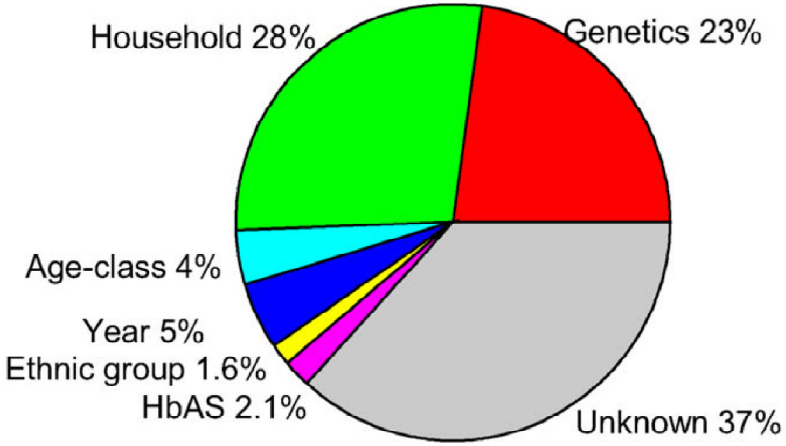
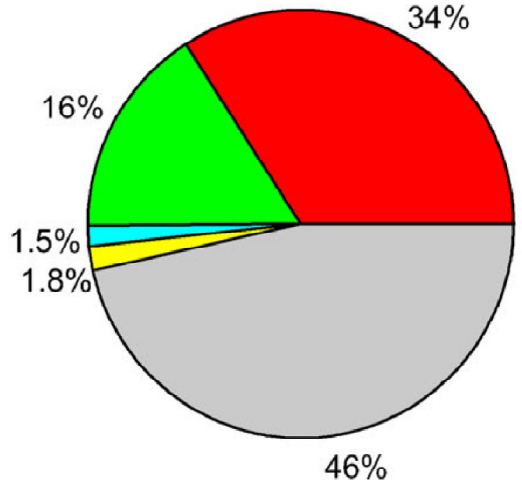
Establishing a genetic birth cohort study within the Kilifi HDSS

Tom Williams

mild malaria

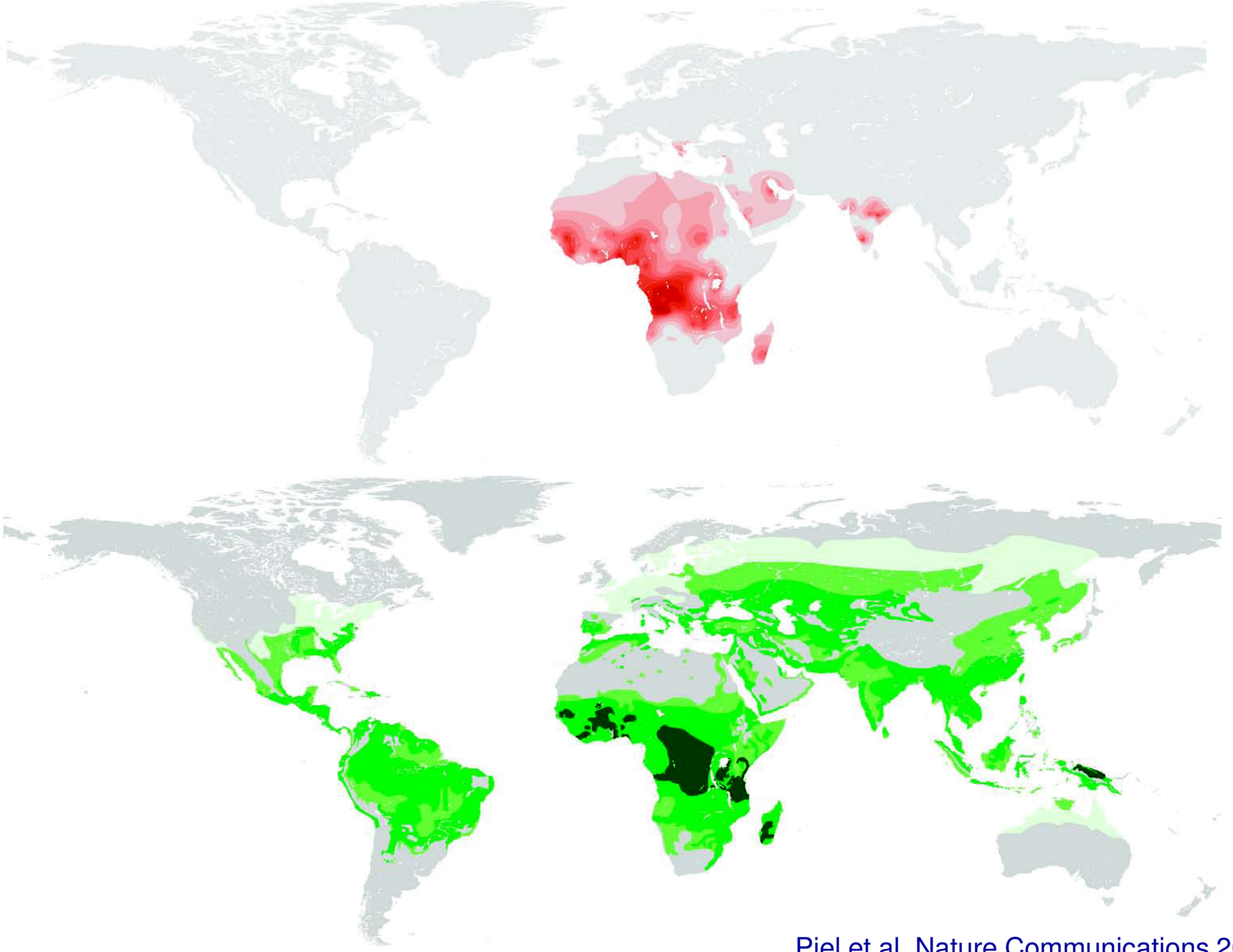


hospital malaria



Mackinnon et al, PLoS Medicine 2005

Sickle cell trait (HbAS)



