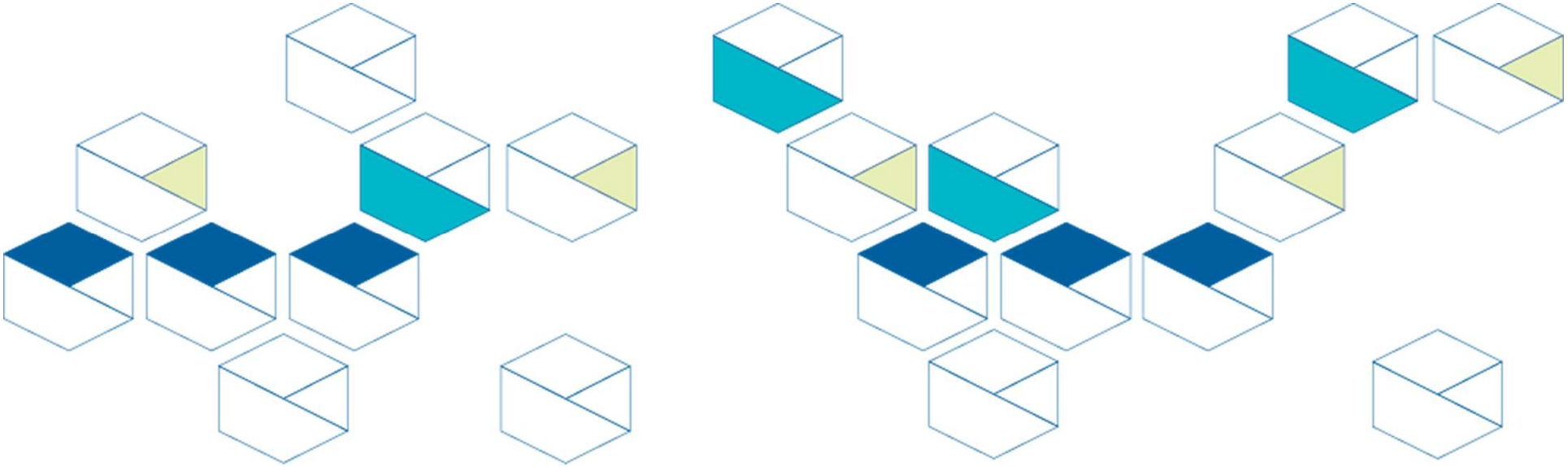
Government of **Western Australia**
South Metropolitan Health Service
Fiona Stanley Fremantle Hospitals Group

Malaria & Anaemia in a Returned Traveller

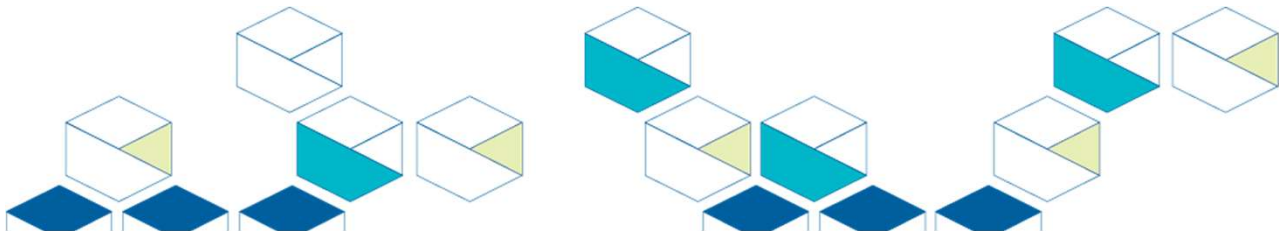
Tim Whitmore

Infectious Diseases & Respiratory Medicine Advanced Trainee
Fiona Stanley Hospital, Perth WA



Disclosure of Interest

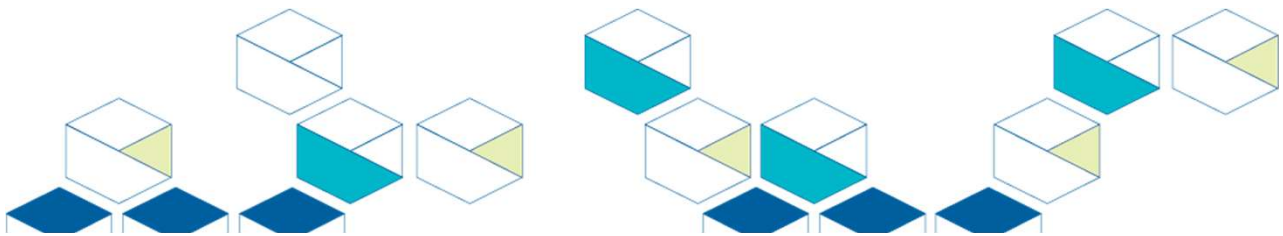
- No conflicts of interest to declare



Case – Mr JS

- 60yo Caucasian M
  - Referred to OPC with anaemia and recent *Falciparum* malaria following return from Zambia
  - Attended ED because family insisted

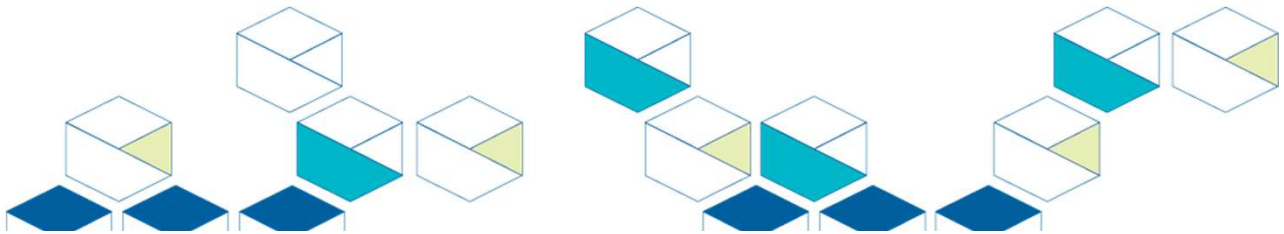
- Background/
  - Hypertension
  - Prior severe malaria (2008, London)
  - No prophylaxis
  - Ex-smoker



