Respiratory problems with severe malaria:

an opportunity to talk about fluid trials!!!

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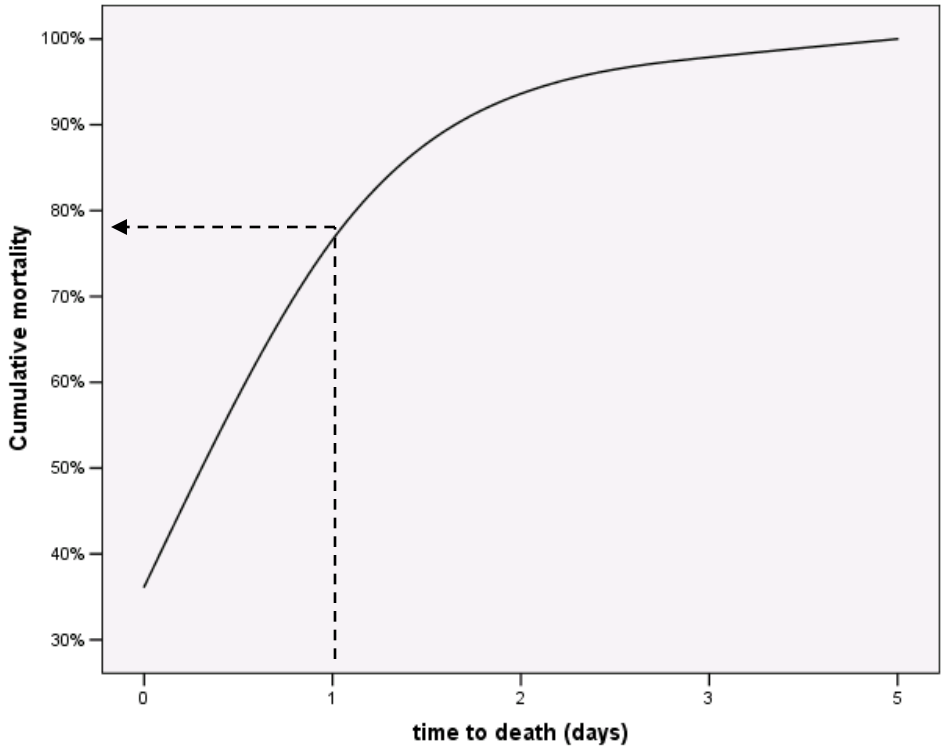
Severe malaria-the numbers

- Up to 1 million deaths in African children <5y
- In-hospital mortality unchanged ~ 20-30%
- Progress towards improving case management hampered by
  - inadequate clinical definition
  - treatment guidelines (WHO) –principally informed by adult studies

Severe malaria in African Children
different from SE Asian adults

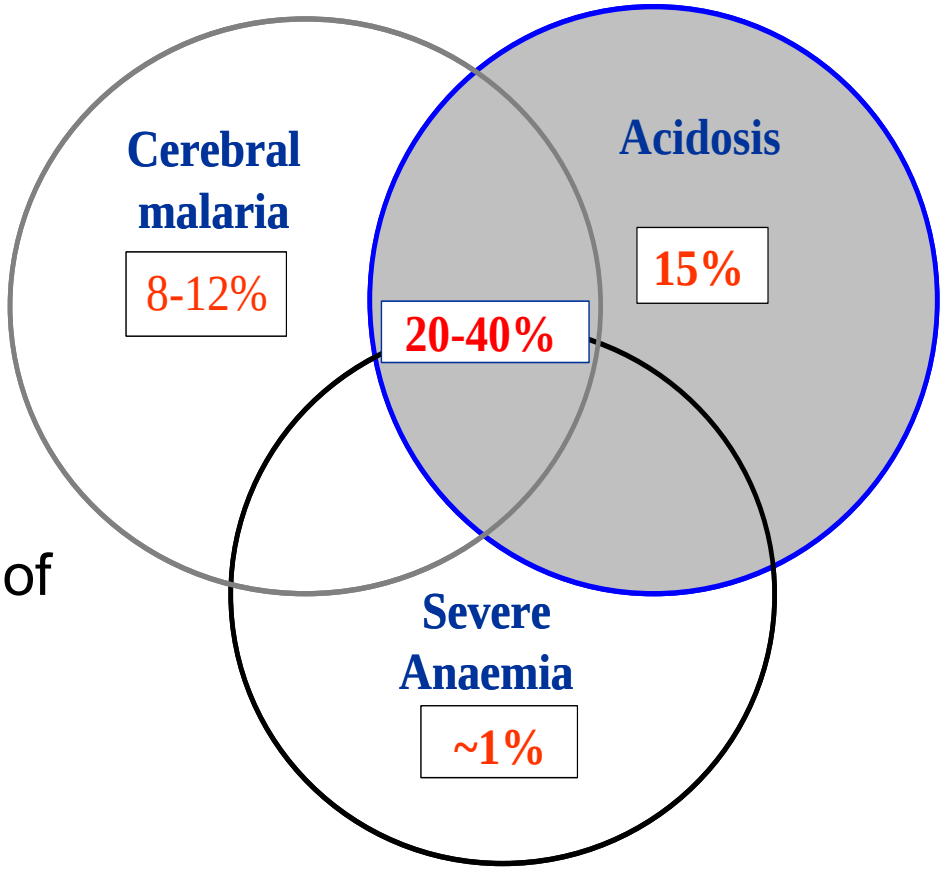
- Fulminant disease course
  - >75% deaths < 24hr
- Jaundice, renal failure and lung damage are rare
- Brain swelling – potential complication of coma
- Respiratory distress -key feature
- Many features in common with severe sepsis/ sepsis syndrome