Piel et al, Nature Communications 2010

α^+thalassaemia

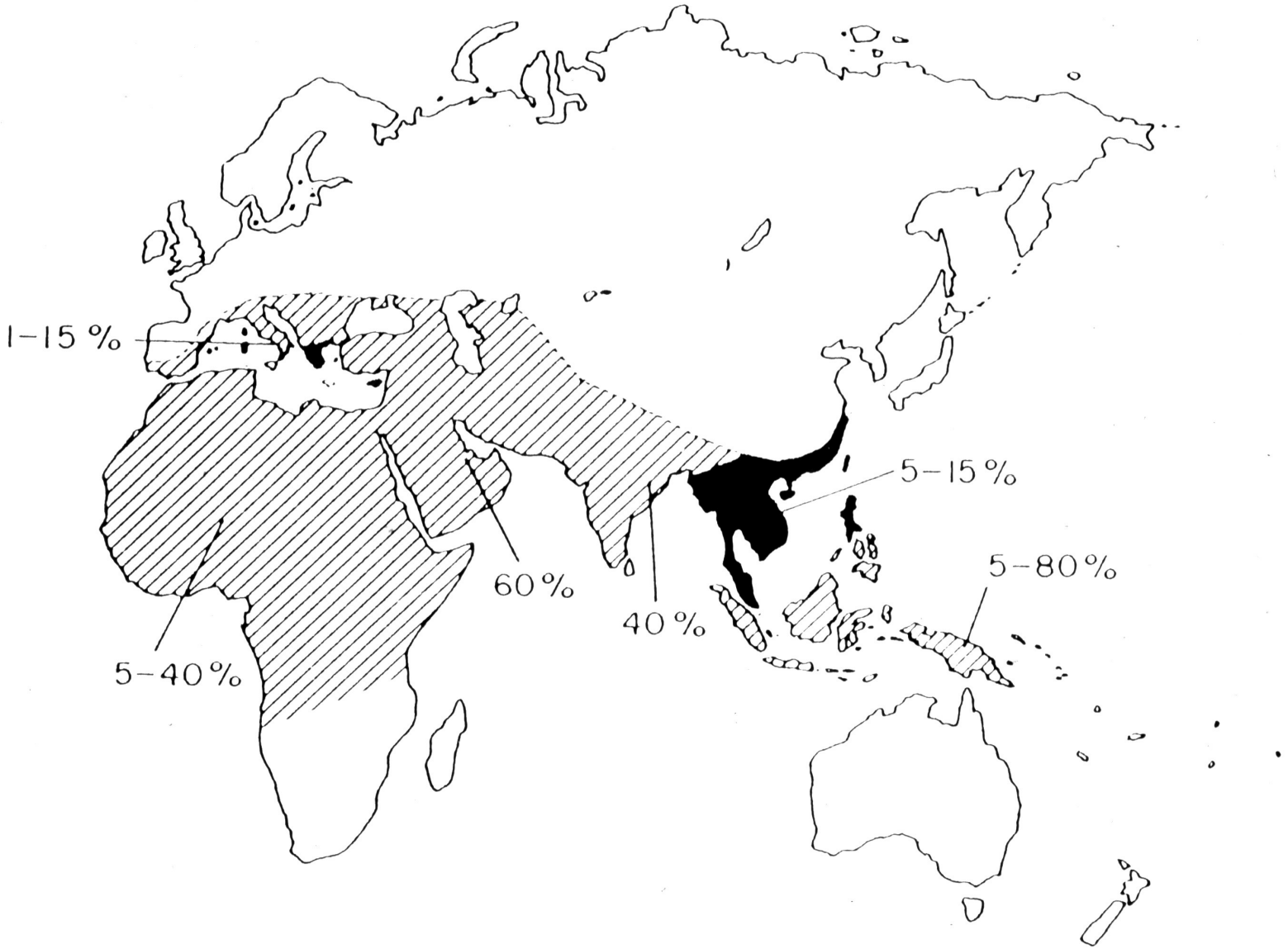
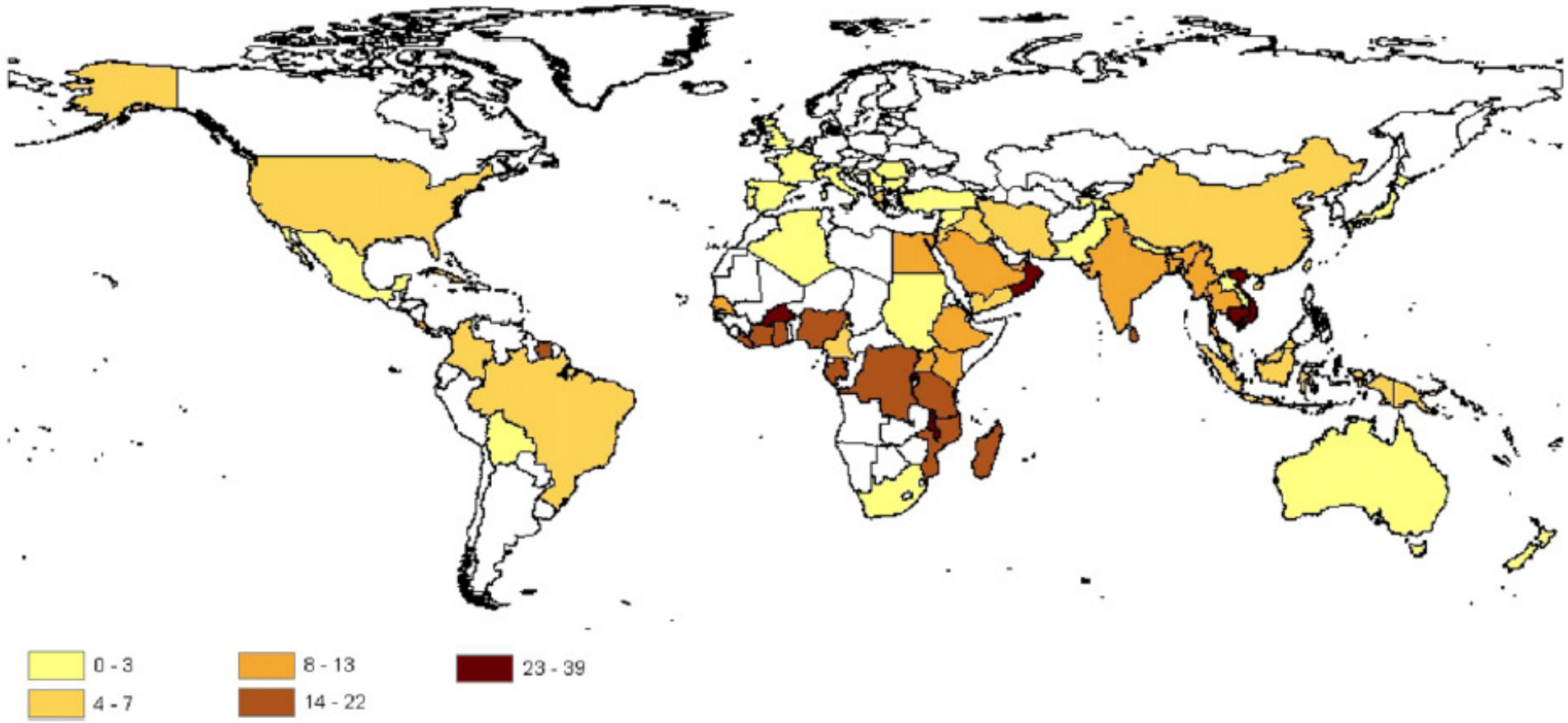