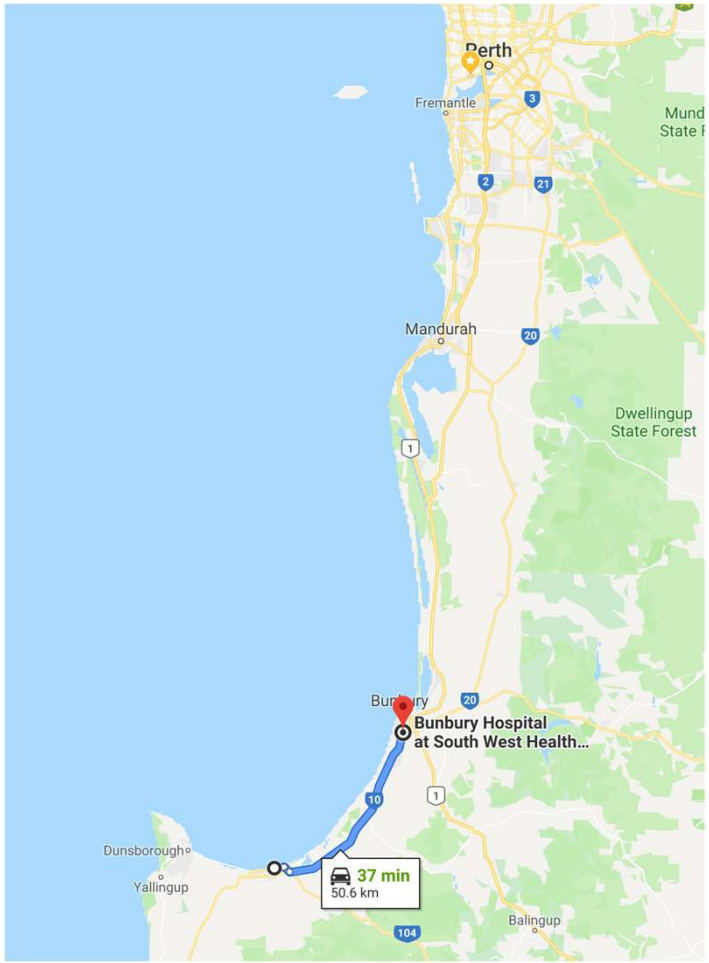
Case – Mr JS

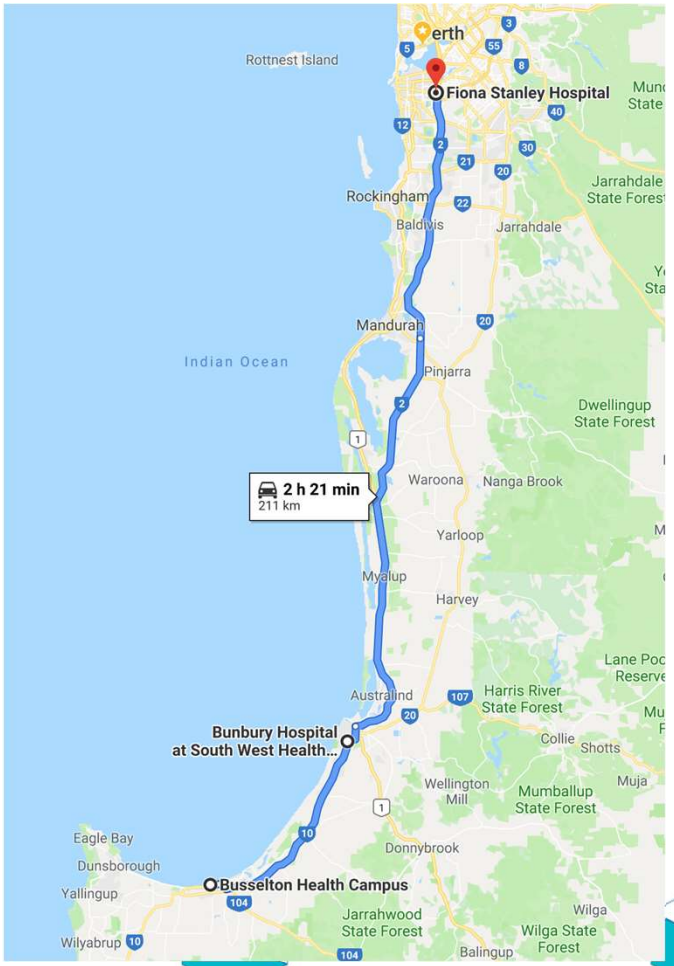
- Initially presented to Busselton Hospital
  - 2 weeks malaise, dry throat, vomiting, rigors, fevers and confusion
  - Returned from Zambia ~1 week previously
  - Concerned he has malaria

