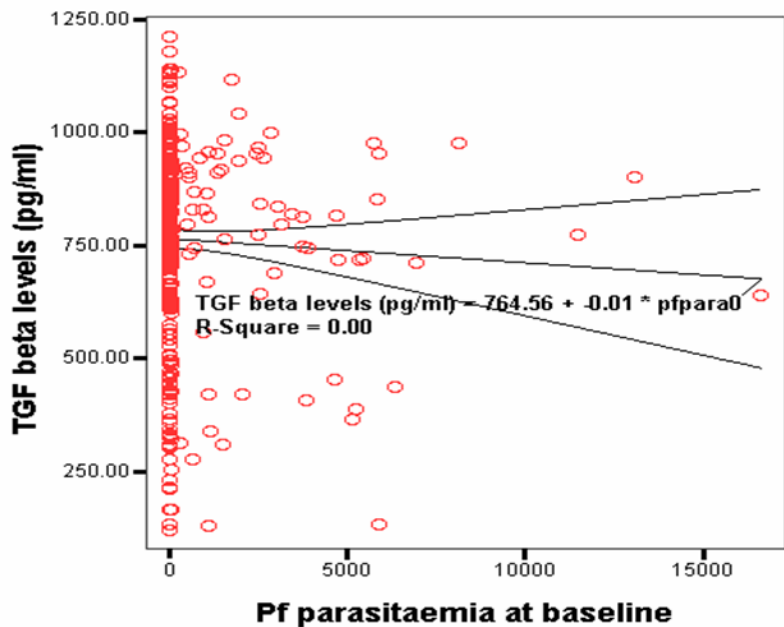
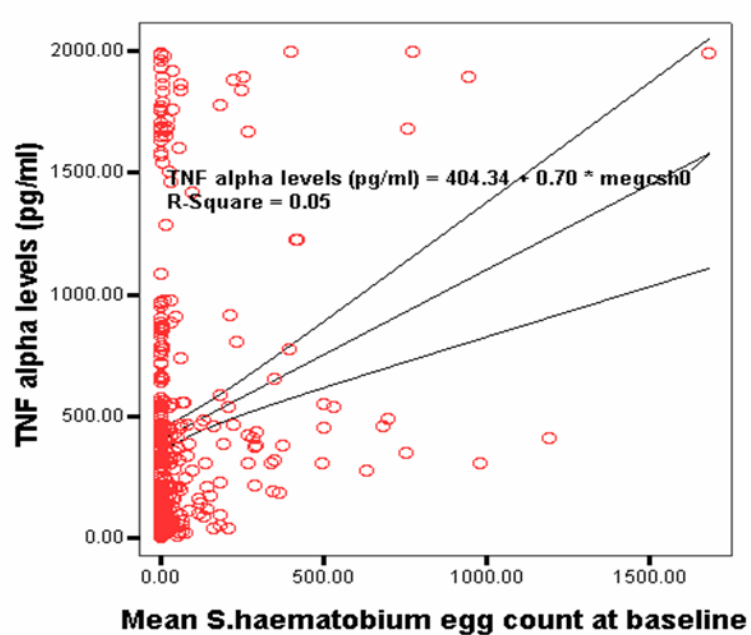
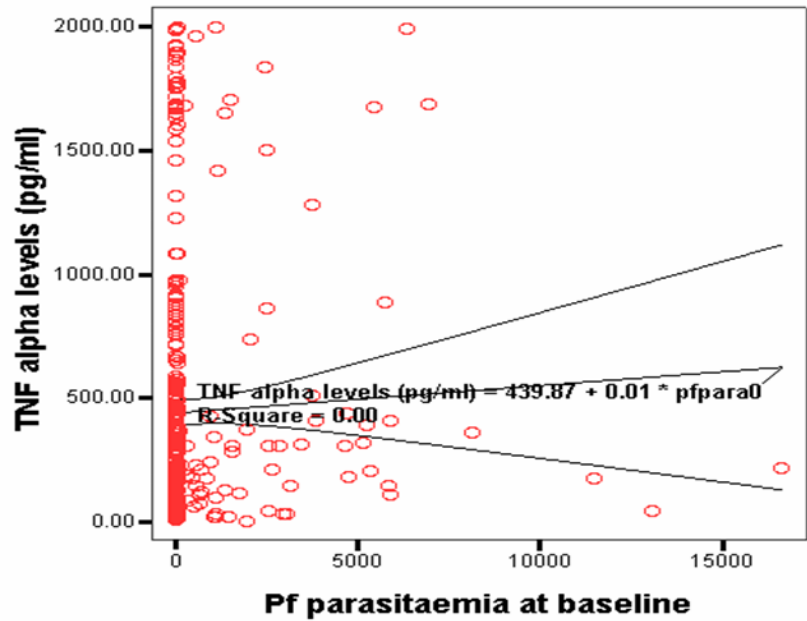


TGFbeta T/C (+869 codon 10)



TGF beta G/C (+915 codon 25)





Allelic frequency comparing different studies and ethnic groups

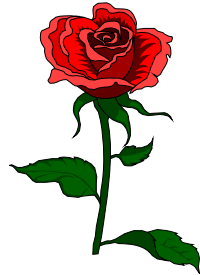
Locus (Allele)	Black Zimbabweans n = 492	African- Americans n = 111	Caucasia ns n = 102	African- Americans n = 691
TNF- α (-308G)	.761	.87	.85	.85
IFN- γ (+874T)	.684	.35	.48	.196
IL-10 (-1082G)	.95	.33	.44	.344
IL-10 (-819/-592C)	.596	.59	.73	.595
TGF- β 1 (codon 10T) +869	.885	.54	.55	.583
TGF- β 1 (codon 25G) +915	.78	.86	.92	.894

Conclusions

- Frequency of specific cytokine mutations related to low or high cytokine production can be used to predict the immunological status of the populations.
- Presence of anti-inflammatory high producing phenotype in the population may be an indicator of the capability of the individuals to resist development of severe disease status.
- We observed a general shift towards anti-inflammatory immune responses in Africans, which may have clinical implications

- Differences in multiple SNPs between different ethnic groups.
- However, previously Africans represented by African-Americans who have considerable admixture.
- The first work looking at a small and ethnically homogenous area of Zimbabwe.
- We examined functional SNPs of pivotal cytokines, which are likely to be of clinical significance.
- Studies are in progress to relate the presence of the polymorphisms to actual plasma cytokine profiles and frequency of attack per individual.

Acknowledgement



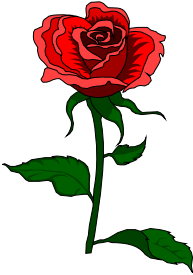
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- Dr Susan Mutambu
- Dr Godfree Mlambo
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- Participants

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- TATENDA