Marsh *et al*, 1996, Newton *et al* 1997, English *at al*, 1996 & 1998
Maitland *et al* 2003

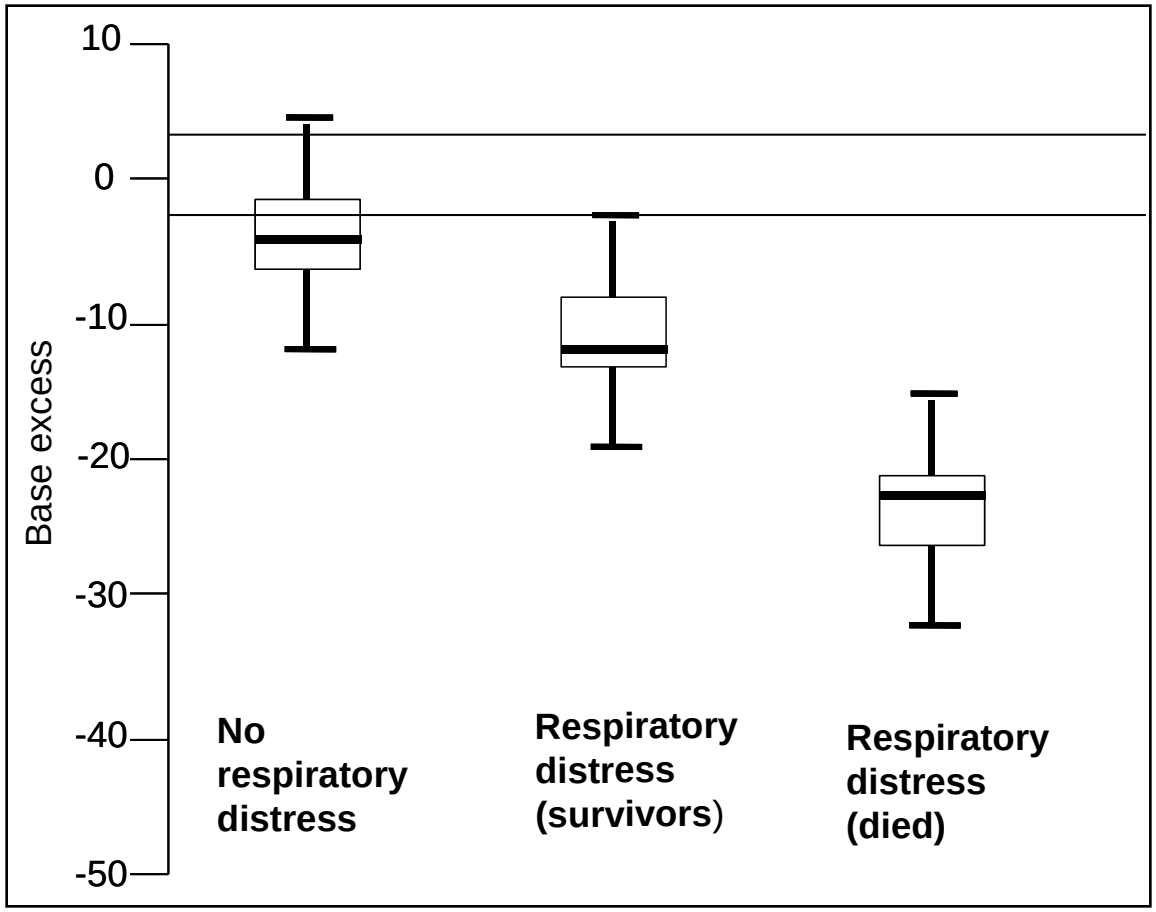
Severe malaria: central role of acidosis

- More common than previously recognised ~70% cases
- Presents as respiratory distress
- Best independent predictor of a fatal outcome



Marsh et al, 1995; English et al, 1997

Association of respiratory distress, acidosis and fatal outcome



English *et al.*, 1996

Severe malaria in African children

- More complex than previously recognised
- Many features in common with the sepsis syndrome
- Acidosis/ respiratory distress: best predictor of a fatal outcome
- Therapies aimed at treatment of acidosis may improve outcome

Common approaches to resuscitation: saves lives

- Kinetics of the innate immune: similar range of responses to a range of pathogens
- Common and complex derangements of host physiology
- Most complications reversible by simple approaches
- Treatment of critically ill children – based on bedside assessments & without primary diagnosis
- Development of separate paediatric protocols: reduced mortality in sepsis from >60% to <10%

