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Royal (Dick) School of Veterinary Studies

One Health research: The Roslin Institute

Eleanor Riley, BVSc, PhD, FMedSci
Director of the Roslin Institute

BBSRC
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University of Edinburgh: Commitment to One Health

- College of Medicine and Veterinary Medicine

  Research institutes in genetics, infectious diseases, population health, inflammation and cancer research all work across species boundaries

- MSc in One Health

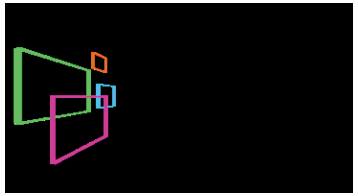
  https://www.ed.ac.uk/vet/studying/postgraduate/taught-programmes/one-health

- One Health PhD programmes with

  Leiden University Medical Centre, Netherlands

  University of Glasgow, UK

  University College Dublin, Ieland



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BBSRC bioscience for the future

Integration of research, teaching, clinical science and commercialisation

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UK's leading animal bioscience research centre

Strategically funded by UK government in the domain of Food Security and Bioscience for Health

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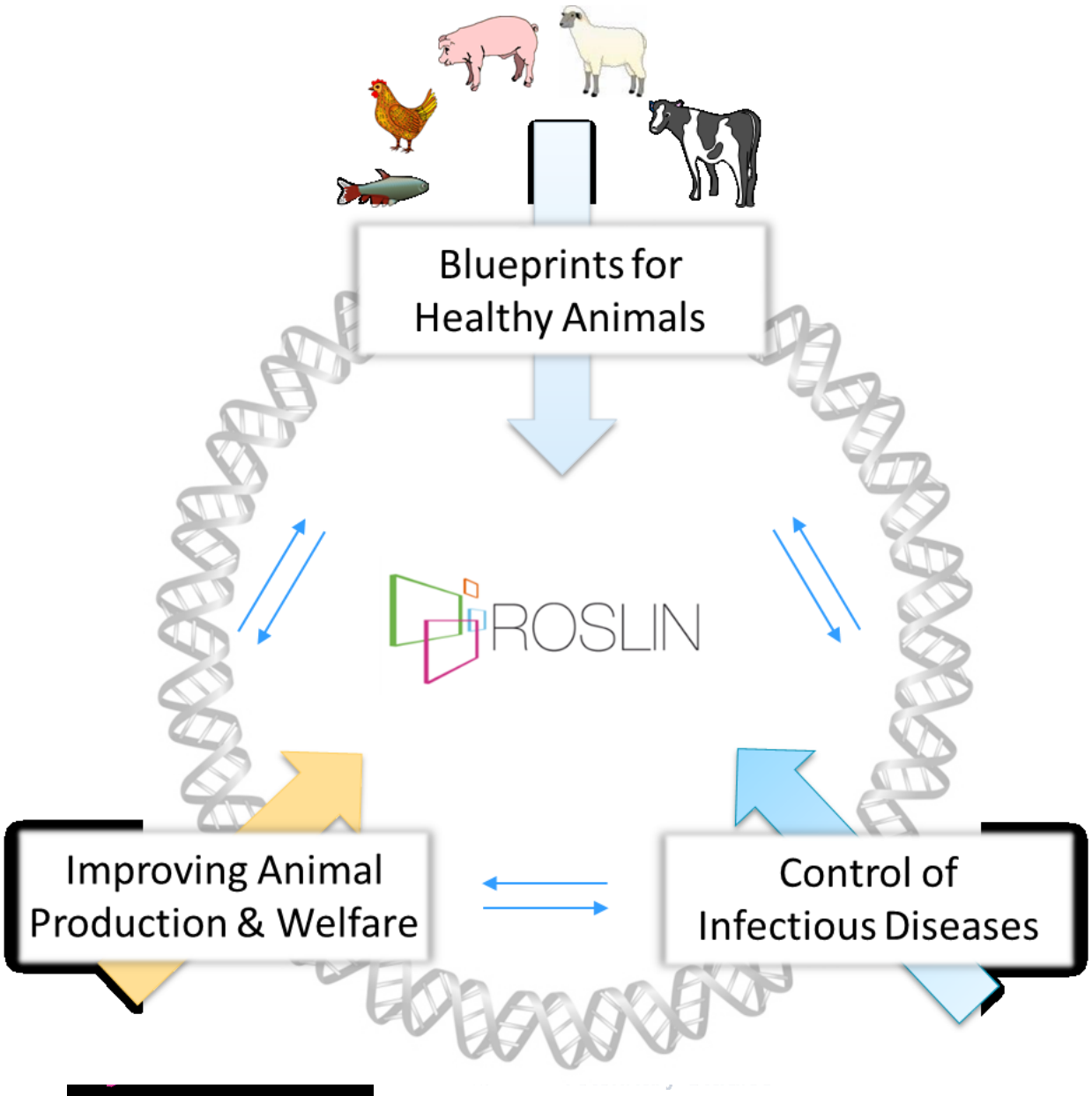


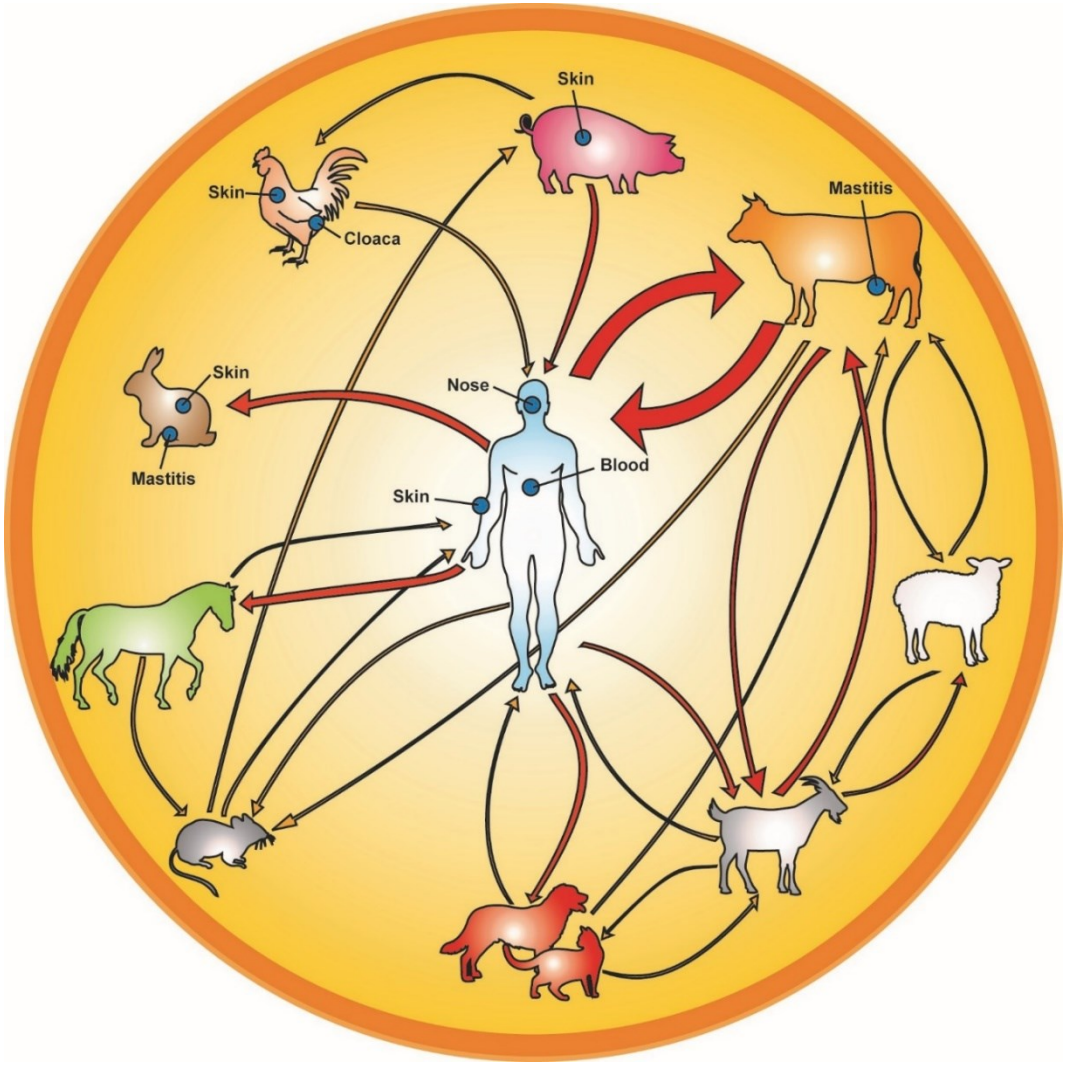
Infections, zoonoses and foodborne pathogens