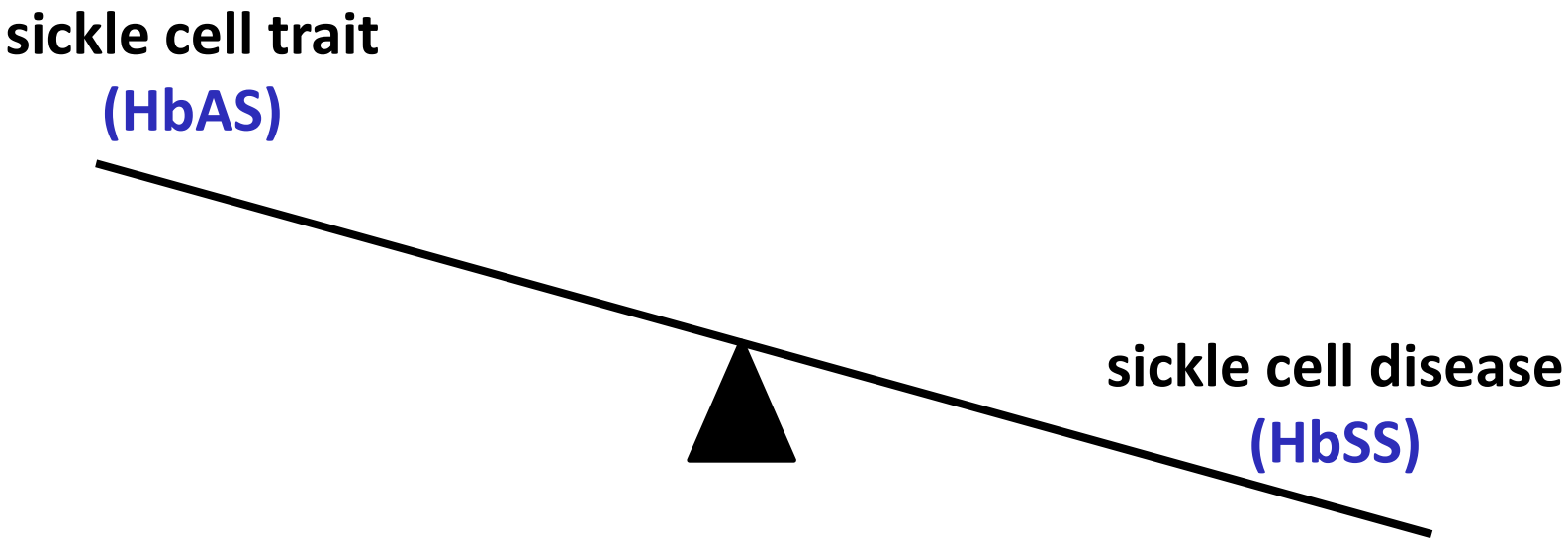


Fig. 1. The world distribution of the α thalassaemias. ▨, α^+ thalassaemia; ■, α^0 thalassaemia.

