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Erasmus Mundus



# *CYP2C8* Polymorphisms among malaria patients from Guinea-Bissau

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19 June 2008



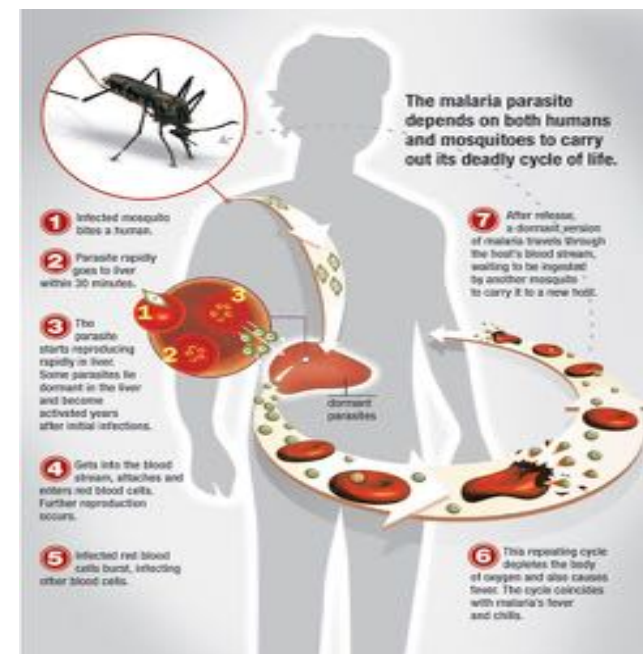
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# INTRODUCTION



Malaria is one of the major public health problems in more than 90 countries, inhabited by a total of some 2.4 billion people, representing about 40% of the world's population (WHO, 2004).



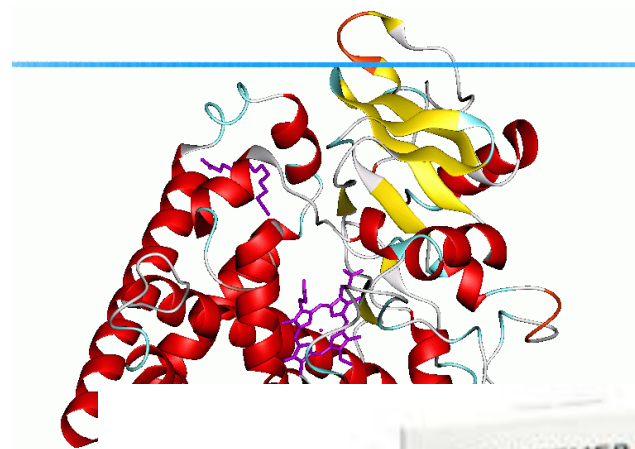
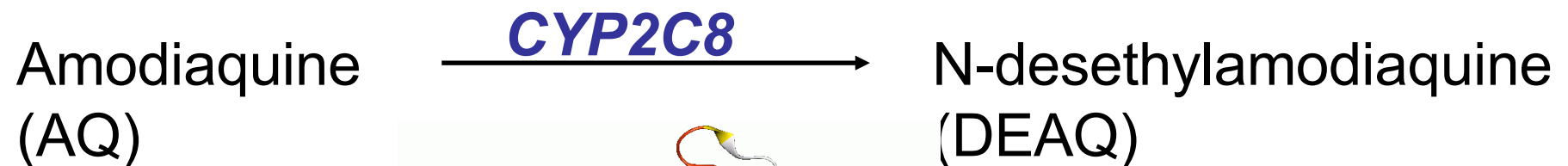
# Malaria endemic areas

■ Distribution of Malaria

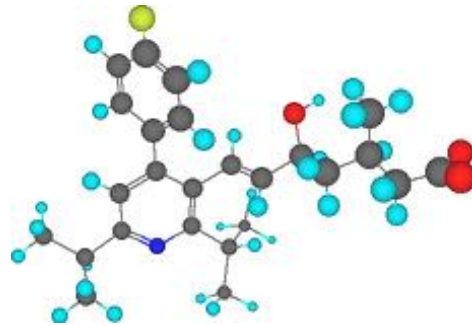


CDC

Amodiaquine (AQ) has been recently introduced into artemisinin-based combination therapy for use in malaria control programmes and as a first line treatment for children with uncomplicated malaria (WHO, 2006).