- Persistence, pathogenesis & protection
- Emergence & spread of pathogens
- Zoonotic risk & virulence
- Foodborne viruses
- Impact of stress, co-infections
- Antimicrobial resistance – emergence and spread
- New and improved vaccines

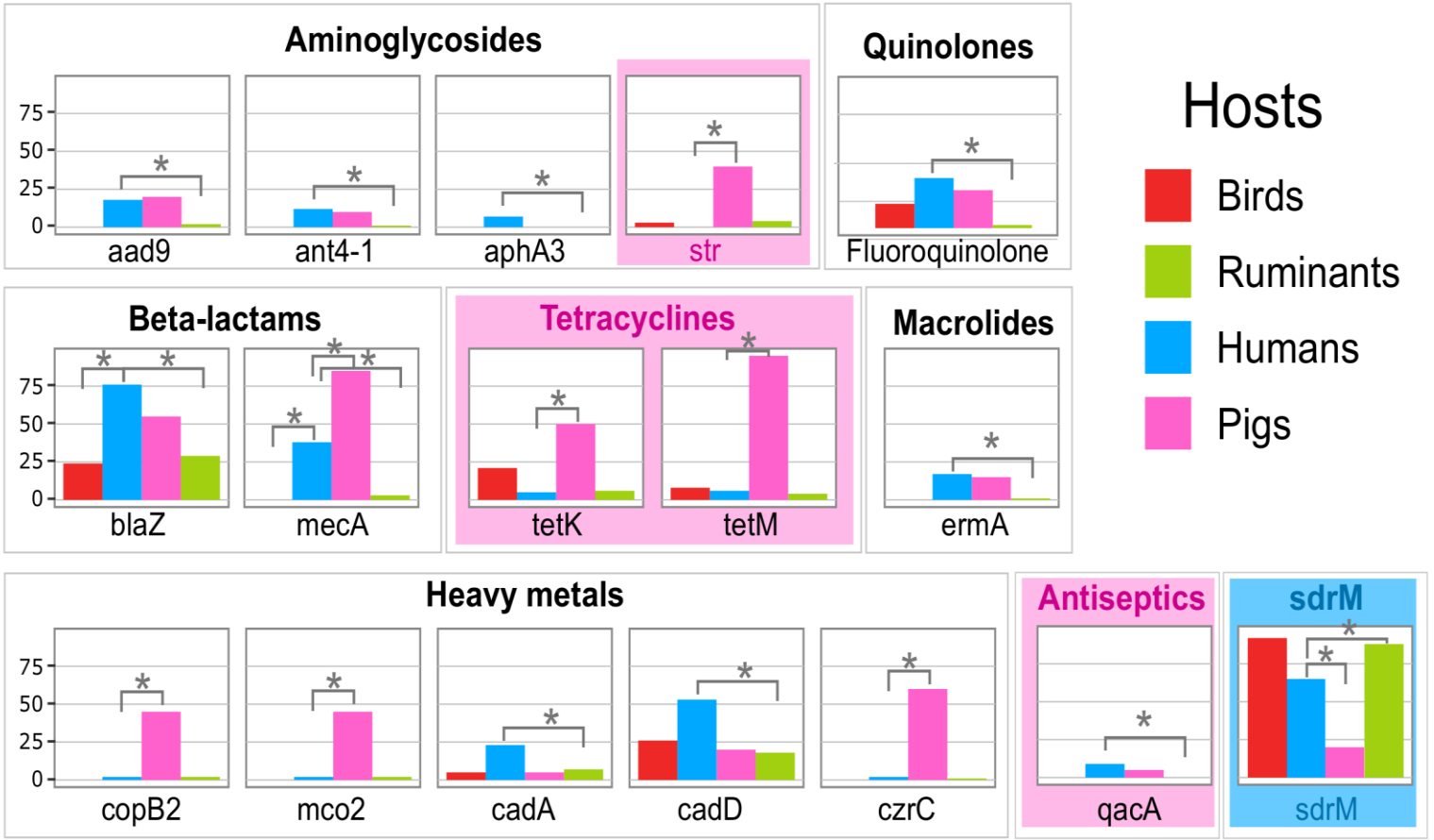
Humans are a major hub for *Staphylococcus aureus* host-switching

Whole genome sequencing and population genetic analysis reveals major routes of cross-species exchange of *S. aureus*



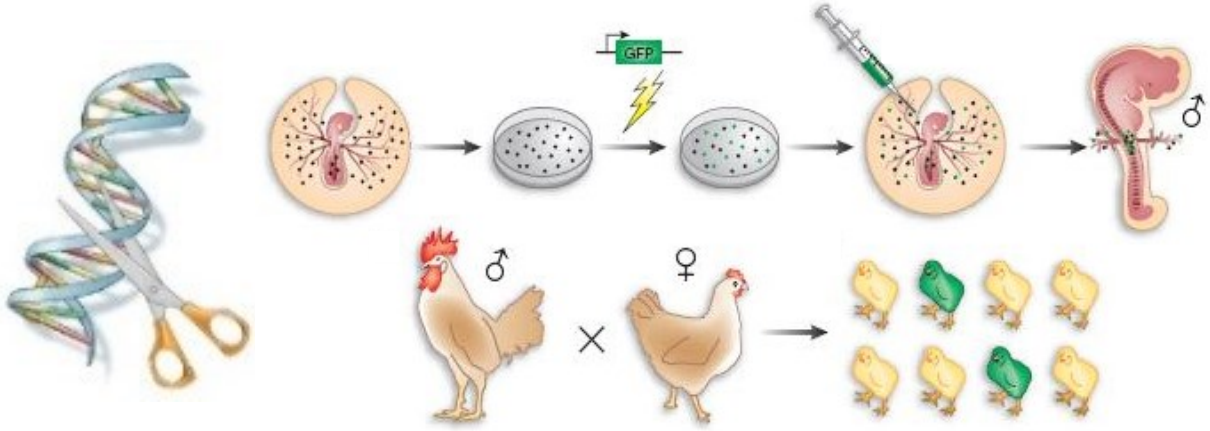
Richardson et al, 2017 Nature Ecol Evol 2:1468-1478