Acidosis: in critically ill children

- Commonest cause of metabolic acidosis in sick children is hypovolaemia
- Limited intravascular reserve of children: shock common response to acute infection
- Hypotension –pre-terminal manifestation; diagnosis overlooked
- *Standard management –volume resuscitation*

Hypovolaemia is not synonymous with dehydration

Current WHO recommendations (2006)

- Volume resuscitation= controversial and thus discouraged
- Should be given with CVP monitoring (CVP 0-5cm H_2O!!)
- Dehydration should be corrected – infusion tied to quinine administration (4 hours)

Consequences

- No agreed 'standard of care'
- Some hospital continue to give frusemide to children with respiratory distress ('heart failure')

Aims of Kilifi programme

1) To determine whether hypovolaemia aetiologically important in the pathogenesis of severe malaria
2) Through clinical trials assess the safety and efficacy of volume resuscitation
3) To determine with is the optimum fluid for correction of volume depletion: is this more safely achieved with colloids (albumin) than crystalloids (saline).

Retrospective review
admission features of children with severe malaria

Triage	Clinical feature present (%)		Fatality
Airway &	O_2 Saturation <90%	(17%)	30%
Breathing	Tachypnoea >60	(17%)	30%
	Deep breathing	(20%)	31%
Circulation	Extreme Tachycardia >180	(16%)	17%
	Hypotension	(13%)	26%
	Capillary refill >2s	(32%)	15%
Disability	Impaired consciousness	(78%)	13%
	Lab features:		
	Acidaemia pH <7.2	(22%)	36%
	Elevated creatinine >80	(19%)	26%
	Potassium >5.5 mmols	(10%)	28%
	Hypoglycaemia	(12%)	28%

Maitland *et al*, QJM 2003

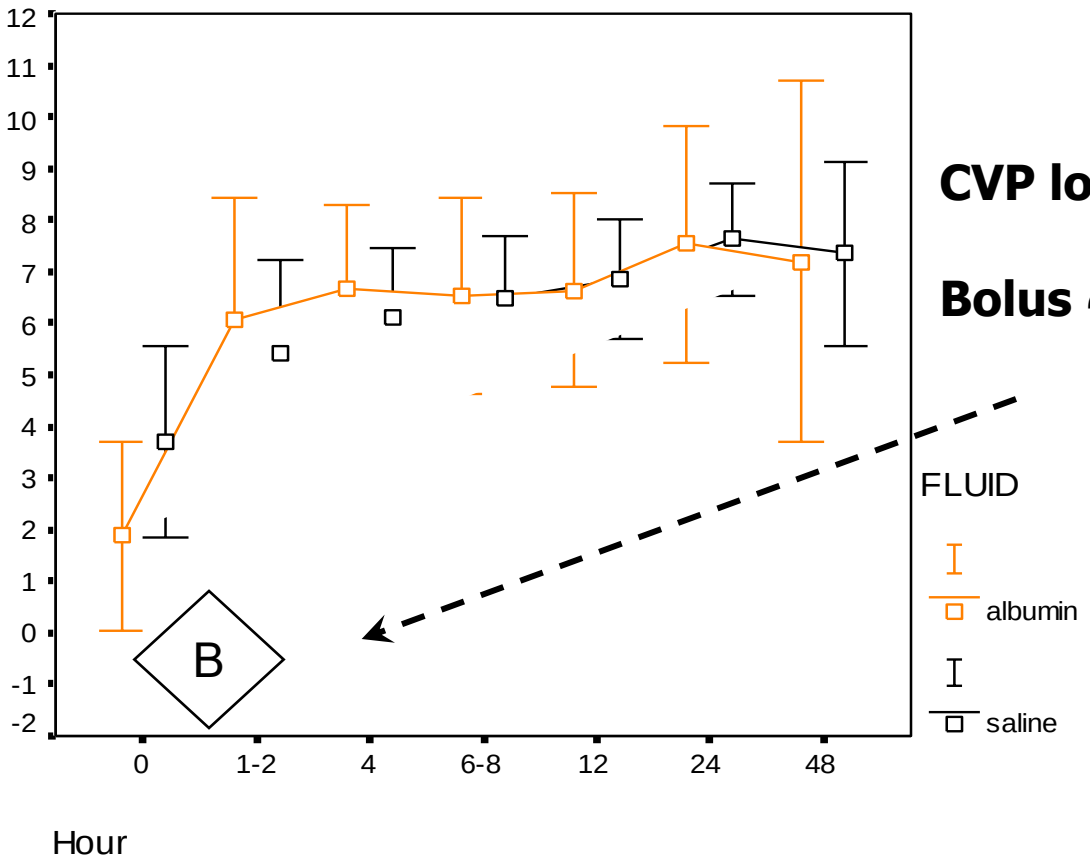
KEMRI Wellcome Trust/Imperial College

- Transfer of intensive care technology
- Children with severe malaria & acidosis
  - Standard methodology to assess volume status
  - Haemodynamic response
  - Continuous haemodynamic monitoring over following 48 hours

Two studies:

- Phase I trial: dose finding studies
- Phase II trial : volume expansion saline or albumin

