

Severe Anaemia and Invasive Non-Typhoidal *Salmonella* Bacteraemia in Kenyan Children

Kelvin Mokaya Abuga

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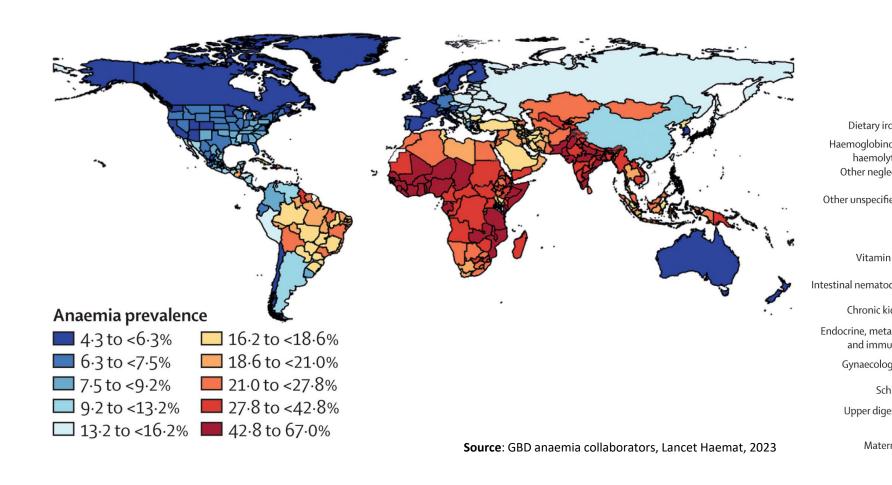








Anaemia – A global problem



	Global	Central Europe, eastern Europe, and central Asia	High income	Latin America and Caribbean	North Africa and Middle East	South Asia	Southeast Asia, east Asia, and Oceania	Sub-Saharan Africa
Dietary iron deficiency	1	1	1	1	1	1	1	1
Haemoglobinopathies and haemolytic anaemias	2	2	2	2	2	2	2	3
Other neglected tropical diseases	3	3	4	3	3	3	3	4
Other unspecified infectious diseases	4	4	5	4	4	4	4	7
Malaria	5	14	15	10	10	8	10	2
Vitamin A deficiency	6	8	10	5	5	6	7	5
ntestinal nematode infections	7	12	14	8	13	5	8	6
Chronic kidney disease	8	5	3	6	7	7	6	9
Endocrine, metabolic, blood, and immune disorders	9	6	6	7	8	9	5	10
Gynaecological diseases	10	7	7	11	6	10	12	13
Schistosomiasis	11	16	16	12	9	16	13	8
Upper digestive system diseases	12	9	8	9	12	11	9	14
Maternal disorders	13	10	11	13	11	12	1	12
HIV/AIDS	14	15	13	14	16	15	16	11
Cirrhosis and other chronic liver diseases	15	13	12	15	14	13	14	15
Inflammatory bowel disease	16	11	9	16	15	14	15	16



Severe anaemia is associated with bacteraemia

Author	Country		OR (95% CI)	n/N	Severe anaemia aetiology	
Nielsen et al.	Ghana		2.5 (1.3, 4.5)	28/46	Children with malaria	
Moon et al.	Mozambique		3.9 (1.7, 9.0)	14/39	HIV-infected adults	✓ Small sample sizes
Were et al.	Kenya	↓ •	1.6 (0.9, 3.0)	30/59	Children with malaria	✓ Single causes of
Nadjm et al.	Tanzania		1.6 (1.1, 2.1)	N/A	Severe anaemia overall	severe anaemia
Sigauque et al.	Mozambique	←	1.1 (0.9, 1.4)	96/1,550	Severe anaemia overall	✓ Reverse causality?
Williams et al.	Kenya	$ \longrightarrow$	26.3 (14.5, 47.6)	108	Sickle cell anaemia	• Neverse causanty:
Calis et al.	Malawi		5.3 (2.6, 10.9)	54	Severe anaemia overall	
Bachou et al.	Uganda —	↓	2.3 (0.5, 10.2)	2/56	Malnourished children	
Lackritz et al.	Kenya —	-	1.0 (0.6, 1.7)	37/303	Severe anaemia overall	
	.25	1 1 1 1 1 1 5 10 20 40	0	N/A - Not	available	