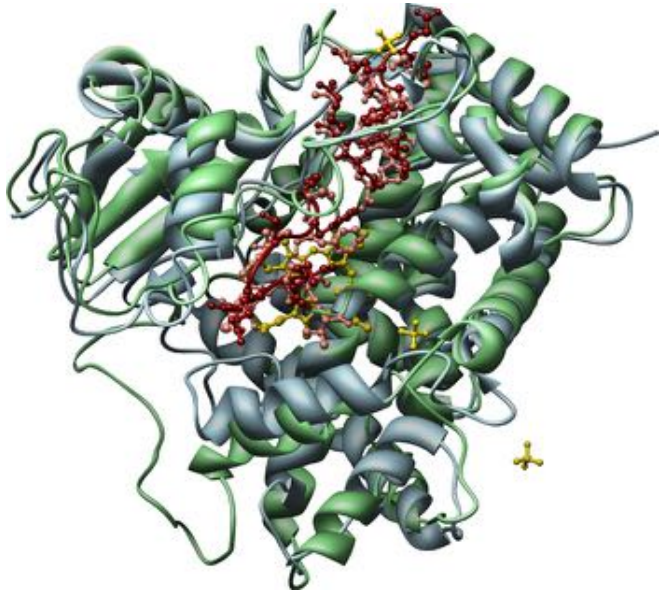


Besides amodiaquine, *CYP2C8* also metabolizes several therapeutically important drugs and endogenous substances including..



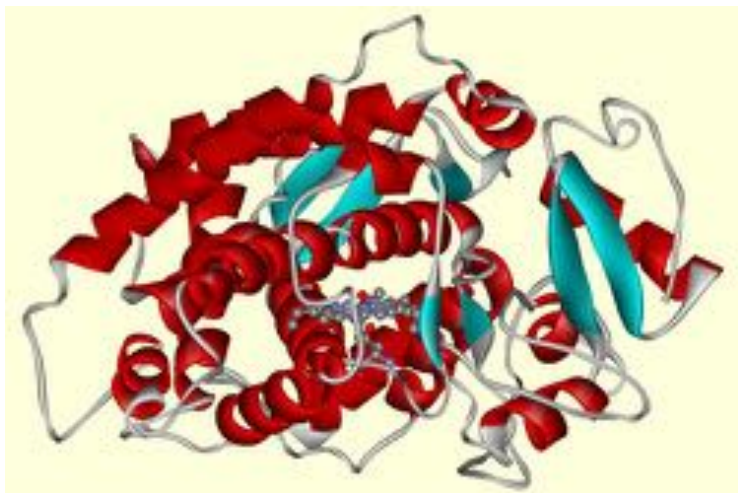
- paclitaxel
- verapamil
- rosiglitazone
- cerivastatin
- amiodarone
- dapsone
- all-*trans*-retinoic acid
- arachidonic acid





*CYP2C8* is mainly expressed in the liver, as well as in various extrahepatic tissues such as the vascular smooth muscles (Klose et al., 1999; Fleming, 2001).

The main *CYP2C8* polymorphisms known code for the amino acid changes I269F, R139K, K399R and I264M.



These SNPs define 3 main non-wild-type alleles: *CYP2C8*\***2**, *CYP2C8*\***3** and *CYP2C8*\***4**.