Prevalence of antimicrobial resistance genes among *S. aureus* differs by host-species



Richardson et al, 2017 Nature Ecol Evol 2:1468-1478

Genome editing & transgenesis

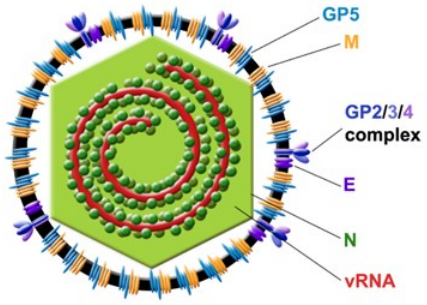


- Farm animal genomes can now be rapidly and reliably modified
- Gene edited disease resistant animals can be produced
- Regulatory constraints & consumer views are beginning to change

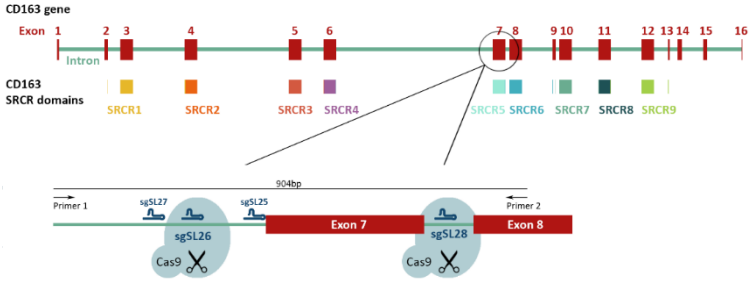
But: Gene editing and genetic manipulation also:

- Enables validation of causal variants underlying resistance
- Genome-scale mutagenesis in cell lines using gene knockout (GeCKO) libraries facilitates identification of host genes associated with resistance & susceptibility
- Opening new routes for conventional approaches to disease control

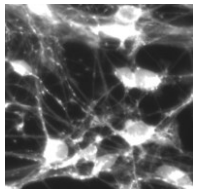
Porcine Reproductive and Respiratory Syndrome (PRRS)



- Globally endemic coronavirus; leads to high levels of routine antibiotic use
- Genome-wide association studies (GWAS) did not identify highly protective variants in commercial pig populations
- In vitro studies identified the essential host cell receptor for PRRS virus
- Mutation of this receptor blocked viral entry into cells
- Gene editing has enabled us to produce pigs that are resistant to PRRS



Benefits of large animal models for human health and medicine: traditional paradigm



Small animal models

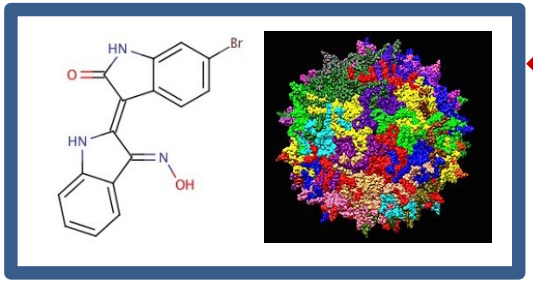
Cell culture

Low predictability

administration, distribution, scale?

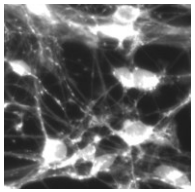
?

Efficacy?

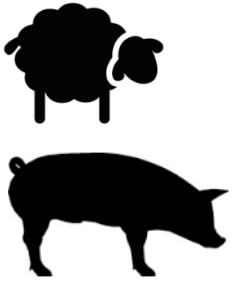


Candidate targeting – pharma, small molecule, viral?

Benefits of large animal models for human health and medicine: improved paradigm?



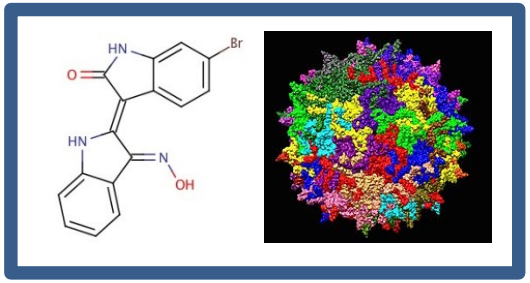
Small animal models



Cell culture

Large animal models

administration,
distribution,
scale?



Candidate targeting – pharma, small molecule, viral?

Batten's Disease: A genetically determined lysosomal storage disease.