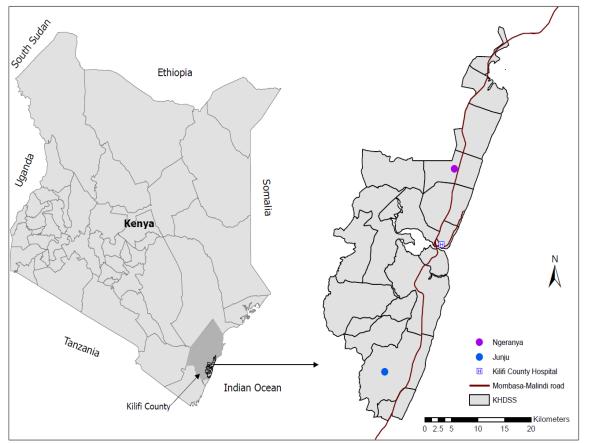
n = Severe anaemia with bacteraemia N = Total bacteraemia

Severe anaemia might increase risk of iNTS Pathogenic bacteria Haem Bone HCP-Fe³⁺ 1 Increased gut Fe²⁺ permeability TfR Commensals HO-1 Erythroblast FPN 2 Increased ERFE Transferrin Fe³⁺ Ferritin Hepcidin Fe² erythropoietic Heph drive Fe²⁺ Cp Pathogenic bacteria **N**TBI Ferritin Tf_R Fe² Gut epithelia X SCV CD163 Impaired 4 Haem -- IFN-vy HO-1 Immune CD91 Neutrophil function **IL-10** Haptoglobin FPN Increased 3 Haemopexin Macrophage haemolysis Haemolysis

Abuga et al. 2021, IJMS



Approaches



- 1. Epidemiological associations between severe anaemia and iNTS.
- 2. Assays of iron and immune-mediated biomarkers.
- 3. Bacterial growth assays.
- 4. Effects of anaemia on NTS vaccine responses.

Anaemia is prevalent among children living in Kilifi, Kenya

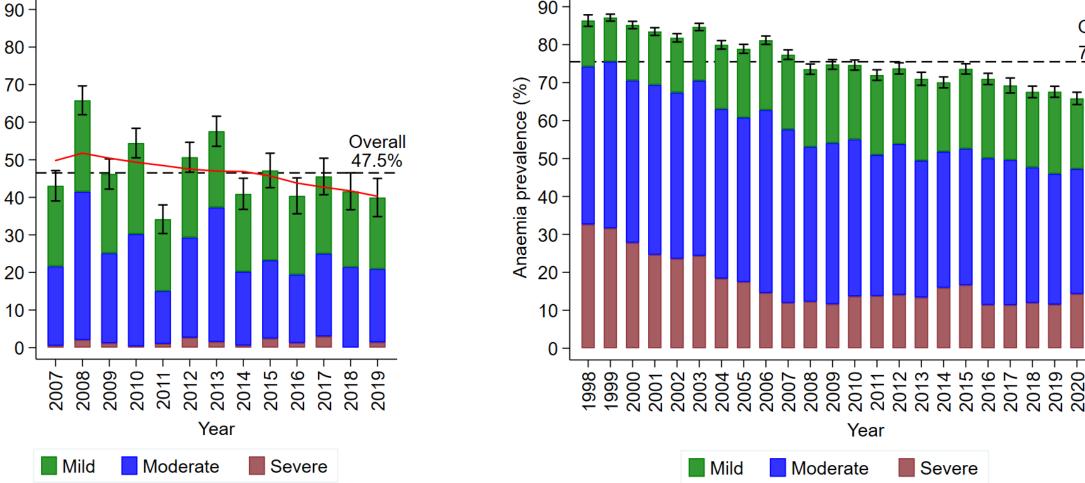
Community surveys (N=6,717)

Anaemia prevalence (%)

Overall 75.5% Anaemia prevalence (%) 1999 Year Mild Moderate Severe

Hospital admissions (N=102,559)

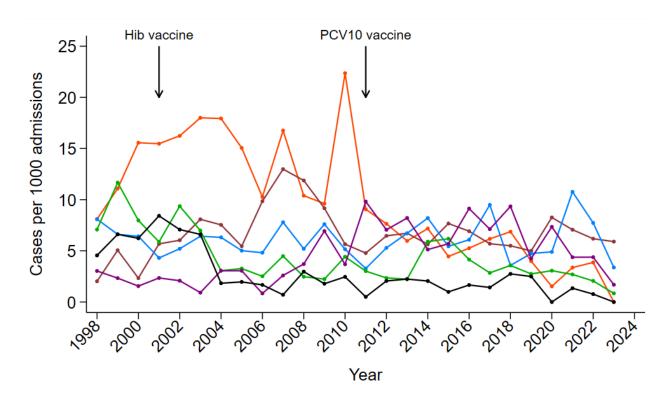
Anaemia classified based on age-dependent World Health Organization (2011) and GBD anaemia collaborators (2023, Lancet Haemat.) cut-offs





iNTS remains an important cause of paediatric admissions

Bacteraemia, n=5,050 (4.9%)