## A glance at Guinea-Bissau



Source: [travelpod.com](http://travelpod.com)

# A glance at Guinea-Bissau



Source: [travelpod.com](http://travelpod.com)



Canchungo hospital, Guinea-Bissau

Source: [www.kalpana.it](http://www.kalpana.it)

# RESEARCH OBJECTIVES



- To **study *CYP2C8* alleles** among malaria patients from Guinea Bissau
- To **assist policy-makers** in the management of malaria in Guinea-Bissau
- To **generate pharmacogenetic data** for the evaluation of treatment and drug dispensation
- To **contribute findings** to other databases and bio-banks within and outside Europe
- To allow **further comparisons** with other populations previously characterized in the Center for Molecular and Structural Biomedicine, Universidade do Algarve, Portugal

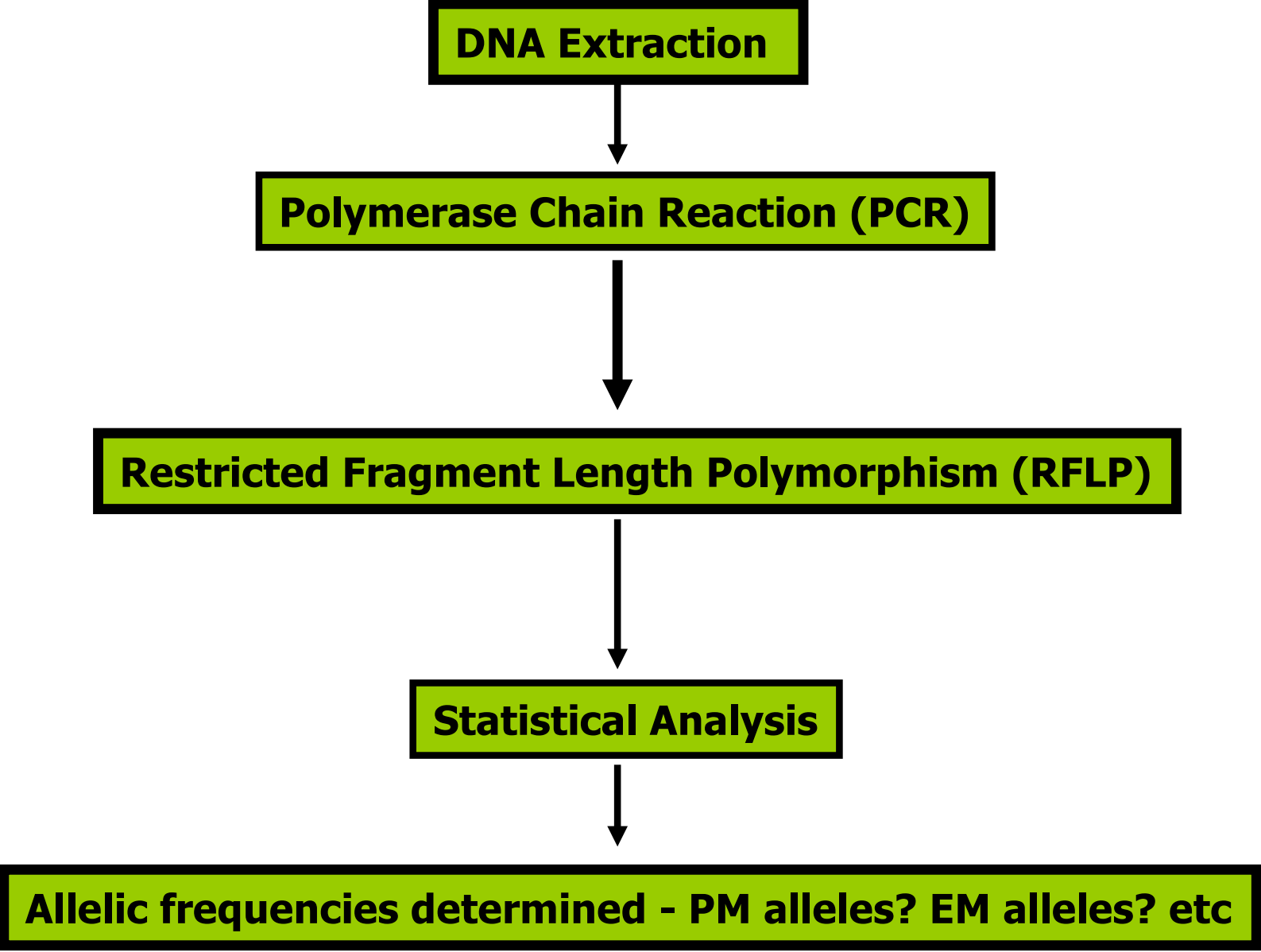
# MATERIALS AND METHODS



Subjects : 91 randomly selected malaria patients from Guinea-Bissau



**DNA Extraction**



```
graph TD; A[DNA Extraction] --> B[Polymerase Chain Reaction (PCR)]; B --> C[Restricted Fragment Length Polymorphism (RFLP)]; C --> D[Statistical Analysis]; D --> E[Allelic frequencies determined - PM alleles? EM alleles? etc];
```

A vertical flowchart with five steps. Each step is contained within a yellow rectangular box with a thick black border. The boxes are connected by downward-pointing black arrows. The steps are: DNA Extraction, Polymerase Chain Reaction (PCR), Restricted Fragment Length Polymorphism (RFLP), Statistical Analysis, and Allelic frequencies determined - PM alleles? EM alleles? etc.