Introducing the human disease-causing PPT1 mutation into Sheep

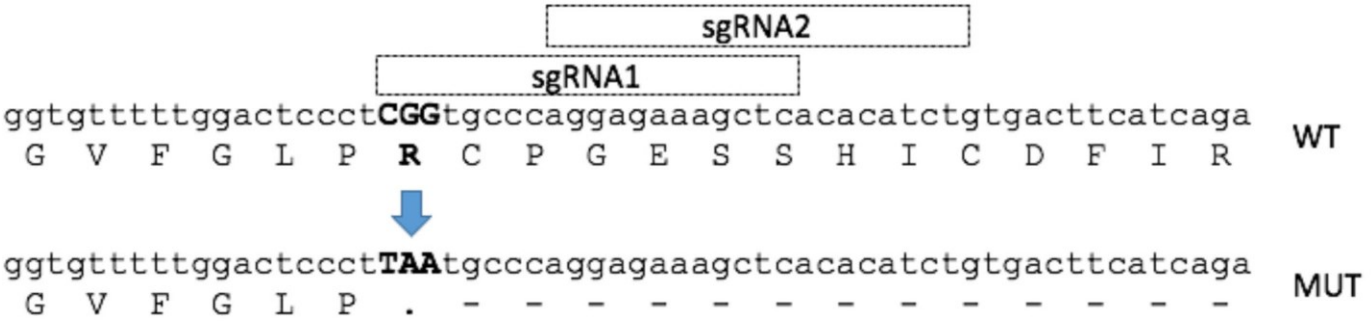
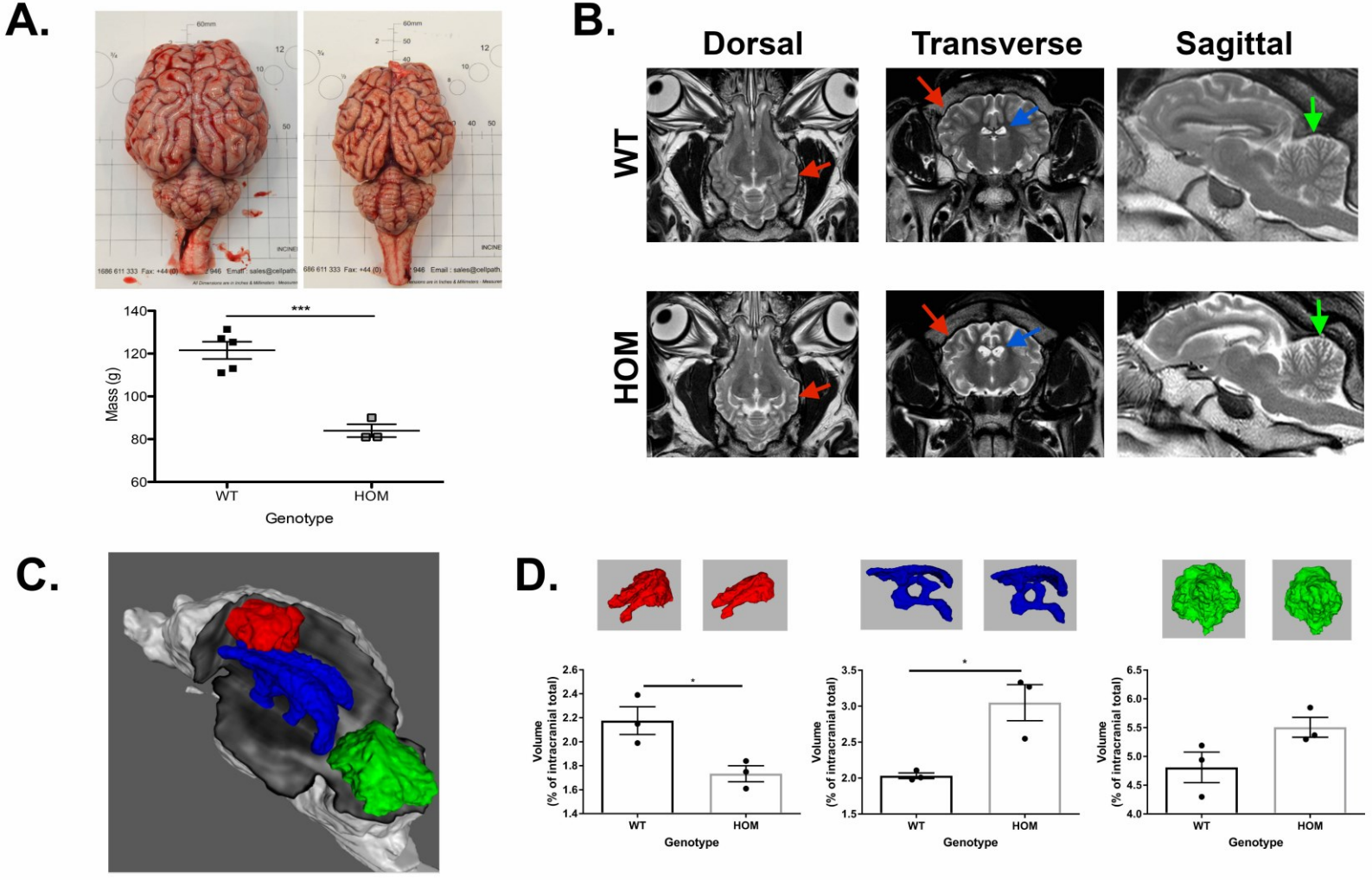


Table 1: Editing the sheep PPT1 locus

					Genotypes			
	Blastocysts	Recipients	Pregnancies	Lambs	WT	Indel	Het HDR	Hom HDR
sgRNA 1	35	17	10	10	3	3	2	2
sgRNA 2	31	16	9	14	9	0	4	1

Eaton *et al* Scientific Reports, *in press*



Eaton *et al* Scientific Reports, *in press*

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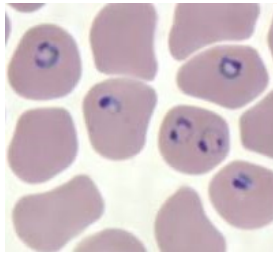
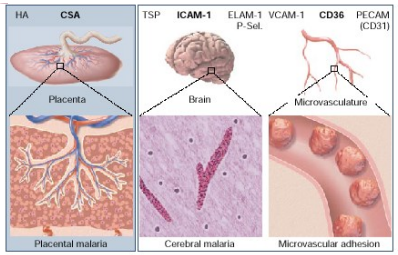
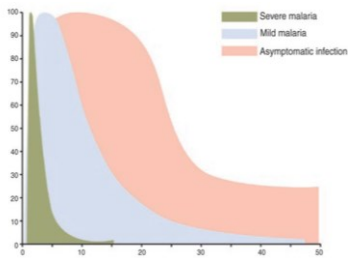
Malaria and invasive bacterial disease