- Blood film – likely *P. falciparum*
  - Treatment recommended…



Case – Mr JS



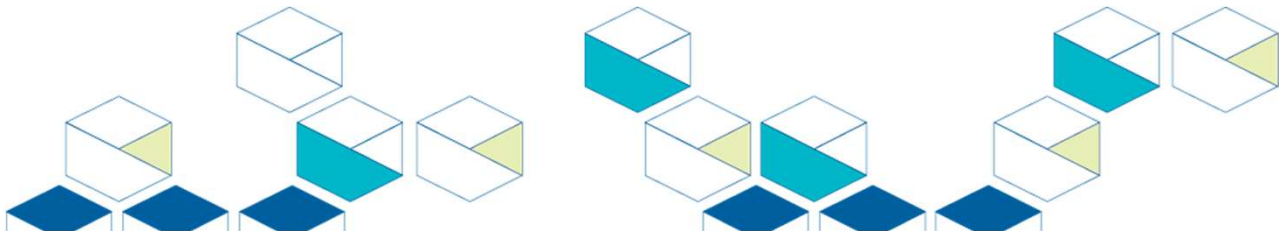


google.com.au/maps, accessed 12/09/2019

Case – Mr JS

- Transferred to Bunbury Hospital by road

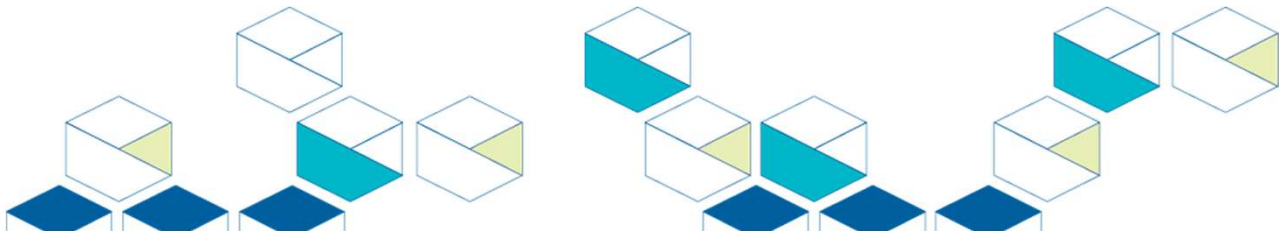
- Commenced artemether/lumefantrine
  - Hb 133, WCC **2.67** (Neut 1.88, Lymph 0.66), platelets **42**
  - Bili **52**, Creat **118**, LDH **1660**
  - Parasitaemia **4.6%**



Case – Mr JS

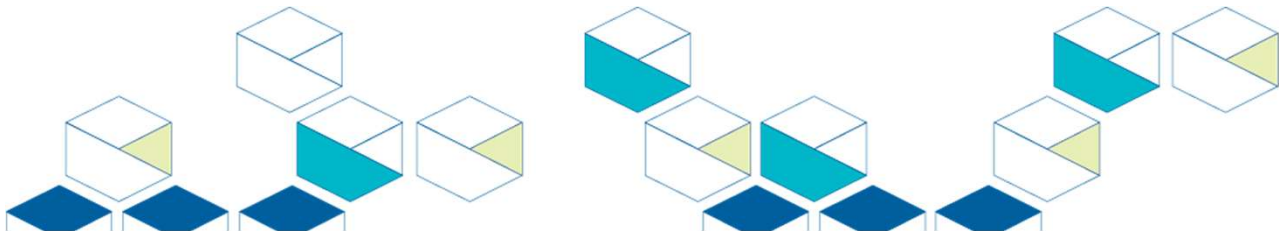
- Febrile (38.2) and clinically dry
- No documented organomegaly

- Severity criteria:
  - Parasitaemia > 2%
  - Jaundice, vomiting, acute kidney injury
  - Impaired consciousness



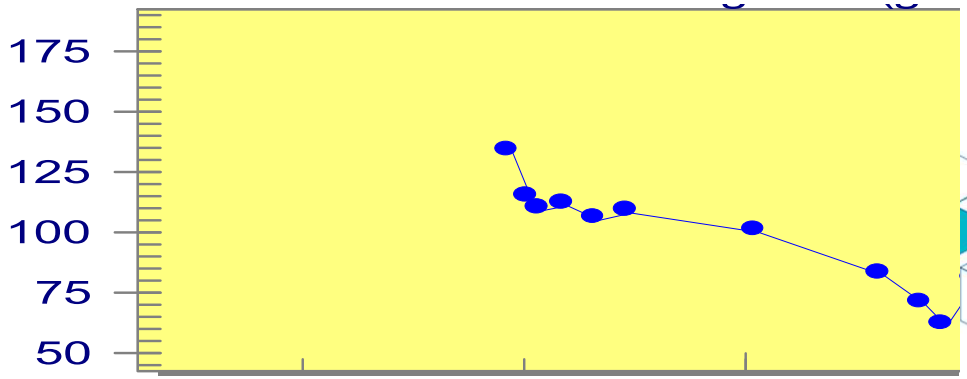
Case – Mr JS

- Received 60hrs (6 doses) artemether/lumefantrine
- Discharged after 5 days
  - Hb **108** (133)
  - WCC 2.88 / Neut **1.29** / Lymph 1.32 (2.67 / 1.88 / 0.66)
  - Plt **48** (42)
  - No parasites on discharge film



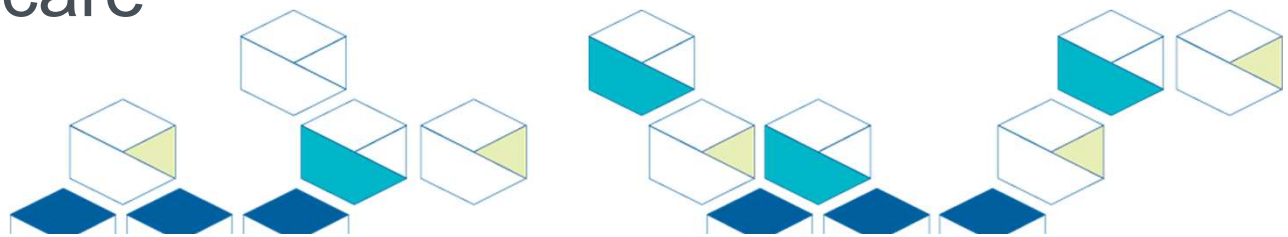
Case – Mr JS

- Seen in OPC ~4 days later
  - Recrudesced fevers (>38)
  - Progressive anaemia (Hb **82**)
  - Worsening nausea, fatigue
  - Jaundiced with new tender hepatosplenomegaly



Case – Mr JS

- Admitted to FSH
  - No evidence of recrudesced malaria
  - Symptom improvement with transfusion and simple analgesia
  - Presumed post-artesunate delayed haemolysis
    - DDx HLH, AIHA, HMS
  - Discharged for close monitoring and supportive care