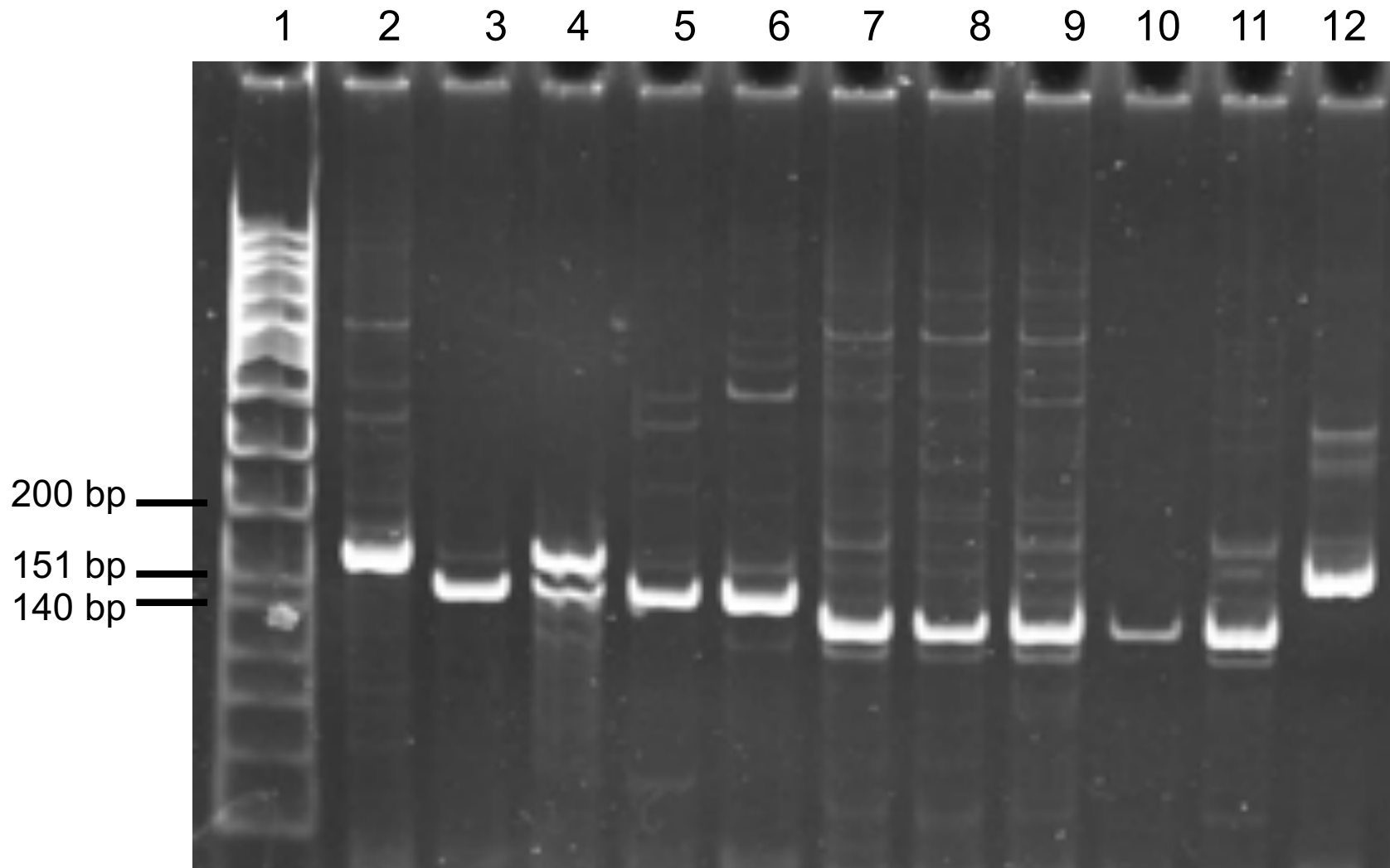
**Polymerase Chain Reaction (PCR)**

**Restricted Fragment Length Polymorphism (RFLP)**

**Statistical Analysis**

**Allelic frequencies determined - PM alleles? EM alleles? etc**

# RESULTS



Lane 1:  $\phi$ X174 DNA/HinfI Marker; Lane 2: Homozygous mutant for the *CYP2C8*\*2 