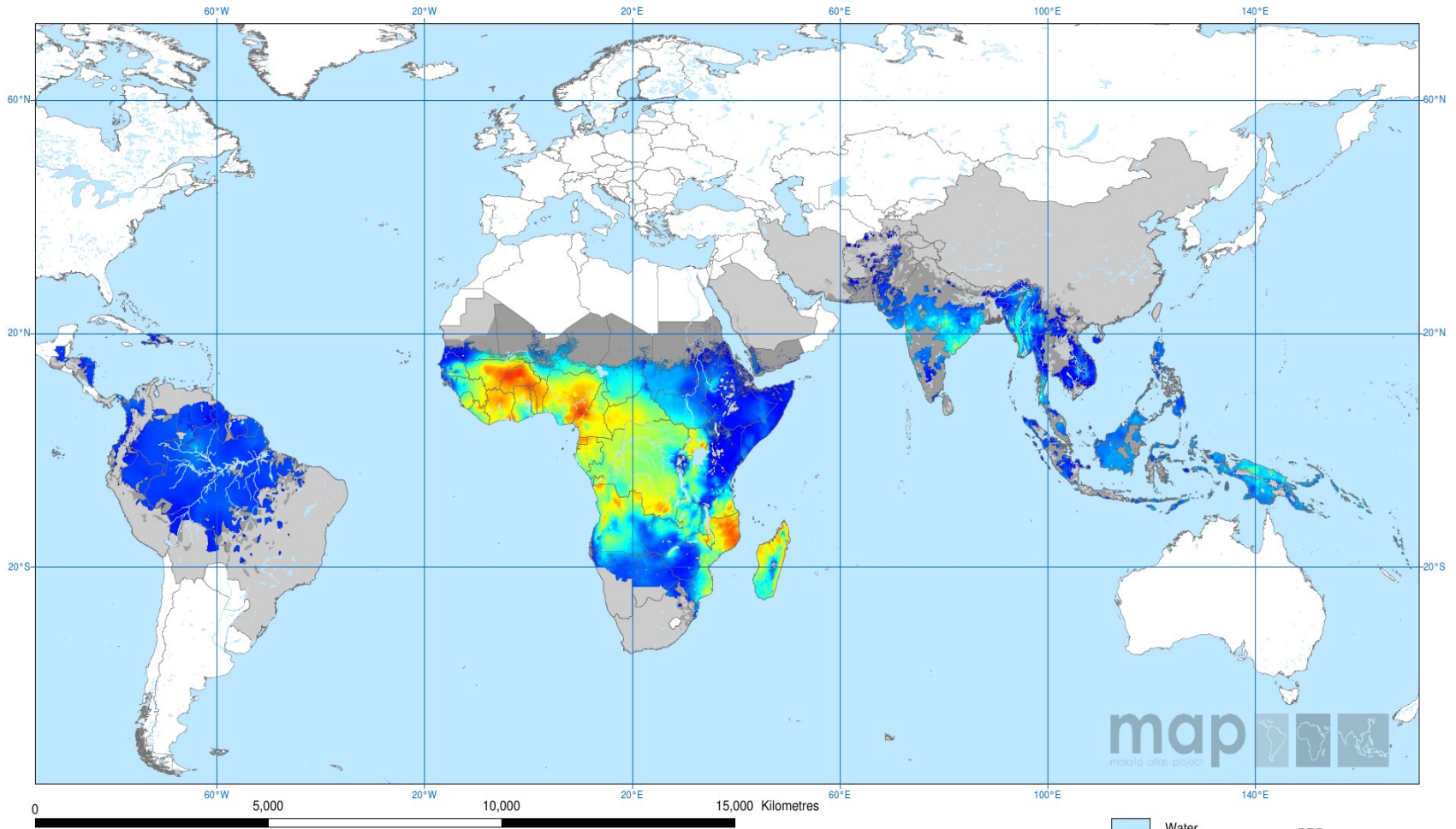




Eleanor Riley

The Roslin Institute, University of Edinburgh

World distribution of falciparum malaria: 2010

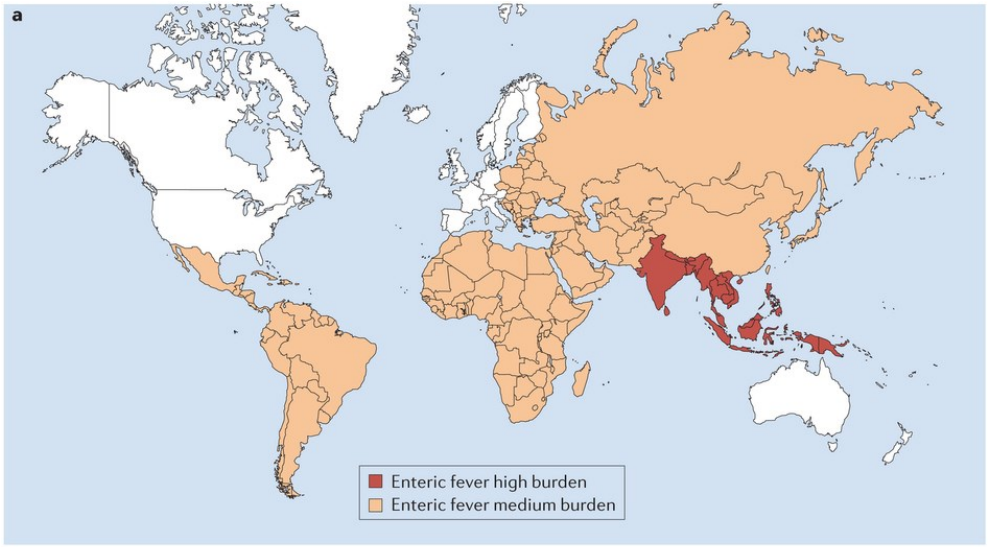


Mean point estimates of the age-standardised annual mean *Plasmodium falciparum* parasite rate in two to ten year olds ($PfPR_{2-10}$) within the spatial limits of stable transmission. Areas of no risk and unstable risk (*Pf*API < 0.1‰) are also shown.

Gething, P.W.*, Patil, A.P.*, Smith, D.L.*, Guerra, C.A., Elyazar, I.R.F., Johnston , G.L., Tatem, A.J. and Hay, S.I. (2011). **A new world malaria map: *Plasmodium falciparum* endemicity in 2010.** *Malaria Journal*, **10**: 378. BMC highly accessed article. *indicates equal authorship.

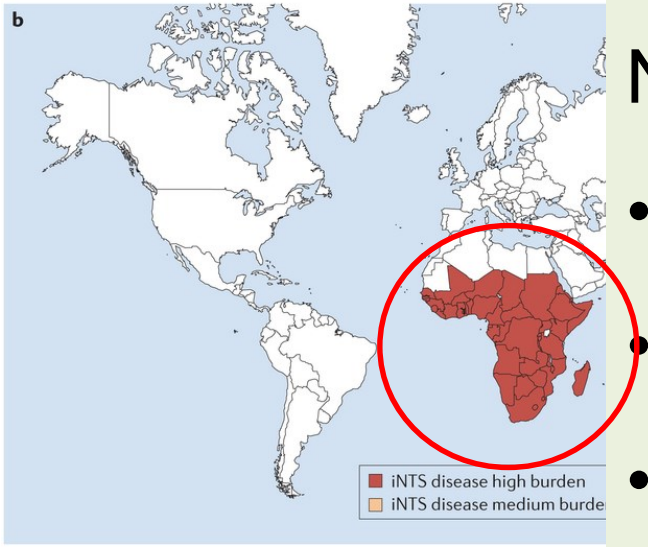
N

Salmonellosis



Enteric fever:

- *Salmonella enterica* serovars Typhi and Paratyphi
- Human restricted



Non-typhoidal *Salmonella* in SSA:

- ~ 30% of all cases of bacteraemia
- 1 million cases per year
- 20% case fatality rate

Nature Reviews | Immunology

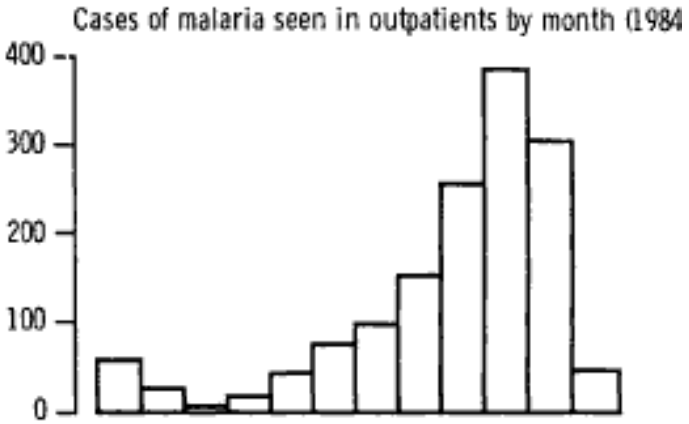
Malaria and Non-typhoid Salmonella

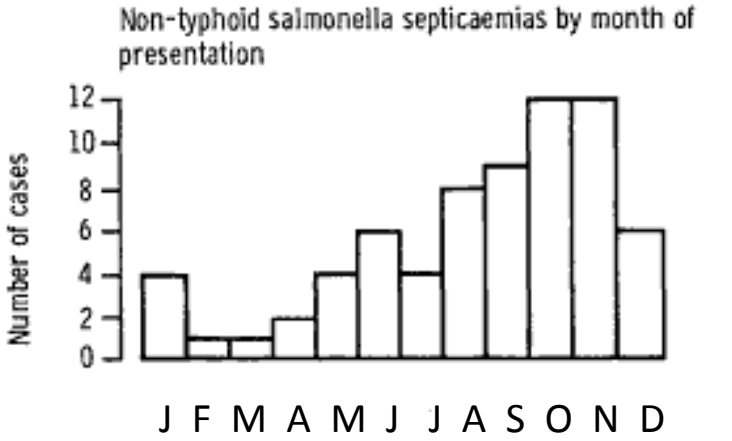
Table 1. Parasitological and hematologic findings in patients with septi