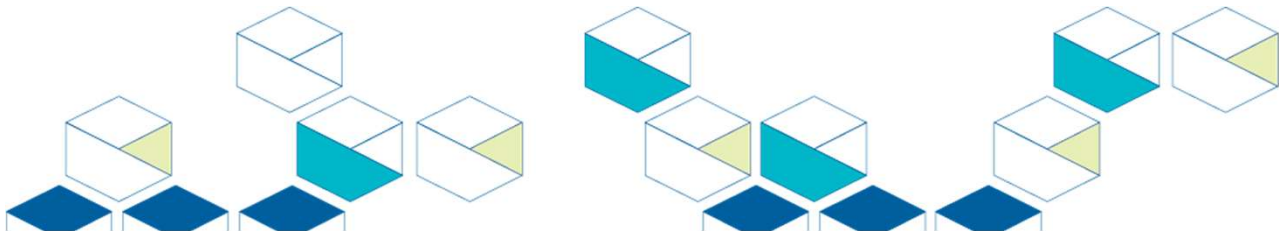
Case – Mr JS

- Presented to FSH ED ~4 days later
  - Worsening fatigue, dyspnea and fevers
  - Received piperacillin/tazobactam and discharged

- At review:
  - Hb **55**, ferritin **11500**, plt **139**
  - Neutrophils **1.07**, lymph **0.49**
  - Creat **129**, bilirubin **129**
  - Haptoglobins undetectable, reticulocytosis

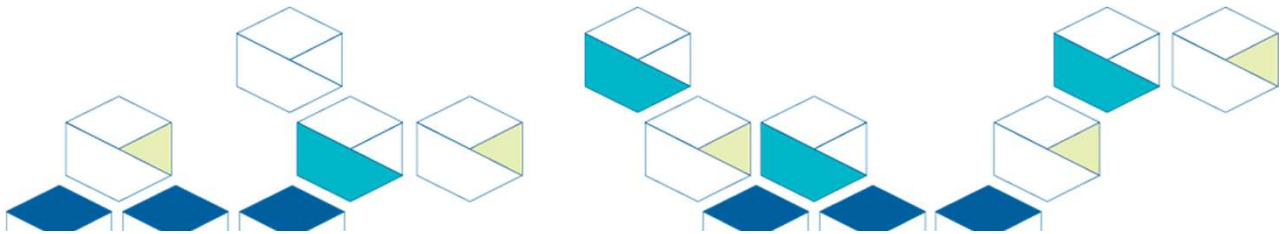
Case – Mr JS

- Haematology DDx:
  - Post-artesunate boosted pitting haemolysis
  - Artesunate-induced AIHA
  - Persistent malaria
  - Haemophagocytic lymphohistiocytosis
  - Hyper-reactive malarial splenomegaly



Case – Mr JS

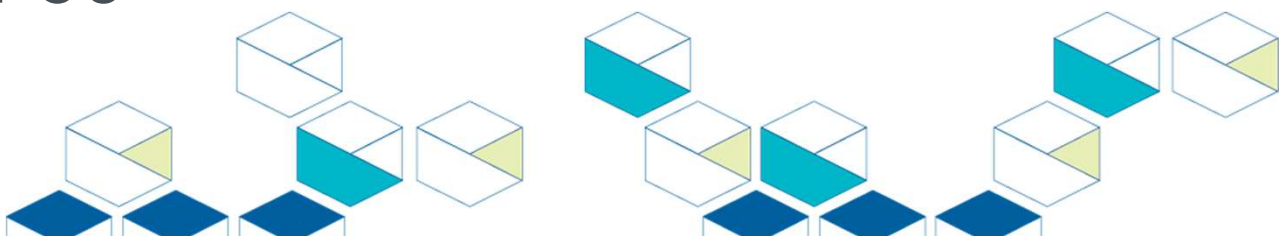
- Ongoing haemolysis
  - Hb 62 from 55, after 2u
  - Commenced 1mg/kg PO prednisone
- HLH work-up commenced
  - Lymphocyte subsets ?NK cell deficiency
  - Triglycerides, BMAT
  - sIL-2R / sCD25



Case – Mr JS

- BMAT – no features of haemophagocytosis
  - 5/8 criteria met
  - Coombs positive (C3d, IgG-)
  - Normal NK cell population
  - Low fragment numbers limiting interpretation

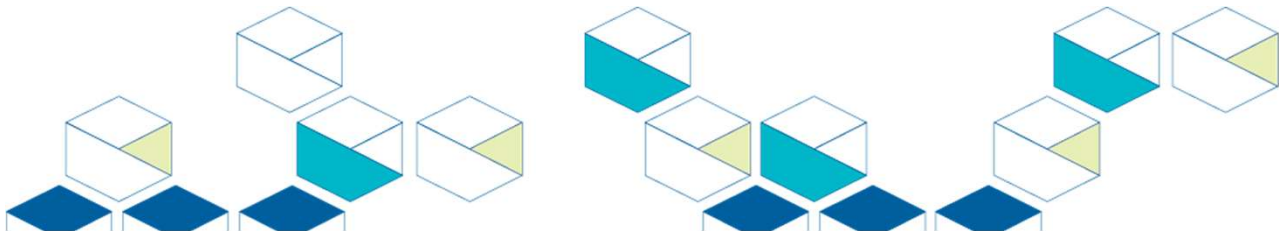
- CD4 count: 60



Case – Mr JS

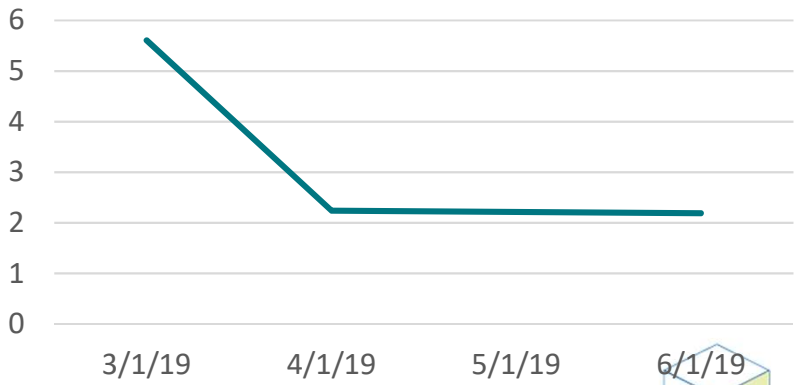
- HIV-1 Ab detected, with mature Western Blot