allele; Lane 3, 5, 6: Homozygous wild-type for the *CYP2C8*\*2 allele; Lane 4: Heterozygous for for *CYP2C8*\*2 allele; Lanes 7 to 11: Homozygous wild-type bands for the *CYP2C8*\*4 variant; Lane 12: PCR amplicon used to generate the RFLPs

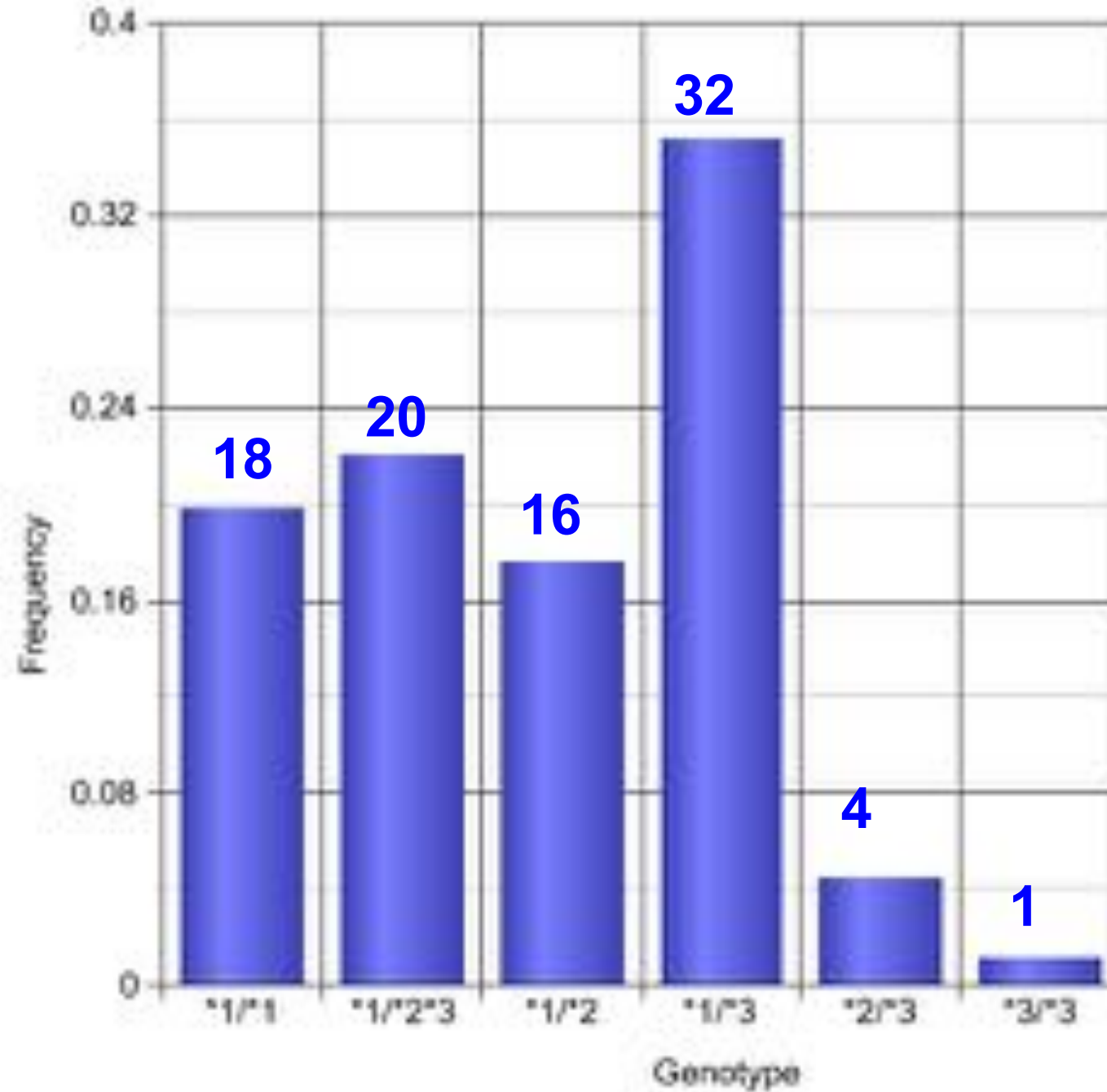
## ***CYP2C8* allele frequencies obtained:**