G6PD deficiency



Nkhoma et al, Blood Cells, Molecules and Diseases 2009


sickle cell trait
(HbAS)
sickle cell disease
(HbSS)

Investigating burden and clinical consequences of genetic disorders in Kilifi

Investigating mechanisms of malaria protection

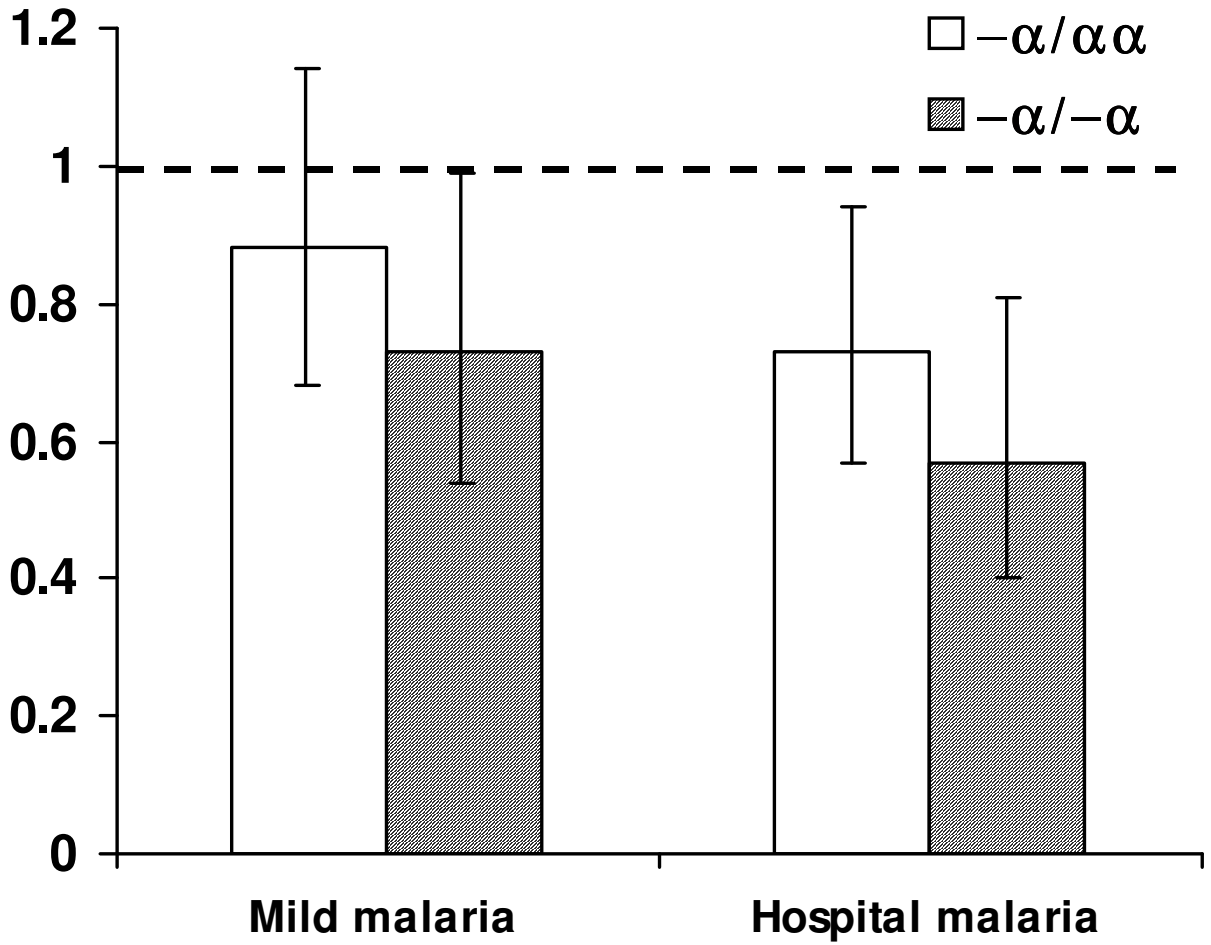
Association studies

Descriptive epidemiology

species, age, syndrome, magnitude, interactions, immunology

Functional studies

Mechanisms for most malaria protective genes remain unknown



Wiilliams et al, Blood 2005

nature genetics

Negative epistasis between the malaria-protective effects of α^+-thalassemia and the sickle cell trait

Thomas N Williams[1–3], Tabitha W Mwangi[1,2], Sammy Wambua[1], Timothy E A Peto[2], David J Weatherall[4], Sunetra Gupta[5], Mario Recker[5], Bridget S Penman[5], Sophie Uyoga[1], Alex Macharia[1], Jedidah K Mwacharo[1], Robert W Snow[1,2] & Kevin Marsh[1,2]

Epistatic interactions between genetic disorders of hemoglobin can explain why the sickle-cell gene is uncommon in the Mediterranean