Physiological studies: hypovolaemia

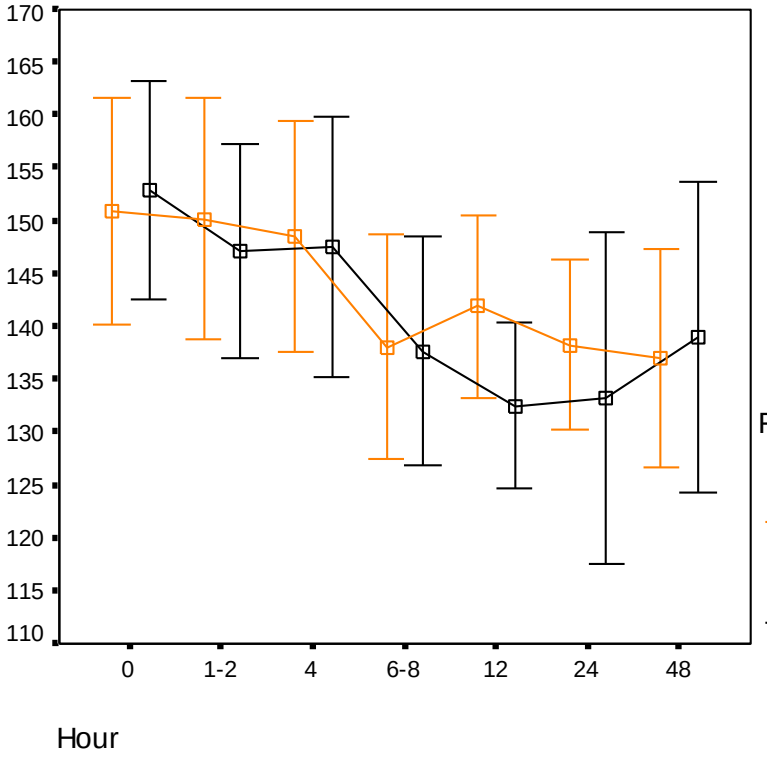


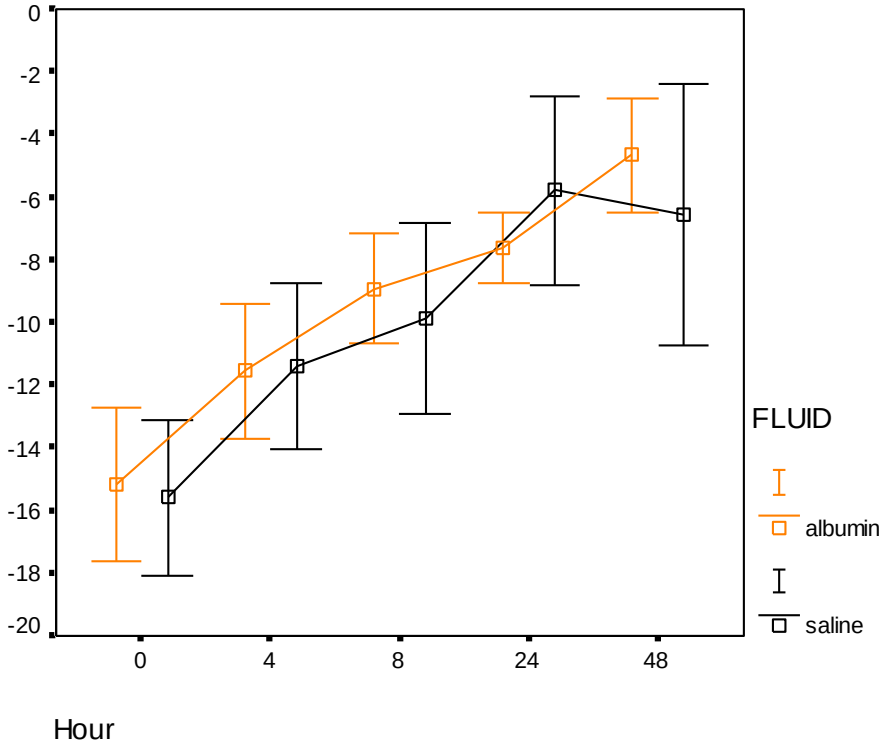
CVP low at admission

Bolus ~ 20-40mls/kg

Maitland *et al* (2005)