$$CYP2C8^*2 = 0.2418$$

$$CYP2C8^*3 = 0.3242$$

$$CYP2C8^*4 = \text{not detected}$$

## Distribution of *CYP2C8* genotypes among GB subjects



# DISCUSSION



- Comparison of ***CYP2C8* genotypes** with other populations
- Comparison of ***CYP2C8* allele frequencies** with other populations
- Comparison of ***CYP2C8* allele frequencies** between malaria patients from **GB** and **Zanzibar**

## Comparison of *CYP2C8* allele frequencies between malaria patients from Guinea-Bissau and Zanzibar



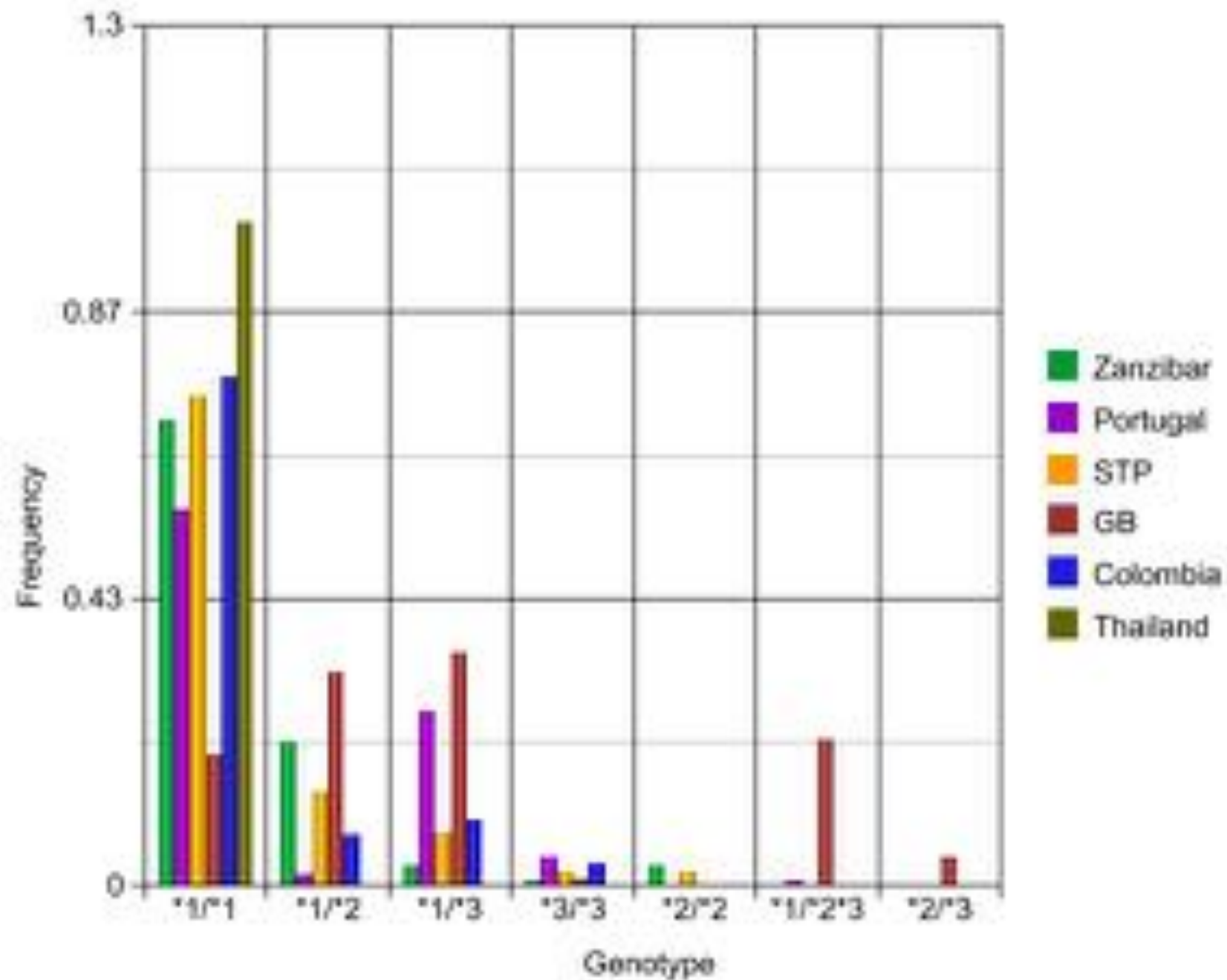
- Higher prevalence of the *CYP2C8*\*3 allele in West Africa