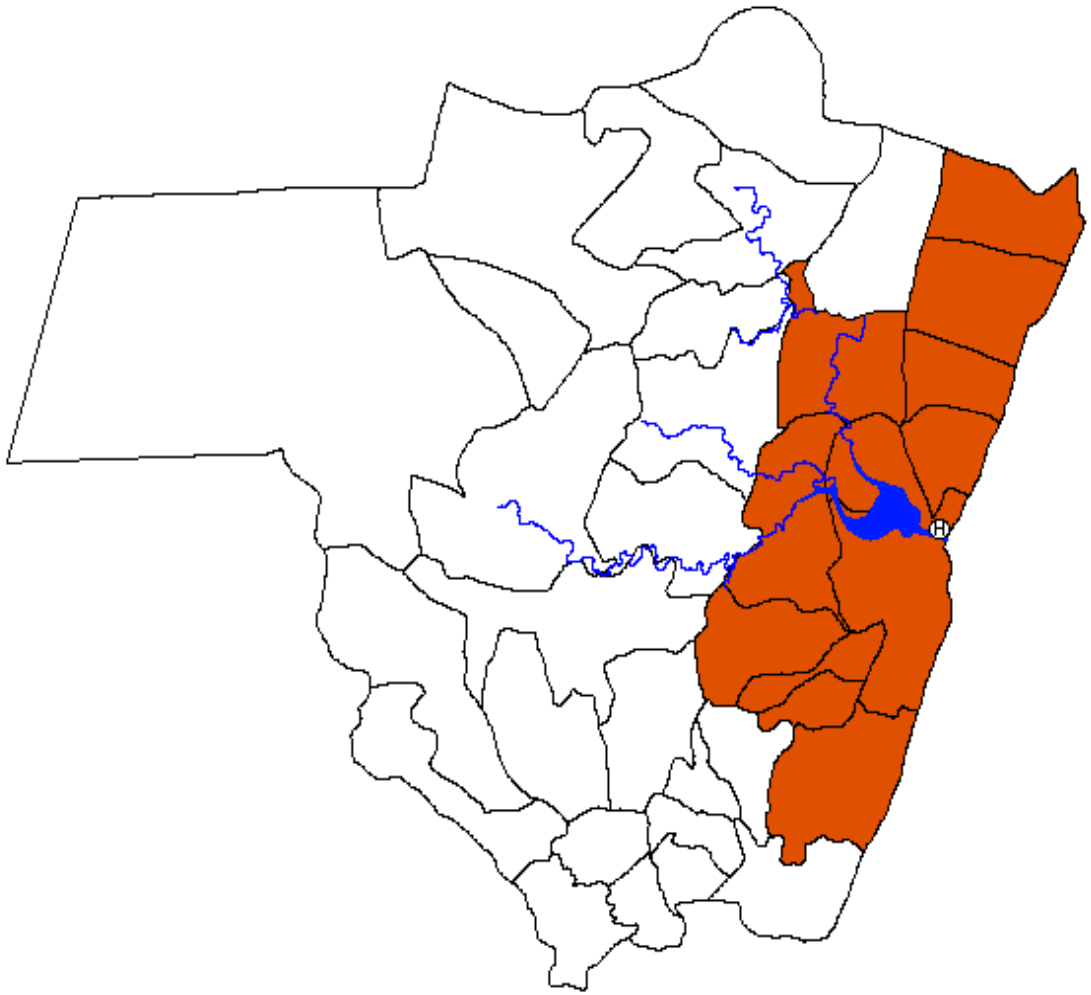
Bridget S. Penman[a], Oliver G. Pybus[a], David J. Weatherall[b,1], and Sunetra Gupta[a,1]

[a]Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, United Kingdom; and [b]Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DS, United Kingdom