Safety of volume expansion



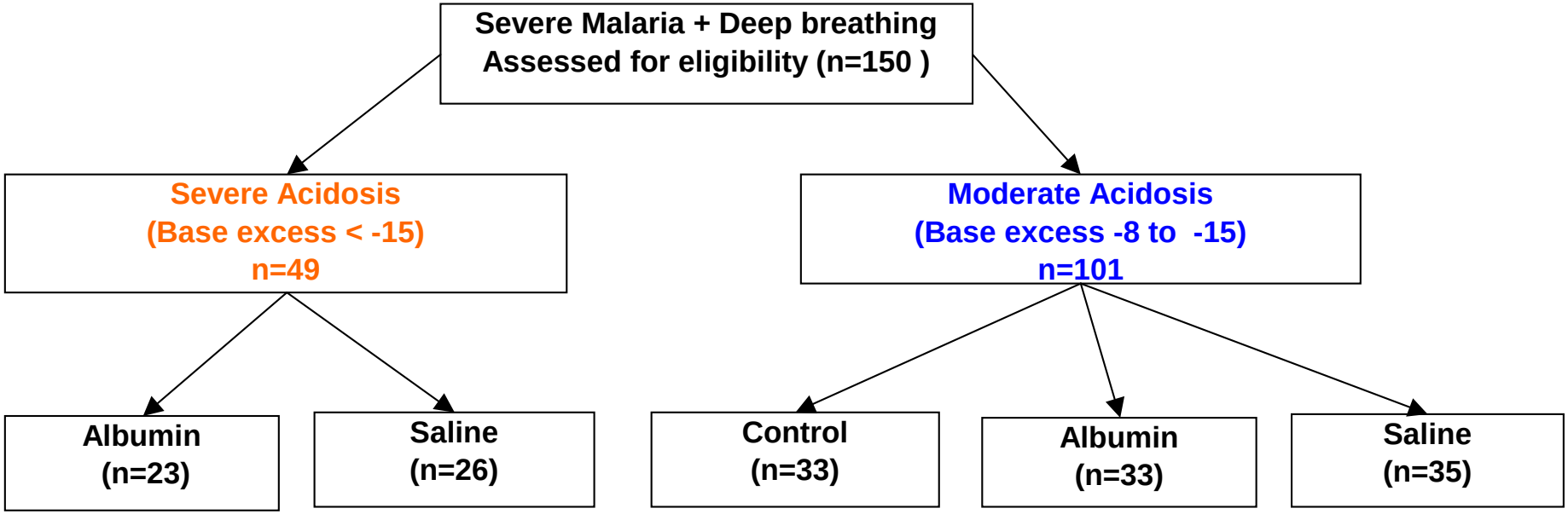


Results

53 children received volume expansion: 4 deaths (8%)

No complications of pulmonary oedema/brain swelling

Trial recruitment



No control arm:

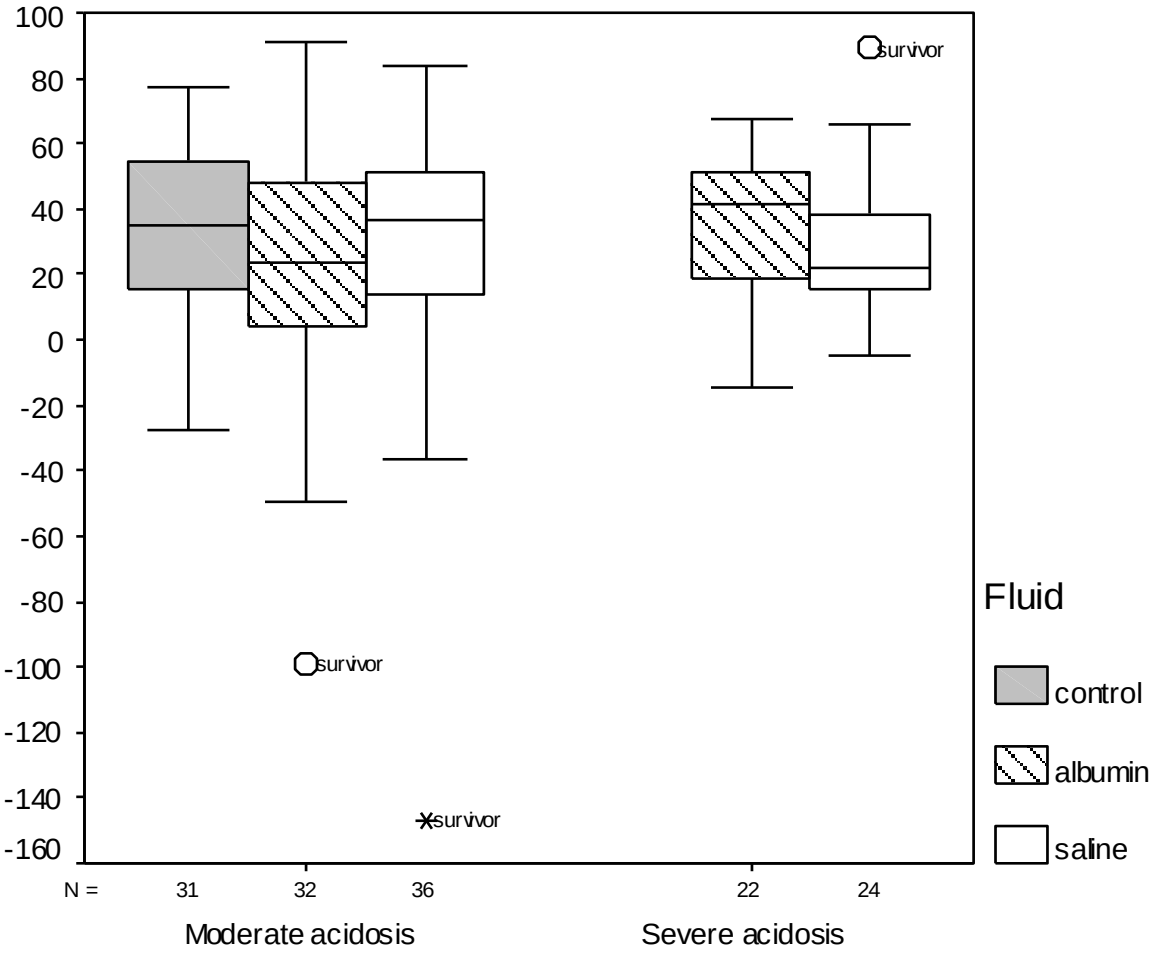
Pilot data: 40% hypotension at admission