--- Non-typhoidal Salmonella

--- Klebsiella pneumoniae

- Haemophilus influenzae

Streptococcus pneumoniae

Staphylococcus aureus

Escherichia coli

iNTS, n=474 (9.4% of bacteraemia)

- Salmonella Enteritidis: 154 (32.5%)
- Salmonella Typhimurium: 149 (31.4%)
- Not typeable: 39 (8.2%)
- Not tested: 132 (27.8%)

In-hospital iNTS mortality = <u>21.4%</u> (vs 8.2% overall)

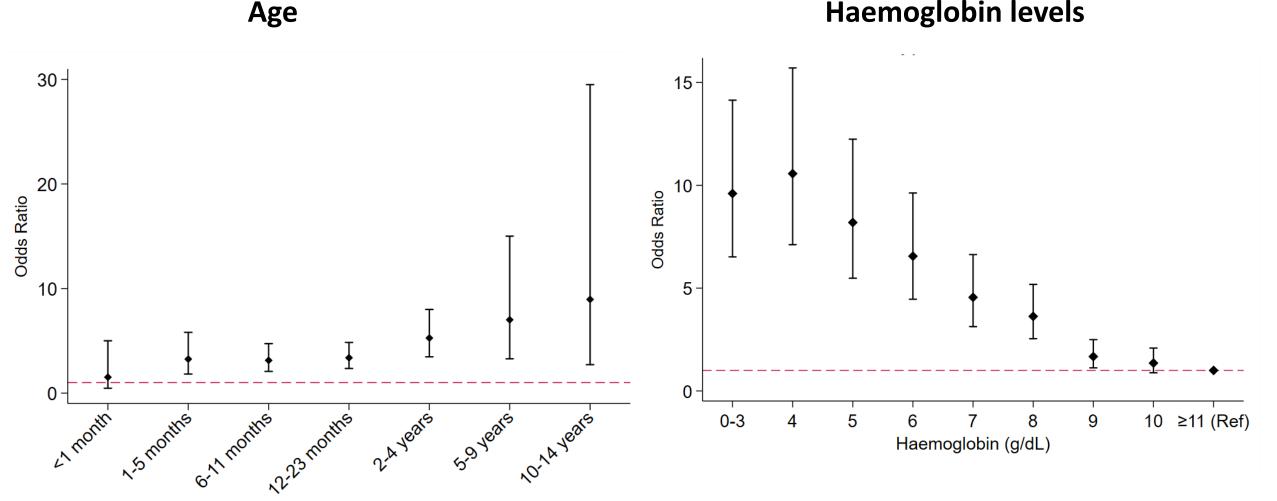
> Abuga et al., haematologica, 2022; Muthumbi et al., CID, 2015

Severe anaemia associated with 4-fold increased risk of iNTS

OR (95% CI) 2.18 (2.03-2.34) Bacteraemia H 2.51 (2.19–2.88) Streptococcus pneumoniae Staphylococcus aureus -0.96 (0.76-1.20) 3.59 (2.98-4.33) Escherichia coli -4.64 (3.81–5.65) Non-typhoidal Salmonella -Klebsiella pneumoniae 1.34 (0.98–1.85) 1.14 (0.86–1.50) Acinetobacter species 3.84 (3.00-4.89) Haemophilus influenzae 2.00 (1.38-2.89) Pseudomonas aeruginosa 1.53 (1.18–1.97) Other Gram Negatives 1.28 (1.01–1.62) Other Gram Positives -5 *Odds ratios adjusted for 0 2 3 4 age, sex, year of admission Odds Ratio and number of readmissions