Bacteria isolated	All patients: No.	All patients: Hemoglobin (mean ± 1 SD)	All patients: No. with malaria (%)*
Nontyphoid salmonellae	71	6.7 ± 2.8	30 (42)
Salmonella typhi	43	10.3 ± 3.2	5 (11)
Others	130	9.5 ± 2.4	8 (6)

NTS = 29% of sepsis cases

NTS = 70% of malarial co-infections





D. C. W. Mabey, A. Brown, B. M. Greenwood
Medical Research Council Laboratories,
Fajara, Banjul, The Gambia

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 155, NO. 6 • JUNE 1987

***Plasmodium falciparum* Malaria and *Salmonella* Infections in Gambian Children**

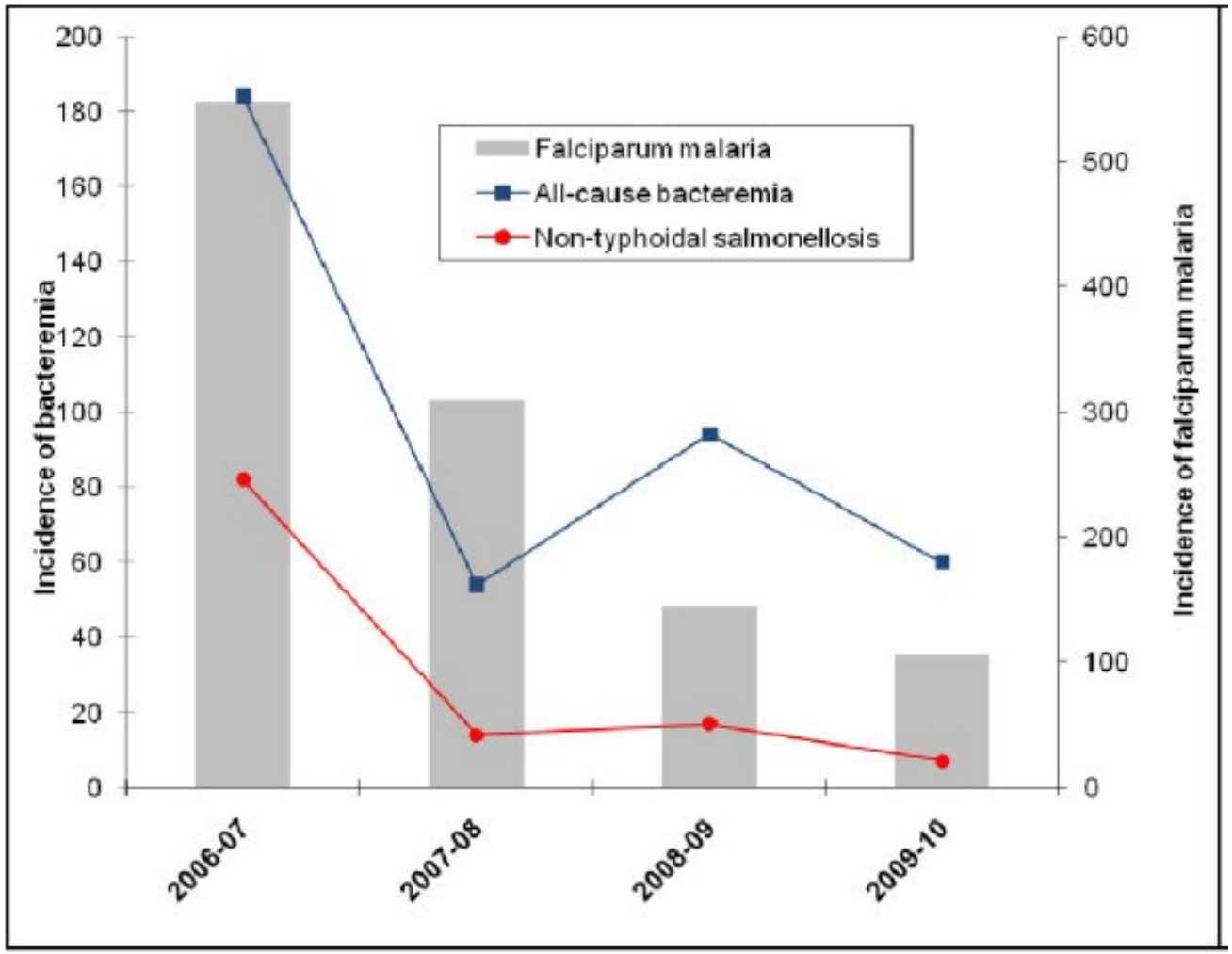
Invasive *Salmonella* infections in Tanzania

Table 3. Malaria, HIV Infection, Bacteremia, and Associated Mortality, Teule

Infection	Teule (n = 3639), no./No. (%)
Malaria	2195/3639 (60.3)
Recent malaria	501/3639 (13.8)
HIV	142/3639 (3.9)
Bacteremia	336/3639 (9.2)
Nontyphoidal *Salmonella*	162/3639 (4.5)
NTS associated with malaria	53/162 (37.7)
NTS associated with recent malaria	67/162 (41.4)
NTS associated with HIV	8/162 (4.9)
Bacteremia if NTS excluded[a]	175/3478 (5.0)
Bacteremia if NTS associated with malaria or recent malaria excluded	216/3519 (6.1)
Salmonella Typhi	11/3639 (0.3)
Escherichia coli	23/3639 (0.6)
Streptococcus pneumoniae	54/3639 (1.5)
Blood culture contaminants[b]	252/3639 (6.9)