Ethical to waiver consent

A priori mortality lower:

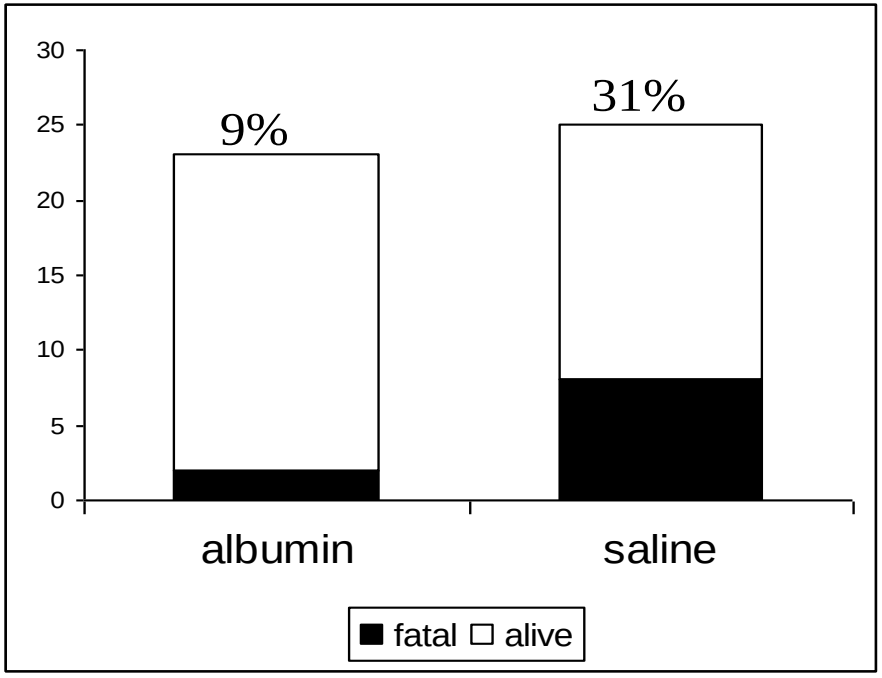
- ethical to include control arm (standard of care)
- Provision for rescue therapy