- In retrospect:
  - Unprotected sexual encounter with local Kenyan woman > 10 years previously
  - No clear seroconversion



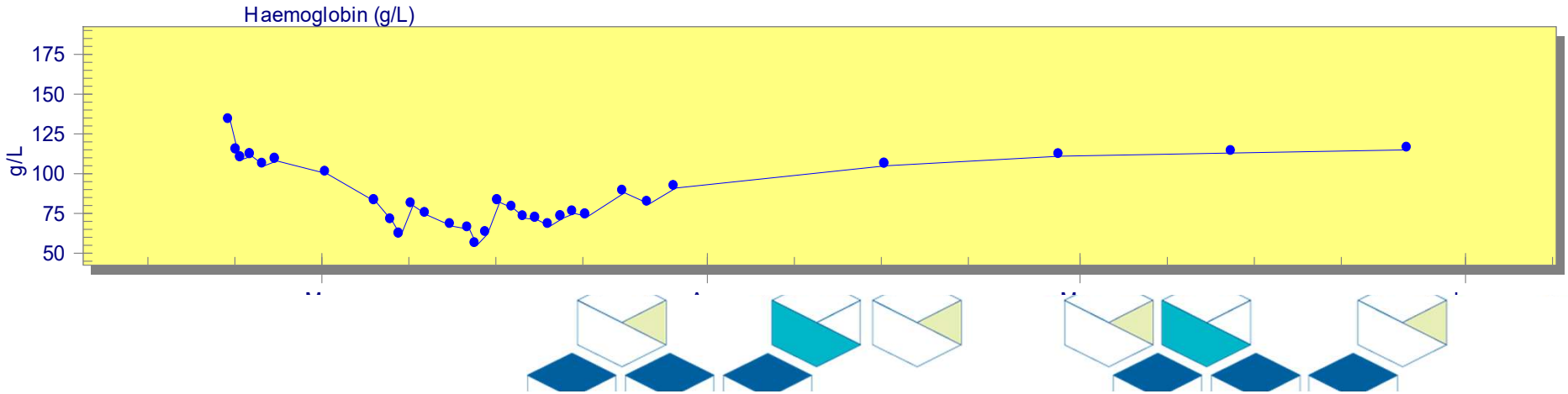
Case – Mr JS

- No evidence of opportunistic infection on screening
  - Commenced azithromycin + cotrimoxazole prophylaxis
- Biktarvy (BIC/FTC/TAF) commenced



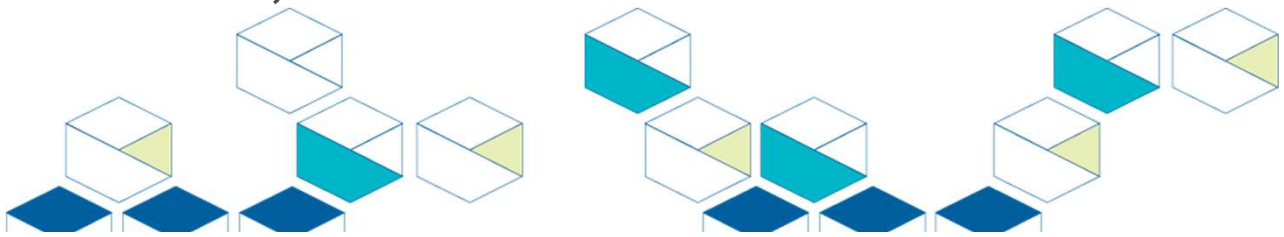
Case – Mr JS

- Prednisolone weaned over 3 months
  - Ongoing biochemical, but not clinical evidence of haemolysis



Case – Mr JS

- As of last review:
- HIV
  - Continues on azithromycin/cotrimoxazole while low CD4
  - No S/E, and no IRIS / OIs to date
  - Returned to Zambia with malarone prophylaxis
- AIHA
  - Clinically quiescent, weaned off steroids

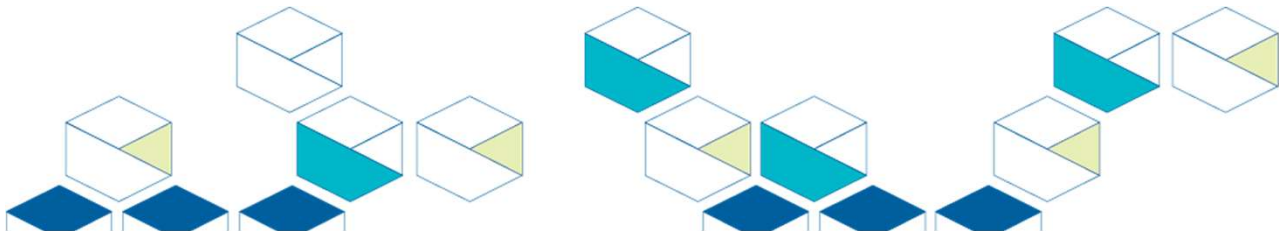


Case – Mr JS

- So what drove the haemolysis?
- HLH?
  - 5/8 criteria met
  - Secondary may respond to steroids alone
  - Absence of significant other inflammation
- AIHA?
  - Described in HIV, malaria and post-artesunate
  - Stabilisation suggestive of DIIHA