21242–21246 | PNAS | December 15, 2009 | vol. 106 | no. 50

Cohort approach has many advantages

(1) Demographic surveillance



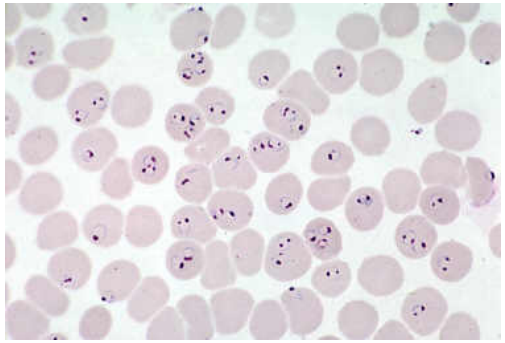
Population ~260,000

(2) Hospital ward surveillance

36 bed paediatric ward
>5000 admissions / year

6 bed research ward
>700 admissions / year

(3) Laboratory surveillance

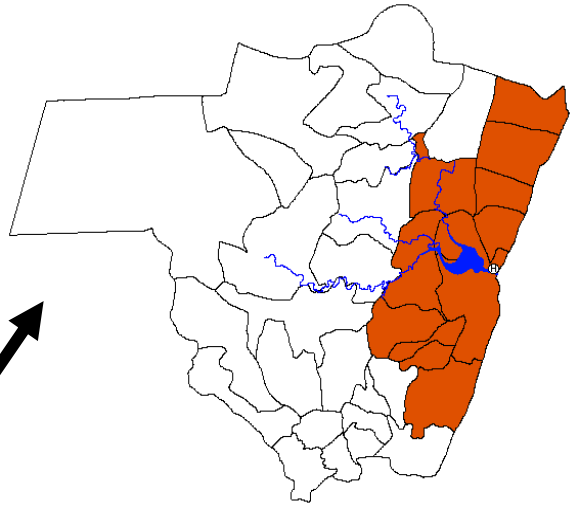


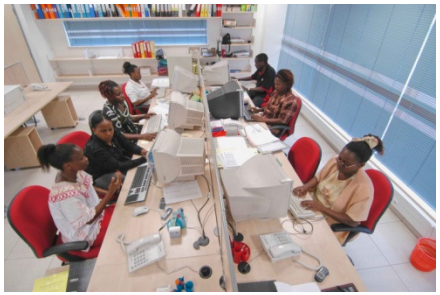
Malaria

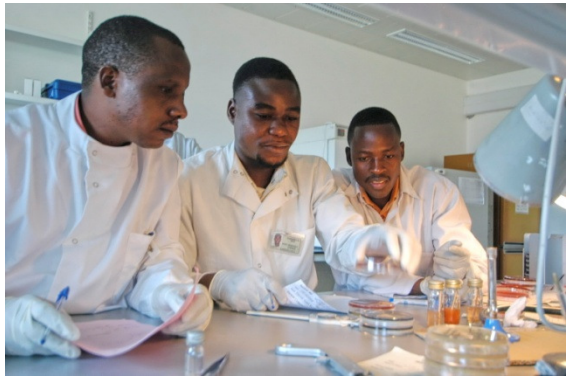
Bacterial diseases

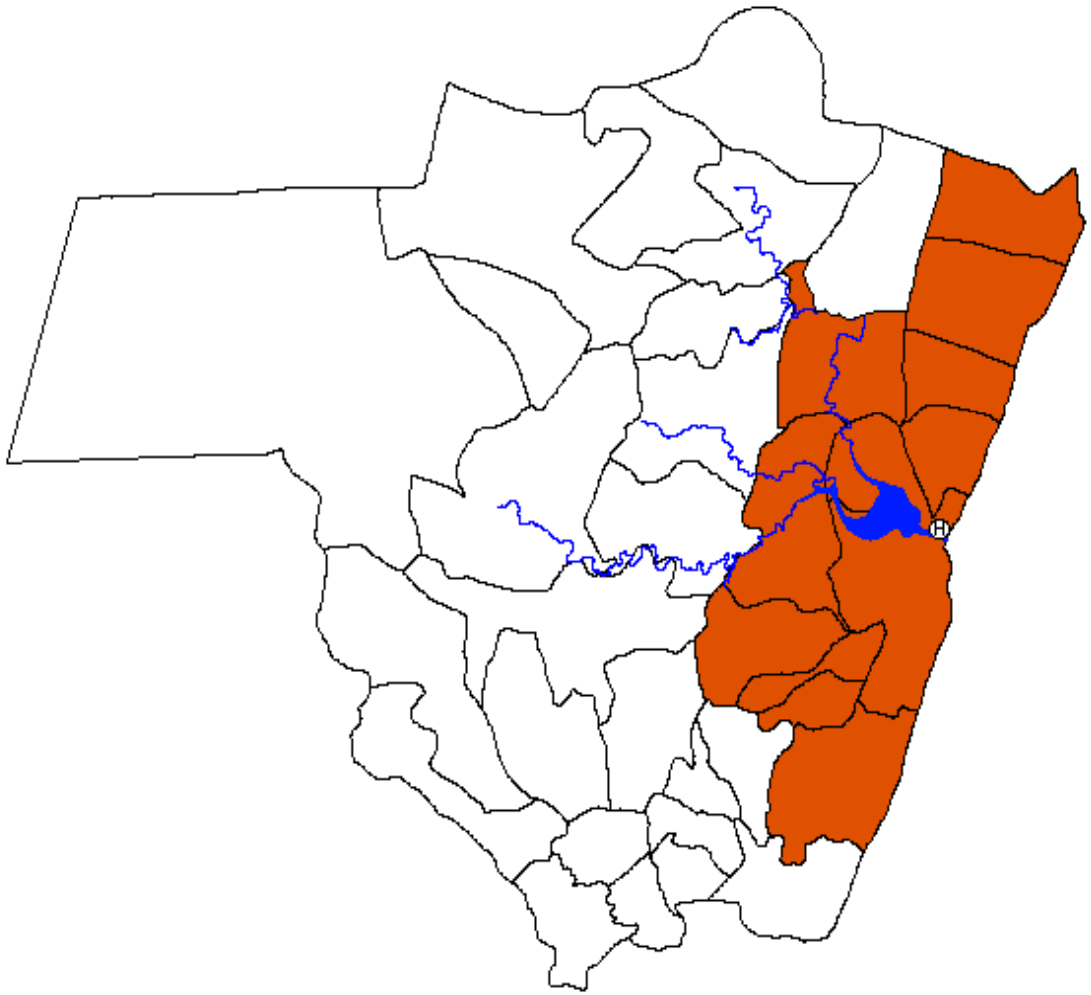
Haematology, biochemistry…..

Linked surveillance systems









8,000 births / year

Birth cohort to study genetic epidemiology of malaria and other diseases

- 16,000 children over ~2 years
- Followed for (i) deaths and (ii) clinical events
- Focused studies in informative children

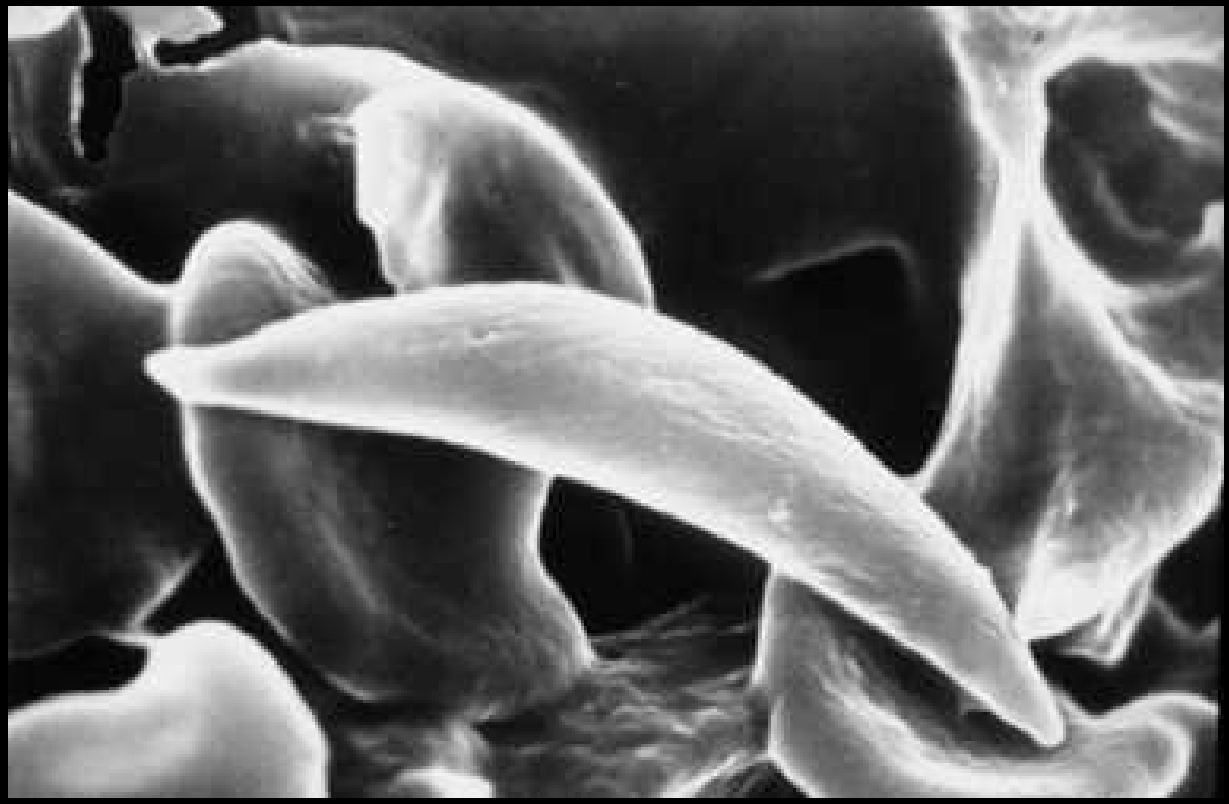
Marsh *et al. BMC Medical Ethics* 2010, **11**:13
http://www.biomedcentral.com/1472-6939/11/13