1^0 endpoint: resolution of acidosis by 8 hours

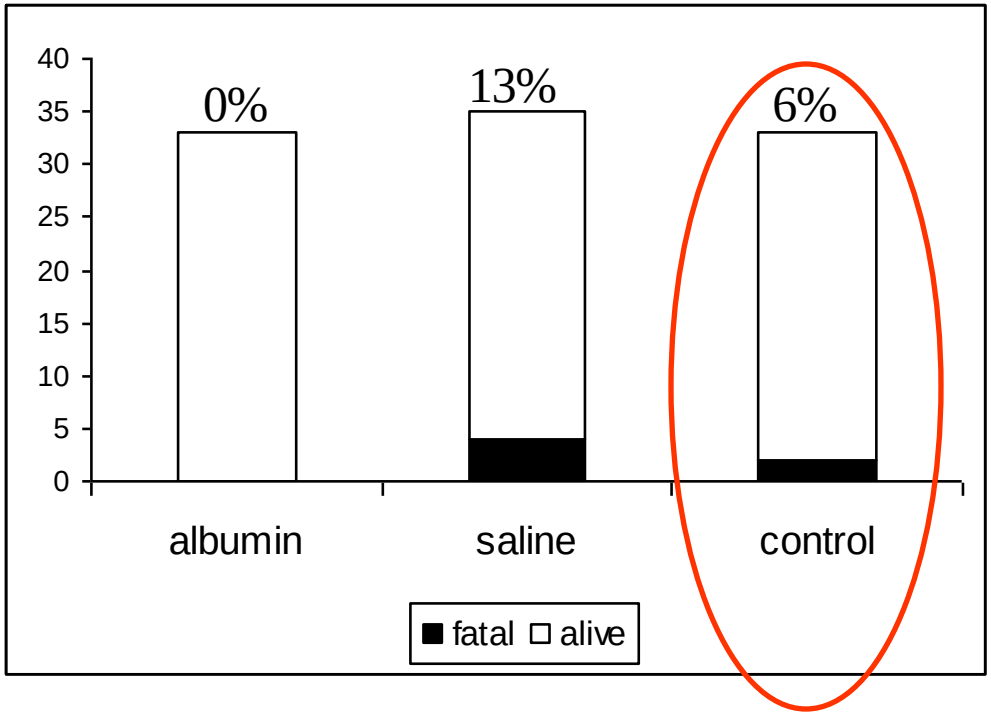


2 ^{0} endpoint: in-hospital mortality

Severe Acidosis



Moderate Acidosis

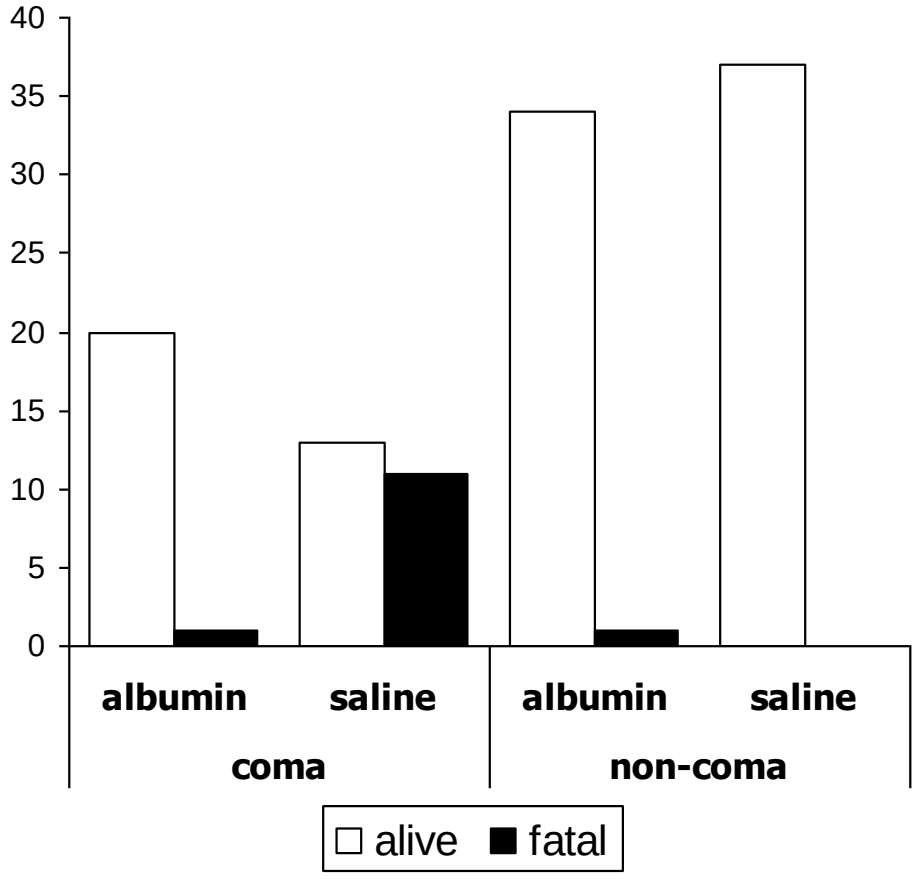


Albumin 2/56 (3.6%) vs Saline 11/61 (16%) P = 0.01

15% rescued

Phase II trial

Albumin as a targeted therapy- coma vs non-coma



Coma (cerebral malaria)

Albumin 1/21 (5%)

Saline 11/24 (46%)

Relative risk: 9.6 [1.4-68]

Non-coma

Albumin 1/35 (3%)

Saline 0/37 (0%)

Maitland *et al* (2005)

External relevance :global context

Report	Year	Mortality	Clinical Sub-group
Observational- Blantyre	1993	28%	coma & acidaemia
Observational- Kilifi	1996/	24%	deep breathing
	1997	28%	coma
		41%	***coma/deep breathing**
Observational- Kumasi	2003	19%	deep breathing
		37%	***coma/deep breathing**
Observational Banjul	2003	24%	deep breathing
		40%	***coma/ deep breathing**
Randomised trial Kilifi	2004	4% (2/56)	albumin arm
		18% (11/61)	saline arm
Coma subgroup		5% (1/25)	albumin arm-coma
		46% (11/24)	**saline arm -coma**

Albumin – relevant for Africa?

- Early evidence of improved outcome with albumin
- HAS expensive and not routinely available
- Cost effective: USD 30-40 per life saved ~ same as the cost of a blood transfusion
- Oncotic effects or due to its other beneficial properties
- Could this be achieved with a cheaper synthetic colloid?
- Aim of Phase II trial : inform the design of the next phase, and NOT to establish statistical superiority of either colloid.

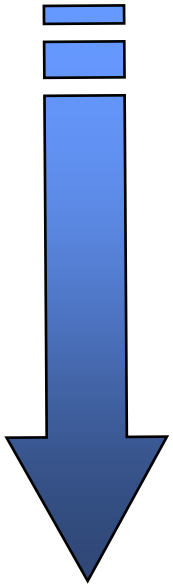
Phase II: Gelofusine Vs albumin RCT

Outcome n/N	Sub-Category	Albumin	Gelofusine	P
Primary				
1° Resolution of shock (%)	0 h	35/42 (83)	37/43 (86)	0.77
	1 h	12/41 (29)	7/37 (19)	0.29
	8 h	9/41 (20)	5/37 (14)	0.24
Secondary				
In-hospital death, (%)	By ITT	1/43 (2.3)	7/44 (16)	0.06
	PP	1/40 (2.5)	4/40 (10)	0.36
Neurological sequelae (%)	By ITT	3/43 (7.0)	1/37 (2.7)	0.61
	PP	3/39 (7.7)	1/36 (2.8)	0.62
Adverse events, (%)	Pulmonary oedema	0	0	—
	Raised intracranial pressure	0	2/44 (5)	—
	Possible allergic reaction	0	1/44 (2.3)	—