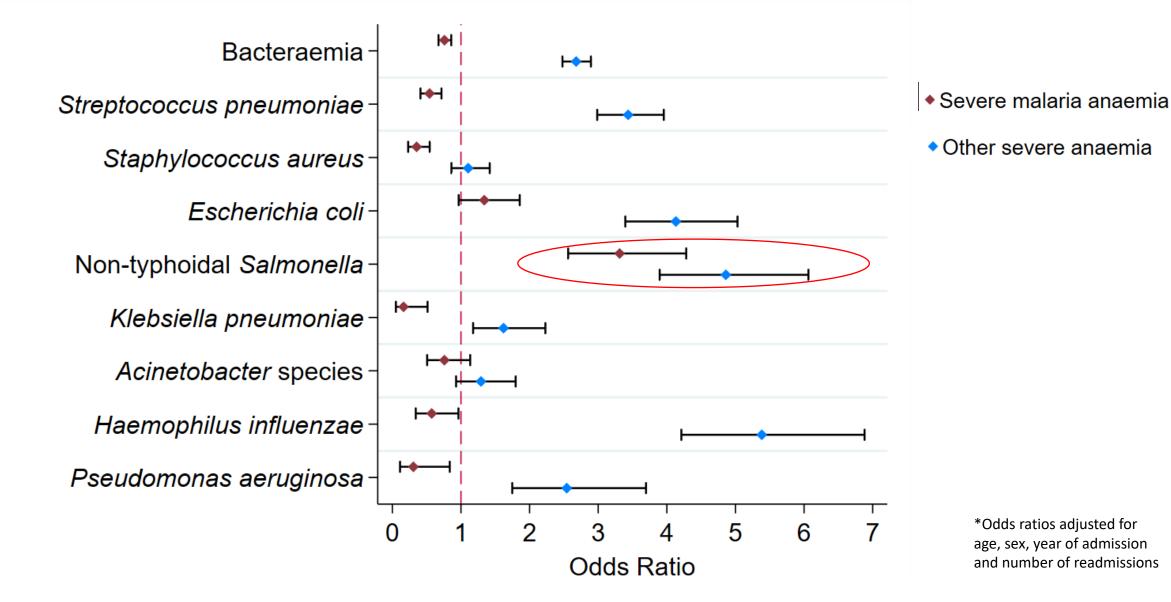
Risk of iNTS was not age-dependent, but increased with each 1g/dL decrease in haemoglobin levels