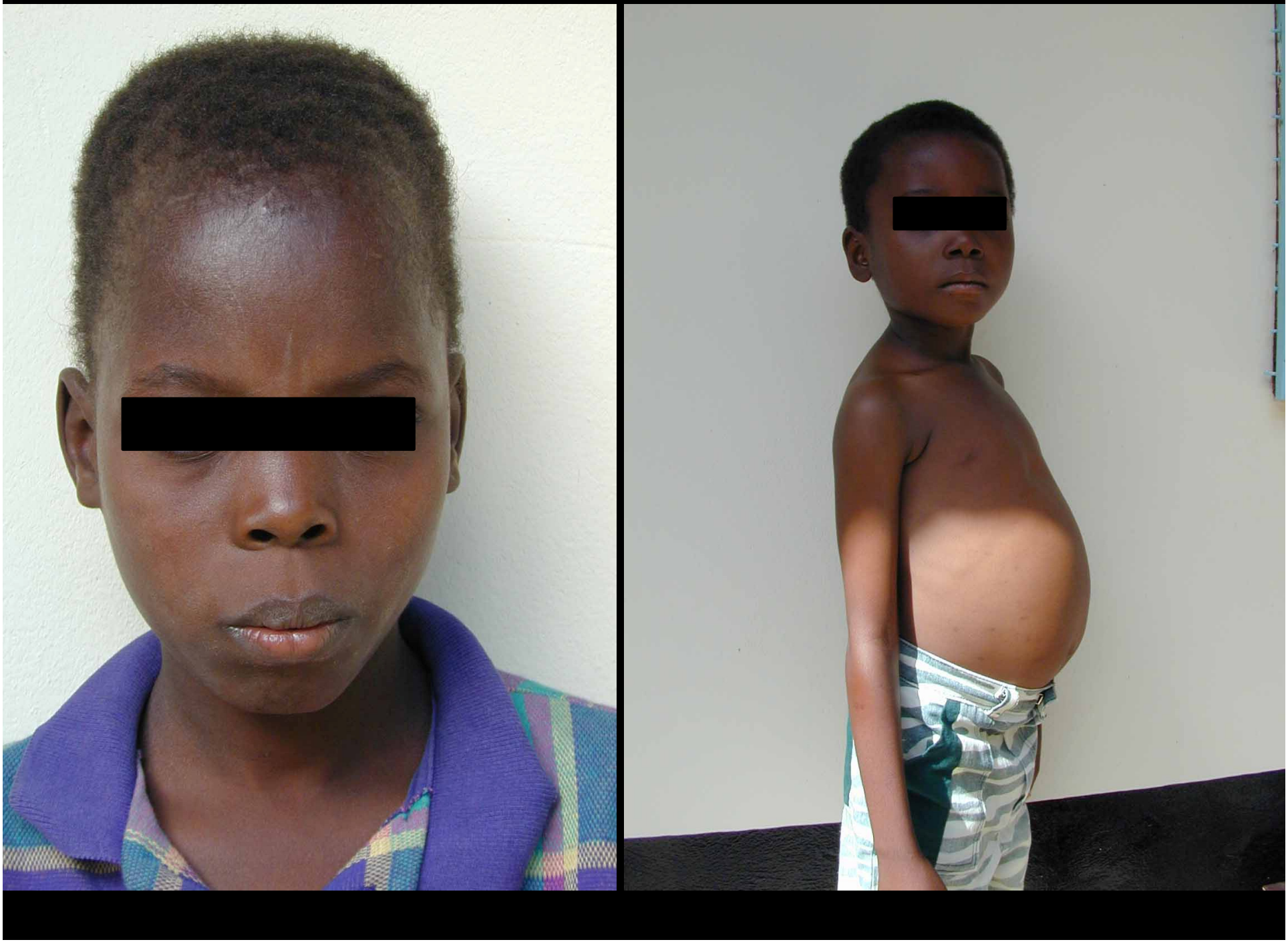
BMC
Medical Ethics

RESEARCH ARTICLE Open Access

Experiences with community engagement and informed consent in a genetic cohort study of severe childhood diseases in Kenya