No difference in mean volumes received

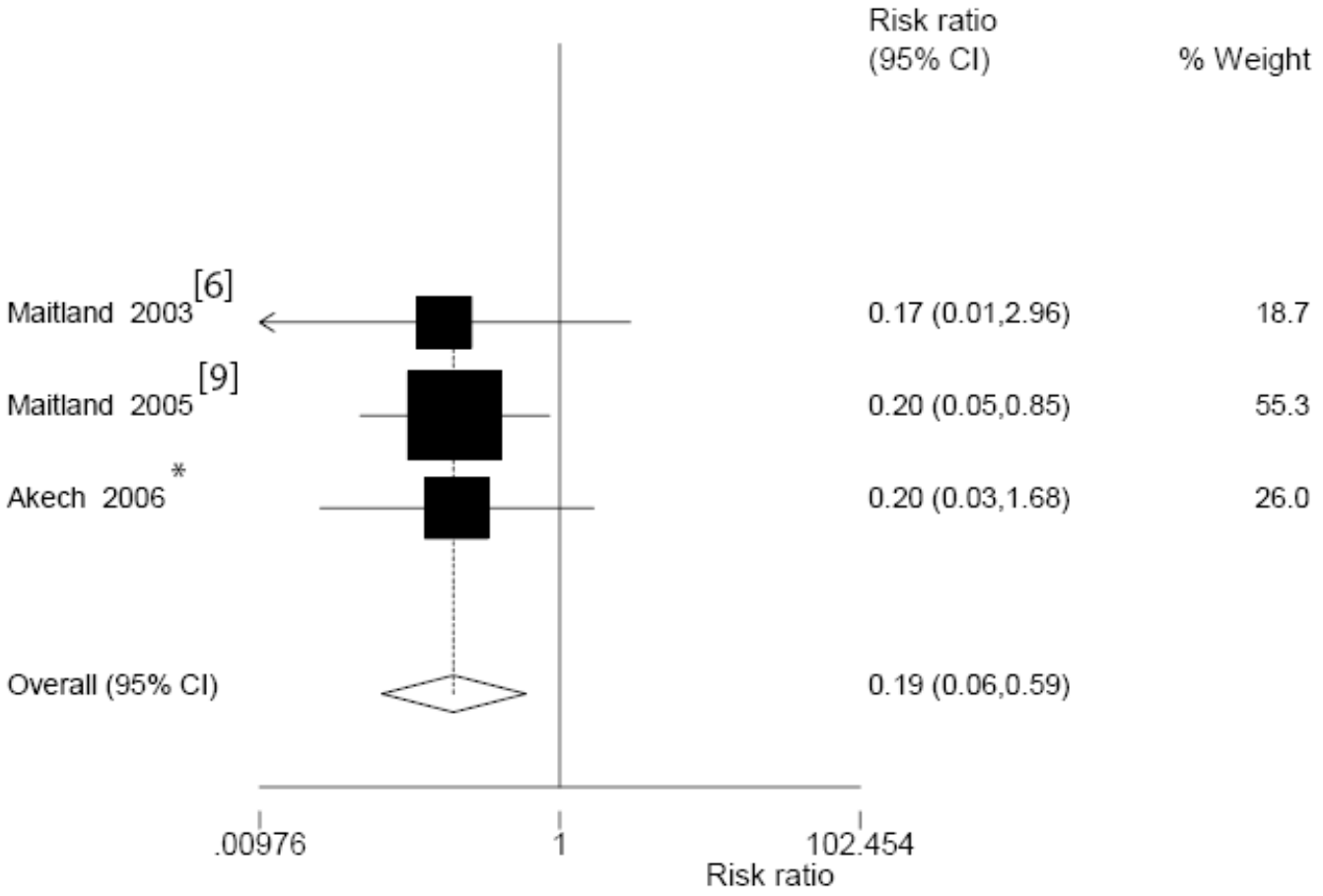
Akech et al, 2006

Summary of trials



	Outcome	n
Pilot Studies	Established hypovolaemia	
	40% severe acidosis - hypotension	60
RCT	Resolution of acidosis and shock	150
	Albumin (4%) mortality lower than saline (18%)	
Colloid trial	Resolution of acidosis and shock	
	Albumin (2%) mortality less than Gelofusine (18%)	88
	Total	**298**

Summary estimate of the effect of albumin on mortality



Akech et al, 2006

Considerations for Phase III

- Consistently low mortality with human albumin solution: should be included despite cost
- Gelofusine no better than saline
- Current standard of care: (no resuscitation fluids) included as a control
- Definitive address whether volume expansion should be used in general management
- Should lead to general improvement in management of other childhood illnesses where benefit of volume expansion is beyond doubt

If confirmed in larger trial…..

- Management of the sick child: protocol implemented by bedside assessments
- Rationale for generic approach to management
- Dispel common misconceptions
- Demonstration that improved outcome can come through effective delivery of emergency care

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