Case – Conclusion

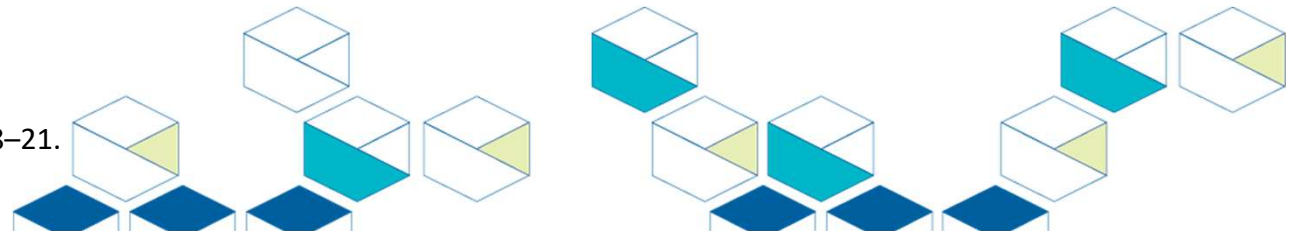
1. Severe falciparum malaria, unmasking
2. Chronic HIV infection with profound immunodeficiency, and
3. Presumed AIHA driving steroid-responsive haemolysis

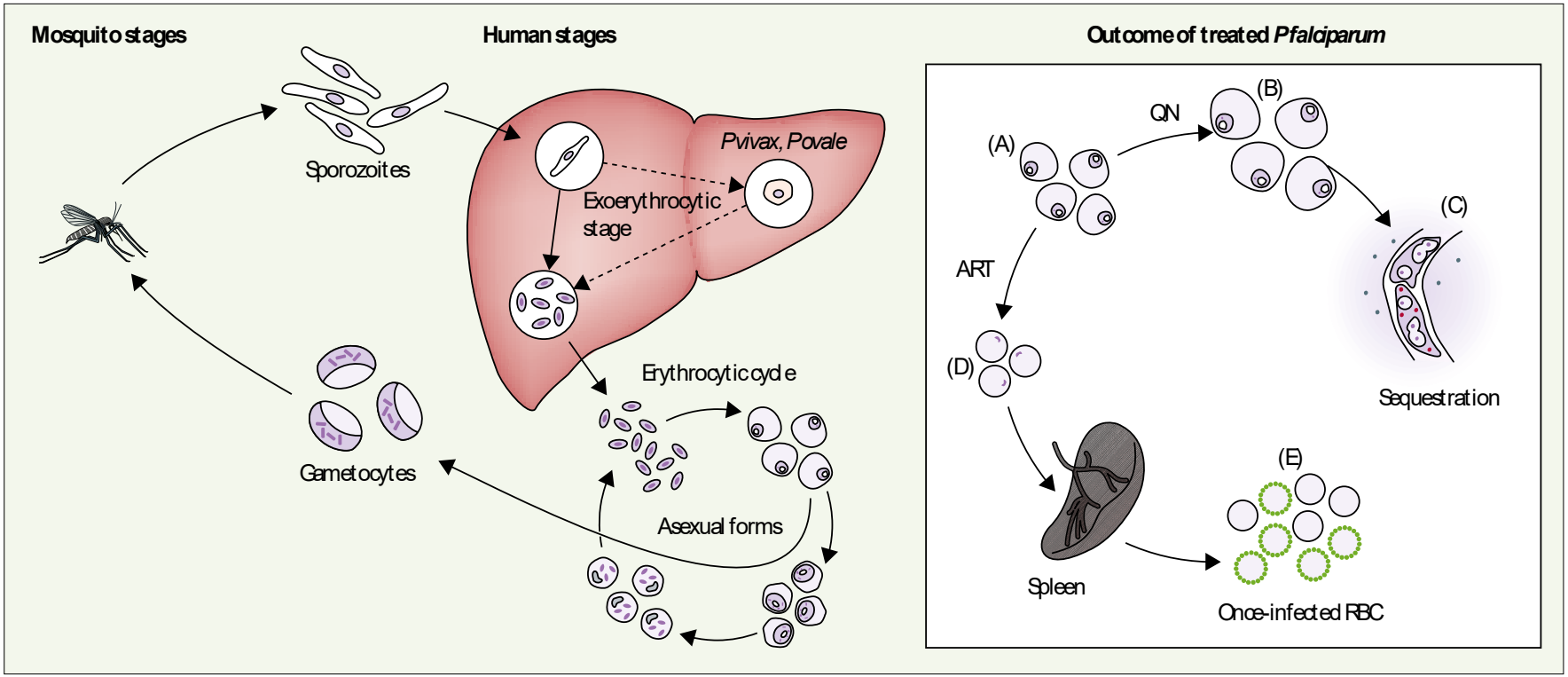


Malaria, HIV and Anaemia

- Malaria
  - Arthropod-borne parasitic tropic disease
  - 2 billion live in endemic regions
  - Transmitted by *Anopheles* mosquito
  - 207 million cases of falciparum in 2016
    - 8.5 million vivax cases

Ashley EA et al. Lancet 2018;391(10130):1608–21.





Ashley EA et al. Lancet 2018;391(10130):1608–21.

Severe Malaria

- Sequestration of parasite-containing RBCs in small & medium vessels
  - Endothelial injury and obstruction, secondary to *Pf*EMP1 adherence proteins
  - Clinical sequelae depends on which organ is involved

- Anaemia – common, but multifactorial
  - Splenic filtration of infected cells
  - Intravascular haemolysis
  - Marrow suppression

Panel 1: **Diagnostic criteria for severe malaria**[20]