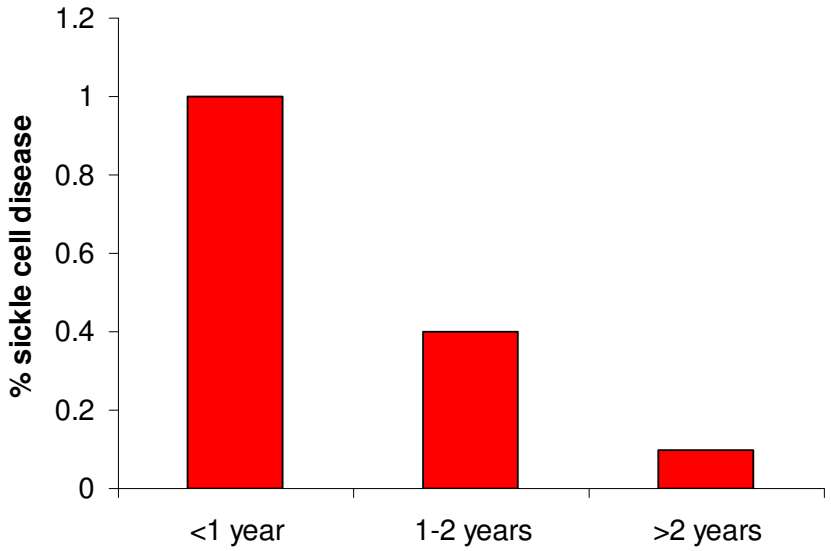
Vicki M Marsh[1,2*], Dorcas M Kamuya[1], Albert M Mlamba[1], Thomas N Williams[1,2,3], Sassy S Molyneux[1,2]





- 300,000 births / year
- 80% SSA
- 90% mortality

Kilifi 10/1000 live births



Ethnicity & Health

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ceth20

'All her children are born that way': gendered experiences of stigma in families affected by sickle cell disorder in rural Kenya

Vicki M. Marsh [a b c] , Dorcas M. Kamuya [a] & Sassy S. Molyneux [a b c]
[a]

Consent to Participate for Children

I, _____ *(name of parent),* having full capacity to consent for my child _____, *(name of patient)* have been informed about this study on inherited factors and protection from malaria and other diseases.

I have been given the opportunity to ask questions concerning the study and these have been answered to my satisfaction.

I understand that I may withdraw my child from the study at any time. Refusal to participate or withdrawal will involve no penalty or loss of benefits to which I am otherwise entitled.

NDIO / NIKARAKARA I wish my child to participate in this study

I agree to a blood sample being taken from my child's heel

I agree to this sample being stored for tests on inherited factors in the future

I agree to part of this sample being sent overseas for tests on inherited factors that cannot be done in Kenya

Parents/guardians signature _____Date_____

Parents/guardians name _____

Village address _____

Child's ID _____

Witness

I have witnessed the consenting process of the parent/guardian. S/he has read/been read the information sheet, had this information explained and been given an opportunity to ask questions. S/he has signed this form to show agreement to participate in the study.

Witness signature _____Date_____

Witness name _____

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Witness signature _____Date_____

Witness name _____

Birth cohort to study genetic epidemiology of malaria and other diseases

- 16,000 children – 2006-2011
- Detailed recruitment questionnaire + blood sample
- Followed for (i) deaths and (ii) clinical events
- Focused laboratory studies in a subset of children


BIO-RAD
VARIANT
2
1


ABI LOG FILE
6100 Nucleic Acid PrepStation
ABI PRISM
6100 Nucleic Acid PrepStation
ABI PRISM
WASTE BOTTLE
WASTE BOTTLE


GENERAL
GENERAL
TW

- further candidate gene typing by Sequenom™
- whole genome amplification
- typing on Affimetrix 2.5M SNP chip


RSV CONVALESCENT BLOOD
FREEZER 7, RACK 8, TRAY 2
RSV – COHORT NEA
TRAY 2
RSV CONVALESCENT BLOOD
FREEZER 7, RACK 8, TRAY 3
RSV COHORT
TRAY 5

	αα/αα	−α/αα	−α/−α	Total
AA	4,624 (28.9%)	6,800 (42.5%)	2,176 (13.6%)	13,600 (85.0%)
AS	816 (5.1%)	1,200 (7.5%)	384 (2.4%)	2,400 (15.0%)
Total	5,440 (34.0%)	8,000 (50.0%)	2,560 (16.0%)	16,000 (100%)

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Final diagnosis[¥]	n	%
Lower respiratory tract infection	657	34.2
Gastroenteritis	428	22.3
Neonatal sepsis	263	13.7
Febrile convulsions	138	7.2
Malnutrition	122	6.4
Upper respiratory tract infection	89	4.6
Anaemia	75	3.9
Bronchiolitis	75	3.9
Neonatal jaundice	72	3.8
Malaria	66	3.4
Sickle cell disease	36	1.9
Burns	29	1.5
HIV	28	1.5

Acknowledgements

Lab team

Alex Macharia

Sophie Uyoga

Emily Orori

Adan Mohammed

Metrine Tendwa

Johnson Makale

Janet Ndirangu

David Ouna

Moses Msobo

Salim Mwarumba

Brett Lowe

KEMRI clinicians

Kevin Marsh

KHDSS

Evasius Bauni

Anthony Scott

Field team

Carolyne Ndila

Hussein Kivugo

Emmanuel Mabibo

Data team

Carolyne Ndila

Gideon Nyutu

MalariaGEN

Dominic Kwiatkowski

Kirk Rockett

Funders

wellcome trust

MalariaGEN

GENOMIC EPIDEMIOLOGY NETWORK