Haemoglobin levels

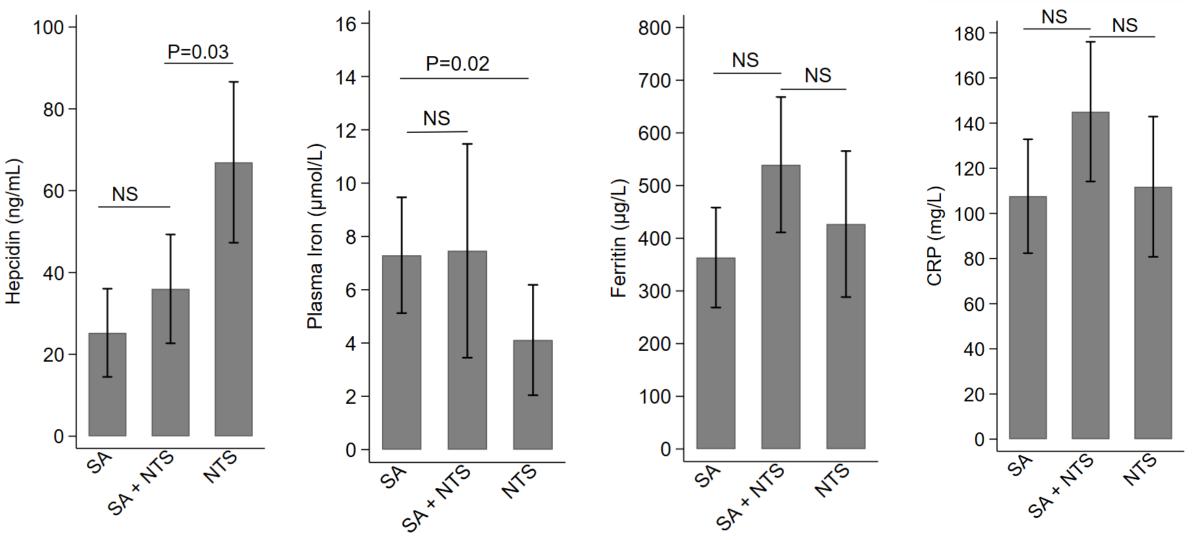




iNTS risk in severely anaemic children with and without malaria



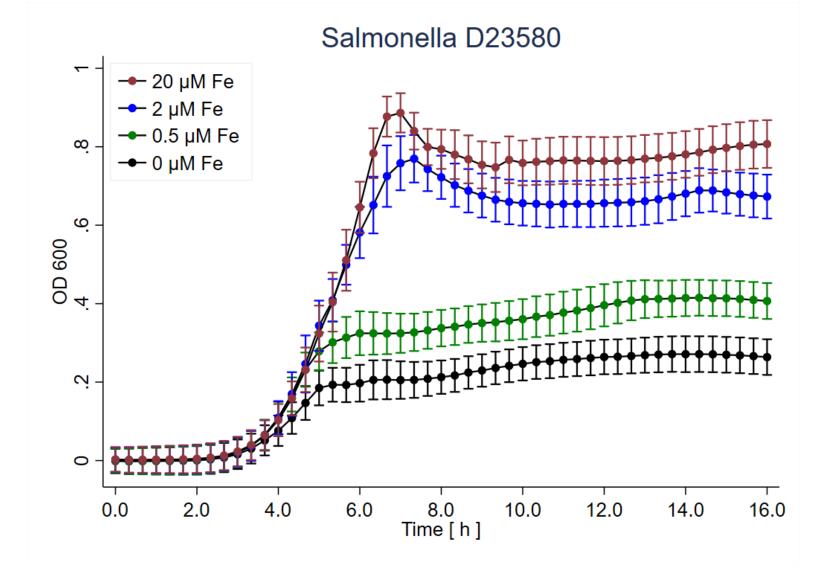
Low hepcidin and high plasma iron levels in severe anaemia



SA – severe anaemia (n=52); NTS – non-typhoidal Salmonella (n=44); SA+NTS (n=29)

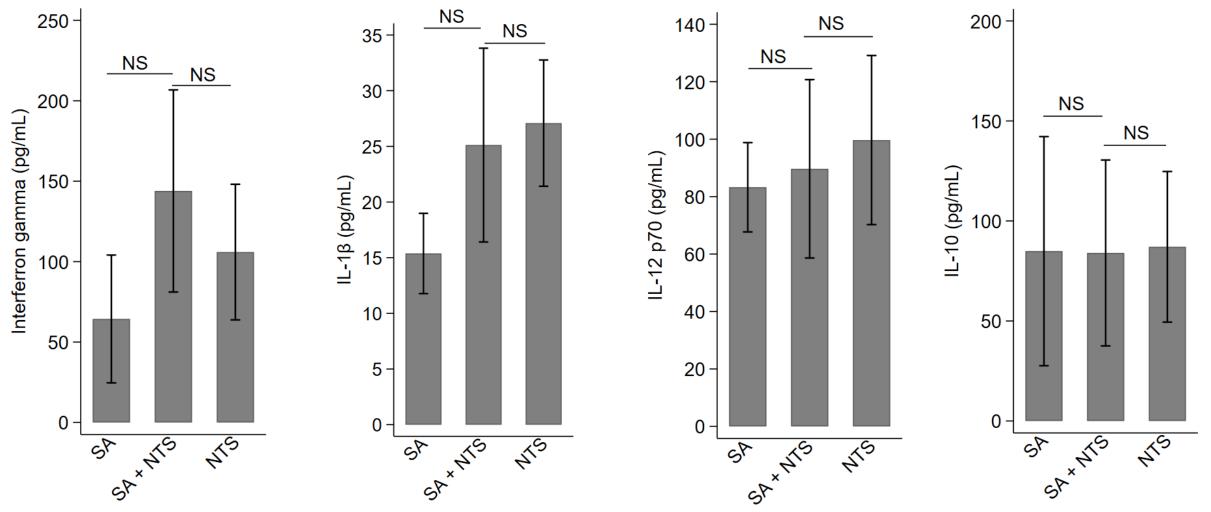


High iron levels associated with bacterial growth in-vitro





Severe anaemia doesn't impair cytokine production in children with iNTS



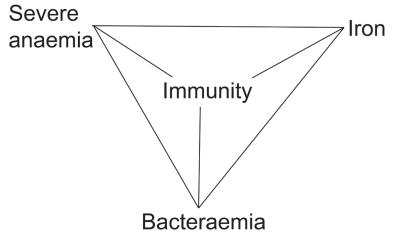
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Why this work is important

- Anaemia and iNTS are important causes of hospitalization and death
- Strategies to manage iNTS remain ineffective.

• Understanding underlying risk factors for iNTS (such as severe anaemia) \rightarrow better interventions.





Summary

• Anaemia and iNTS are prevalent among Kenyan children.

• Severe anaemia is associated with a four-fold increased risk of iNTS.

• The risk is independent of malaria parasitaemia.

• Severe anaemia may increase iNTS risk through iron-dependent mechanisms.



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