## Comparison with Asian and Oceanic *CYP2C8* allele frequencies

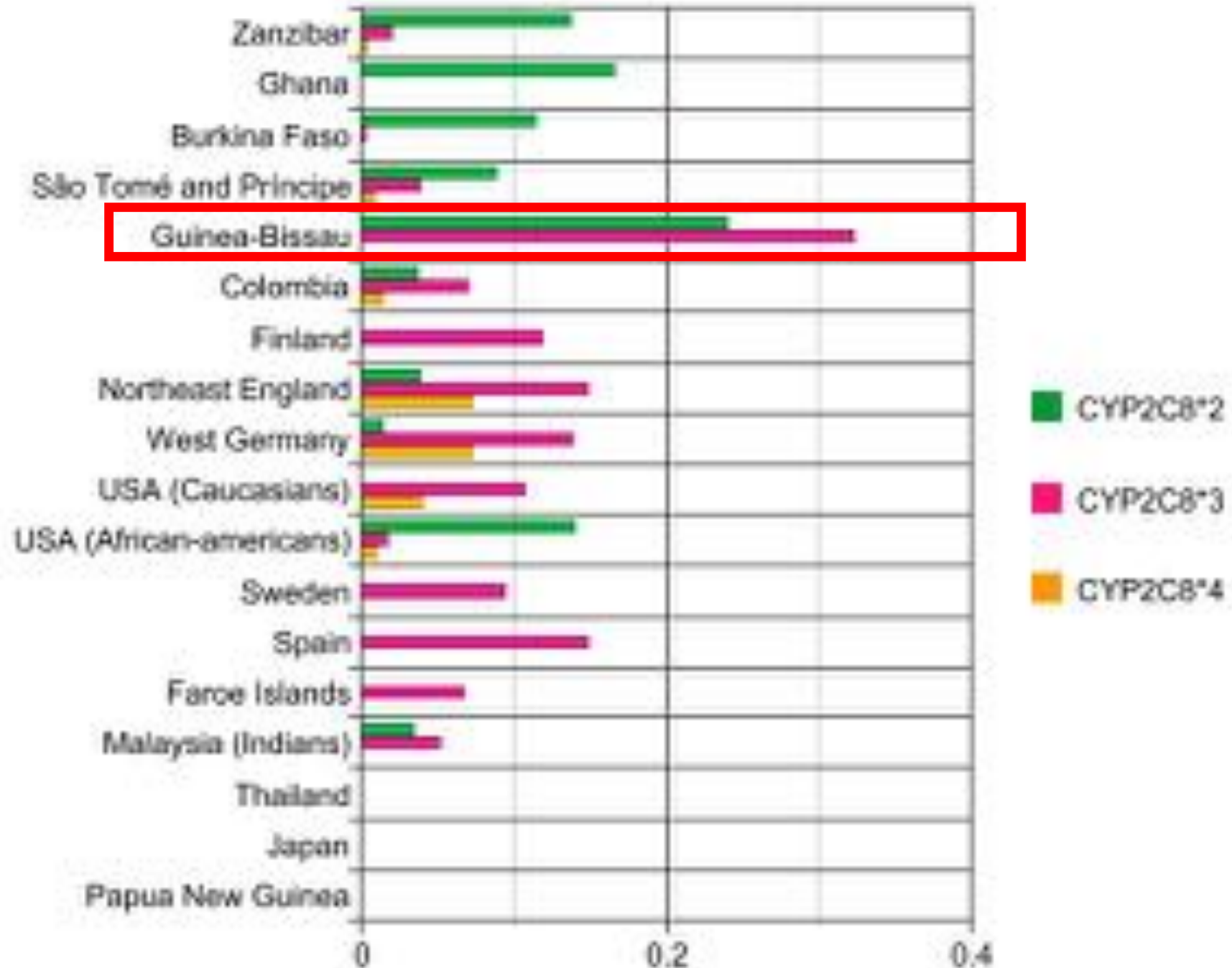


- Significant differences not detected

## CYP2C8 genotype comparison with 5 other populations



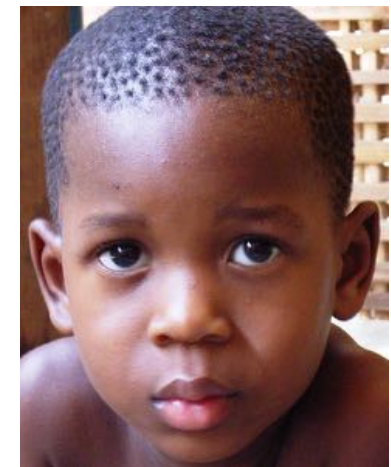
# Comparison of *CYP2C8* allele frequencies with other populations



# CONCLUSION



- Highest frequency of *CYP2C8* variant alleles ever recorded in a population of African descent.
- High occurrence of *CYP2C8*\*2 and *CYP2C8*\*3 alleles among malaria patients in Guinea-Bissau.
- This implies a high incidence of *CYP2C8* poor metabolizer alleles among malaria patients in Guinea-Bissau who may be at a greater risk of adverse effects compared to other populations previously characterized.



# FUTURE RECOMMENDATIONS



- Further investigation taking into account the effects of *CYP2C8* metabolism on the pharmacokinetics of antimalarials



- Study of polymorphisms in healthy subjects

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