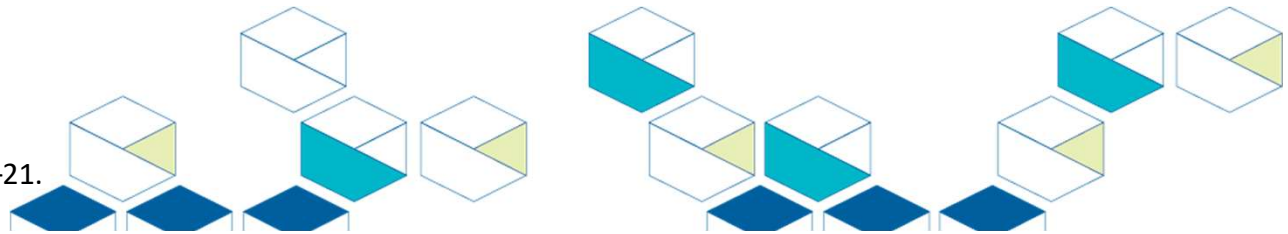
Clinical criteria

- Prostration
- Confusion or agitation (with Glasgow Coma Scale [GCS] >11)
- Coma (GCS ≤11 or Blantyre Coma Scale <3 in children)
- Respiratory distress (acidotic breathing)
- Convulsions
- Shock: prolonged capillary refill time (>2 s), with or without systolic blood pressure <80 mm Hg in adults (<70 in children)
- Pulmonary oedema (should be confirmed radiologically)
- Abnormal bleeding
- Jaundice
- Anuria
- Repeated vomiting

Laboratory criteria

- Haemoglobin <7 g/dL in adults, <5 g/dL in children
- Haemoglobinuria
- Hypoglycaemia (blood glucose <2·2 mmol/L or <40 mg/dL)
- Acidosis (ie, base deficit >8 meq/L or plasma bicarbonate <15 mmol/L or venous plasma lactate >5 mmol/L)
- Acute kidney injury (creatinine >3 mg/dL or urea >20 mmol/L)
- Asexual parasitaemia >10% of infected red blood cells (Note: national guidelines can vary—eg, UK parasitaemia cutoff is 2%[21])

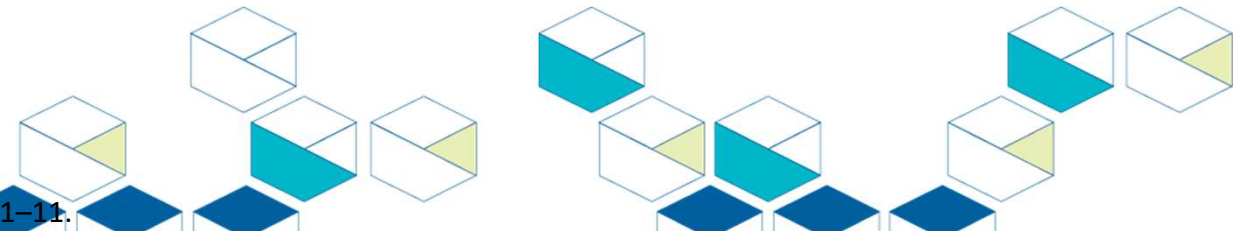
Ashley EA et al. Lancet 2018;391(10130):1608–21.



Malaria

- Diagnosis
  - Thick & thin films for parasitaemia
  - RDTs – *Pf*HRP2 vs LDH ICTs

- Treatment
  - Artemesinin derivatives + second agent
  - Primaquine for hypnozoite phase

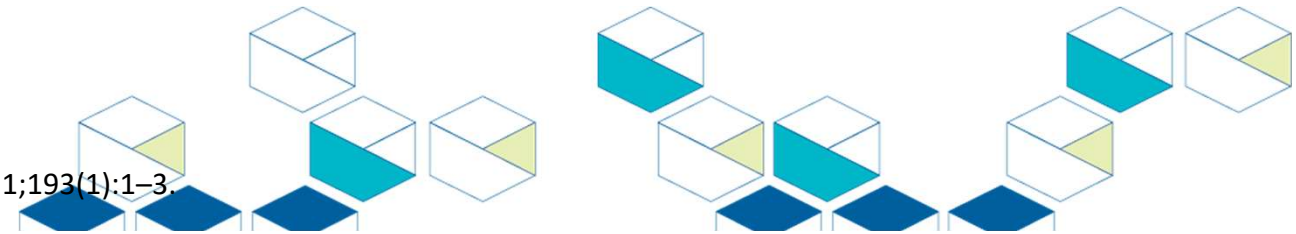


Ashley EA et al. Lancet 2018;391(10130):1608–21.
Zhang C-J et al. Nature Communications 2015;6(1):1–11.

HIV & Malaria

- Significant geographical overlap
- HIV infection increases susceptibility to malarial infection and disease severit
  - Low CD4 counts may be associated with treatment failure
- Malaria infection increases HIV viral replication and viral load

World Health Organization; 2005.
Kublin JG, Steketee RW. J Infect Dis. 2006 Jan 1;193(1):1–3.



Malaria & Anaemia

- Dependent on species
  - *Falciparum*; all ages with rapid spread
  - *Vivax, ovale*; reticulocytes only
- Manifest:
  - Intravascular haemolysis (*Pf*EMP1) and opsonisation
  - Splenic sequestration
  - *Falciparum* may infect erythroblasts
- AIHA secondary to either malaria or to artemisin derivatives

White NJ. Malar J 2018;17(1):371–17.

Malaria & Anaemia

- Wide range of presentations:
  - Simple febrile illness
  - Cytopaenias and hepatosplenomegaly
  - Splenic rupture (hyper-reactive malarial splenomegaly)
  - Blackwater fever – massive intravascular haemolysis

- Complicated by haemolysis or sequestration of non-infected RBCs
  - 10:1 ratio, with deposition of Ig/ completement on uninfected RBCs

White NJ. Malar J 2018;17(1):371–17.