Biggs *et al* (2014) Clinical Infectious disease

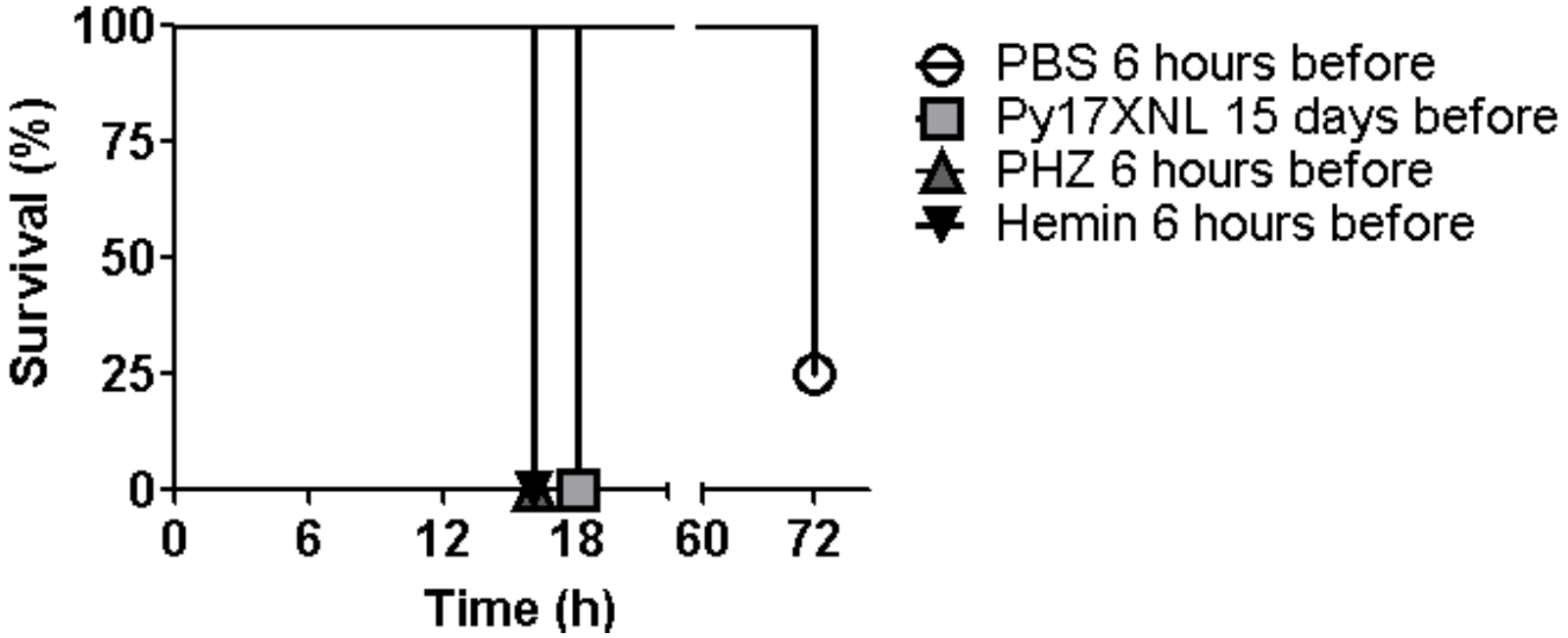
Incidence of NTS declines as malaria declines



Mtove *et al*, 2011, *Malaria J*. **10**: 320.

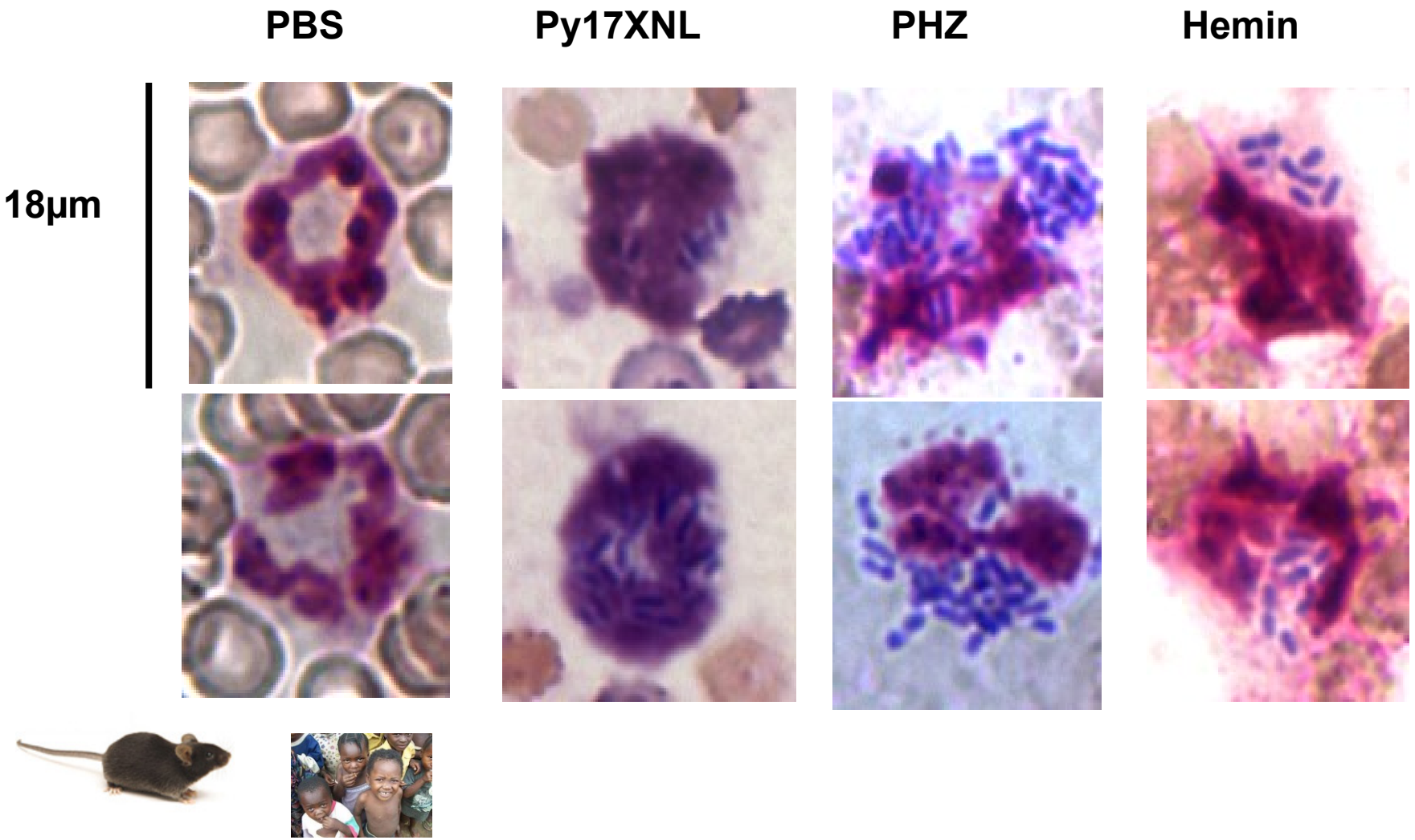
Data from Tanzania; similar observations have been made in The Gambia and Kenya

Malaria infection, haemolysis and hemin all hasten death during *S.* Typhimurium infection

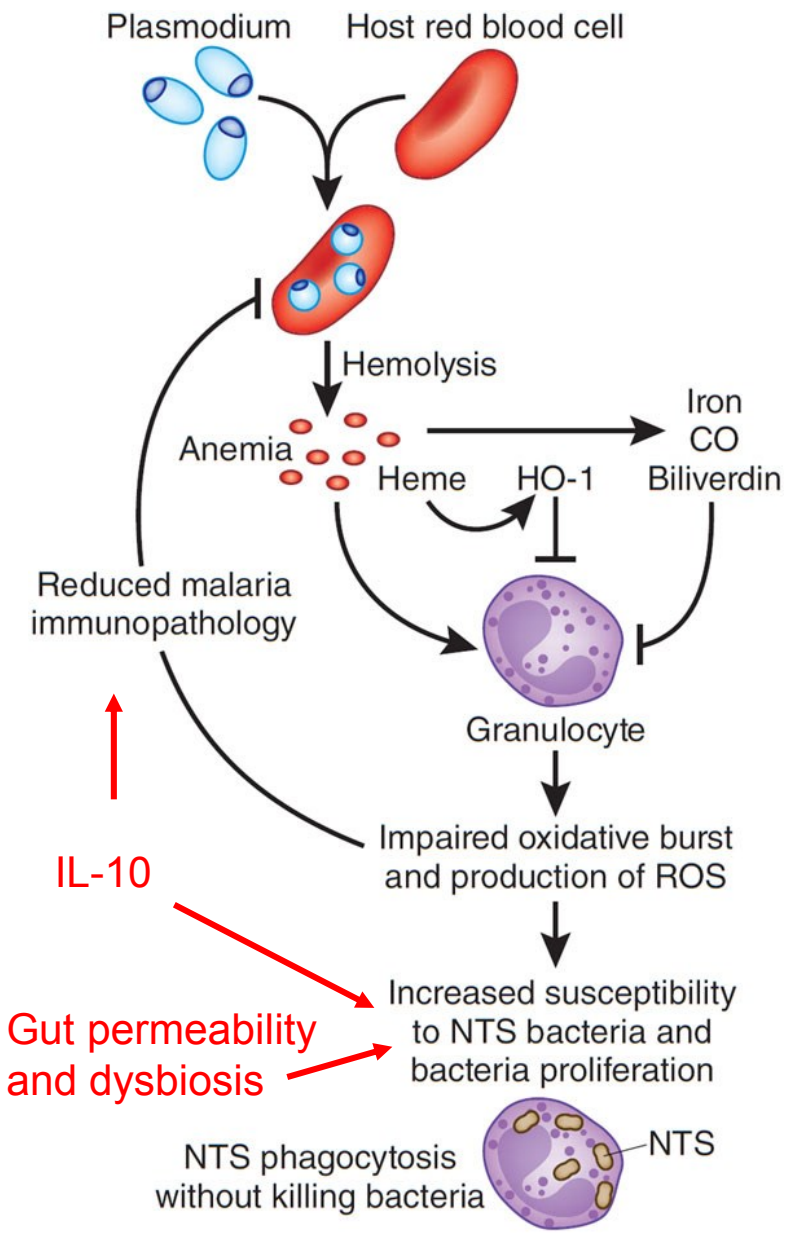


Cunnington et al, *Nat Med* (2012)

Salmonella survive and replicate within neutrophil granulocytes



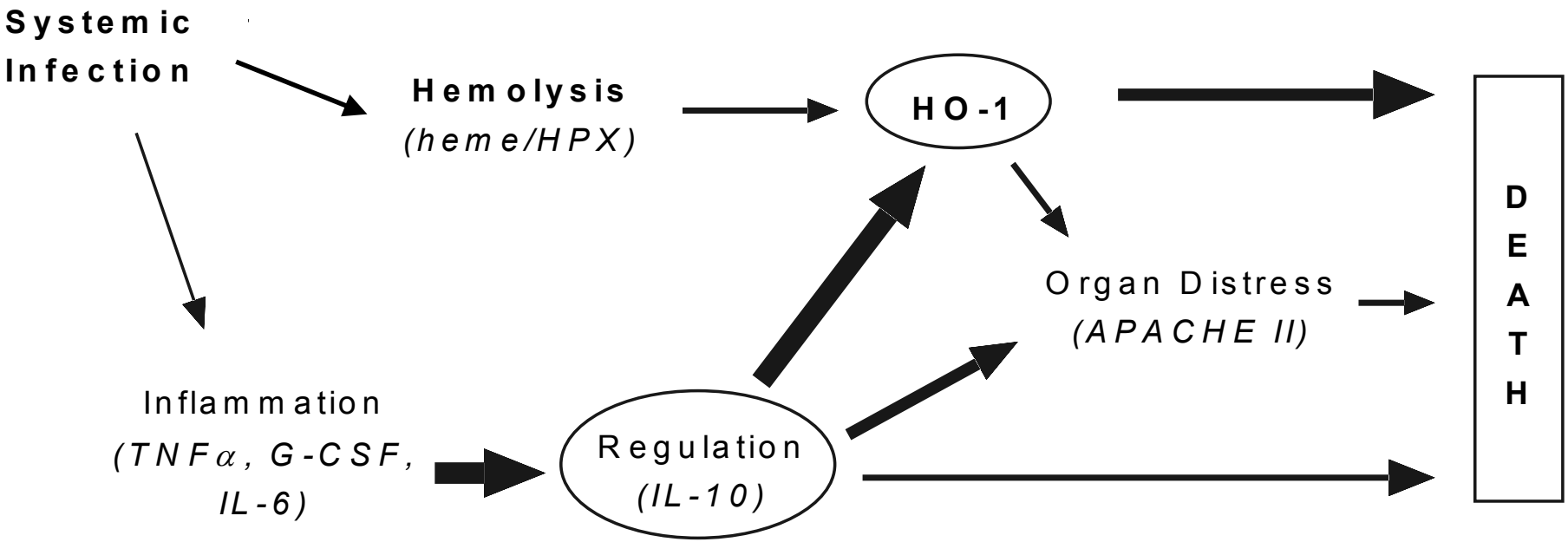
Clinical implications



MacLennan, *News & Views, Nat Med* (2012)

- Haemolysis is a risk factor for iNTS
- HO-1 inhibitors may restore neutrophil function (SnPP has been trialled for R_x of neonatal jaundice)
- Defective neutrophil oxidative burst may be a biomarker of individuals at risk of bacterial infection after treatment for malaria or anaemia
- Persistent “asymptomatic” malaria may be a risk factor for iNTS
- Other haemolytic infections may also lead to neutrophil dysfunction

Anemia, inflammation and Sepsis



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MRC Medical Research Council

NHS National Institute for Health Research

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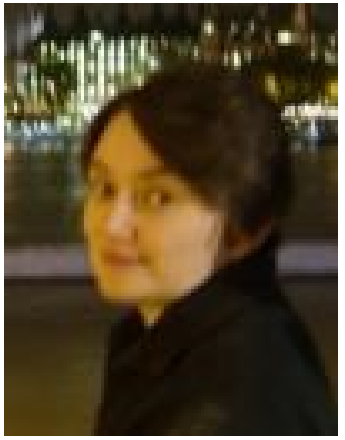

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