Malaria & Haemophagocytosis

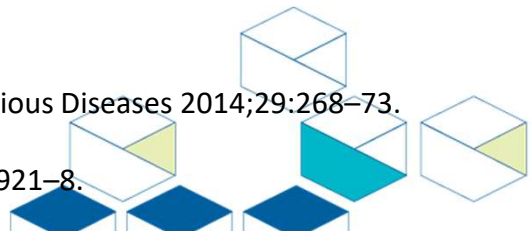
- Excessive and life-threatening syndrome of excess immune activation; multiple triggers
- Described rarely secondary to severe malaria
  - Felt secondary to excess TNF-α
  - Responsive to steroids (cf. primary HLH)

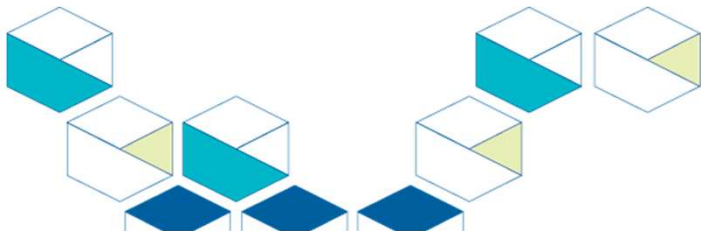
Ohnishi K et al. Am J Trop Med Hyg. 2007 Jun;76(6):1016–8.
Muthu V et al. Indian J Med Res. 2017 Mar;145(3):399–404.

Artesunate and Anaemia

- Post-artemisinin delayed haemolysis
  - 7 – 22% incidence, with median fall 13g/L
  - 15% will be < 70 g/L
  - Splenic sequestration due to pitting
    - Persistent *Pf*HRP2 antigen on RBC
  - May see prolonged haemolysis for up to 4 weeks

Raffray L et al. Malar J 2014;13:398.
Rehman K et al. International Journal of Infectious Diseases 2014;29:268–73.
Leoni S et al. Malar J 2015;14(1):185.
Agbenyega T et al. J Infect Dis 2013;209(12):1921–8.





AIHA and Malaria, HIV and Artesunate

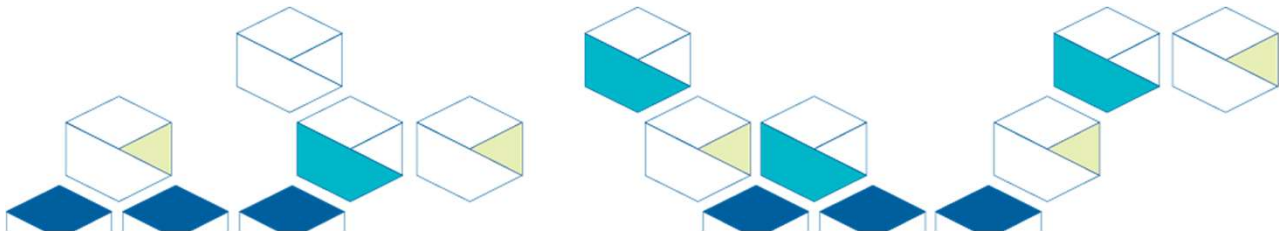
- Immune-mediated
- Development described with:
  - Artesunate
  - Malaria
  - HIV (0.012%)

- Managed with drug withdrawal + corticosteroids

Yen Y-F et al. Journal of Infectious Diseases 2017;216(8):1000–7.
Jauréguiberry S et al. Emerg Infect Dis 2015;21(5):804–12.
Johnson AS et al. Transfusion and Apheresis Science 2013;49(3):571–3.

Conclusion

- Co-infection is common
- Retain a high degree of suspicion
- Investigate further if behaving atypically



References

1. White NJ. Anaemia and malaria. Malar J 2018;17(1):371–17.
2. Yen Y-F, Lan Y-C, Huang C-T, et al. Human Immunodeficiency Virus Infection Increases the Risk of Incident Autoimmune Hemolytic Anemia: A Population-Based Cohort Study in Taiwan. Journal of Infectious Diseases 2017;216(8):1000–7.
3. Raffray L, Receveur M-C, Beguet M, Lauroua P, Pistone T, Malvy D. Severe delayed autoimmune haemolytic anaemia following artesunate administration in severe malaria: a case report. Malar J 2014;13:398.
4. Ohnishi K, Mitsui K, Komiya N, Iwasaki N, Akashi A, Hamabe Y. CLINICAL case report: falciparum malaria with hemophagocytic syndrome. Am J Trop Med Hyg 2007;76(6):1016–8.
5. Muthu V, Dhooria S, Sehgal IS, Agarwal R, Behera D, Varma N. Malaria-associated secondary haemophagocytic lymphohistiocytosis: Report of two cases & a review of literature. Indian J Med Res 2017;145(3):399–404.
6. World Health Organization. Malaria and HIV interactions and their implications for public health policy. World Health Organization; 2005.
7. Kublin JG, Steketee RW. HIV infection and malaria--understanding the interactions. J Infect Dis 2006;193(1):1–3.
8. Kai OK, Roberts DJ. The pathophysiology of malarial anaemia: where have all the red cells gone? BMC Med 2008;6(1):23–4.
9. Jauréguiberry S, Thellier M, Ndour PA, et al. Delayed-Onset Hemolytic Anemia in Patients with Travel-Associated Severe Malaria Treated with Artesunate, France, 2011–2013. Emerg Infect Dis 2015;21(5):804–12.
10. Agbenyega T, Issifou S, Adegnika AA, et al. Delayed Hemolysis After Treatment With Parenteral Artesunate in African Children With Severe Malaria—A Double-center Prospective Study. J Infect Dis 2013;209(12):1921–8.
11. Zhang C-J, Chia WN, Loh CCY, et al. Haem-activated promiscuous targeting of artemisinin in Plasmodium falciparum. Nature Communications 2015;6(1):1–11.
12. Ashley EA, Pyae Phyo A, Woodrow CJ. Malaria. Lancet 2018;391(10130):1608–21.
13. Singh S, Singh S, Tentu A, et al. Artesunate-induced severe autoimmune hemolytic anemia in complicated malaria. Indian J Crit Care Med 2018;22(10):753–8.
14. Rehman K, Lötsch F, Kremsner PG, Ramharter M. Haemolysis associated with the treatment of malaria with artemisinin derivatives: a systematic review of current evidence. International Journal of Infectious Diseases 2014;29:268–73.