Point-of-care measurement of blood lactate in children admitted with febrile illness to an African district hospital.

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Abstract

Background. Lactic acidosis is a consistent predictor of mortality due to severe infectious disease but its detection in low-income settings is limited to the clinical sign of 'deep breathing' due to lack of accessible technology for its measurement. We evaluated the use of a point-of-care (POC) diagnostic device for blood lactate to assess the severity of illness in children admitted to a district hospital in Tanzania.

Methods. Children between the age of 2 months and 13 years with a history of fever were enrolled in the study over 1 year. A full clinical history and examination were undertaken and blood drawn for culture, microscopy, complete blood count and POC measurement of blood lactate and sugar.

Results. 3,248 children were included in the study of whom 164 (5.0%) died; 45 (27.4%) of these had raised blood lactate (>5mmol/L) but no deep breathing. Compared to mortality in children with lactate of >=3mmol/L, the unadjusted odds of dying were 1.6 (95%CI 0.8-3.0), 3.4 (95%CI 1.5-7.5) and 8.9 (95%CI 4.7-16.8) in children with blood lactates of 3.1-5.0mmol/L, 5.1-8.0 mmol/L and >8.0mmol/L respectively. The prevalence of raised lactate (>5mmol/L) was greater in children with malaria than in children with non malarial febrile illness (P<0.001) although the associated mortality was greater in slide-negative children.

Conclusions. POC lactate measurement can contribute to the assessment of children admitted to hospital with febrile illness and can also create an opportunity for more hospitals in resource-poor settings to participate in clinical trials of interventions to reduce mortality associated with hyperlactataemia.

Introduction

Metabolic acidosis, predominantly associated with hyperlactataemia, is a common manifestation of severe infection. This is particularly pronounced in malaria where up to a third of all childhood deaths occur in association with metabolic acidosis [1-3]. The 2006 WHO definition of severe malaria includes 'malaria with respiratory distress' and this was updated in 2010 to include 'deep breathing, respiratory distress (acidotic breathing) or hyperlactataemia (>5.0mmol/L) or metabolic acidosis (plasma bicarbonate <15mmol/L)' [4-5].

The detailed pathogenesis of acidosis associated with infection is not well understood and may differ between malaria and bacterial disease [6]. Metabolic acidosis in children with malaria has been found in association with severe anemia, hypoglycemia, altered consciousness and fluid and electrolyte disturbance [7-10]. In addition Day et al found evidence that renal and hepatic dysfunction may be contributory causes in adults with severe malaria [11].

Identifying acidosis in hospitalized children in Africa is important to assess the risk of a fatal outcome and, although the treatment of acidosis remains unclear, may contribute to clinical decisions for the use of oxygen, antibiotics, blood and possibly other fluids. However, laboratory measures of acidosis are rarely available in resource-poor settings due to the cost of a blood gas analyzer or other laboratory equipment [12]. The clinical sign of 'abnormally deep breathing' has been shown in a specialist unit to reliably detect severe metabolic acidosis (defined as a base deficit of >12mmol/L)[13] but the sign is based on subjective judgment and high levels of inter-observer variation have been documented among non-physician clinicians assessing children admitted to African district hospitals [14-15]. In addition, the high mortality associated with malaria complicated by respiratory distress

suggests that children with deep breathing may represent the tip of an 'acidosis iceberg' and a more sensitive test might detect lesser degrees of acidosis that may still be associated with substantial mortality.

Hand-held 'point of care' (POC) lactate meters to monitor athletic fitness have been in use for a number of years and a study in Uganda found that a POC measure of lactate in predominantly HIV infected adults effectively identified patients at risk of dying [16]. Although POC lactate meters have been used in a few African hospitals to assess children with severe malaria, as far as we are aware only one study has so far reported on the results [3] and no study has yet reported on their use in non-malarial febrile illness in hospitalized children.

In this study we have analyzed data from a 1-year study of children admitted to a district hospital in an area of intense transmission of *P.falciparum* in NE Tanzania where a POC device to measure blood lactate (Lactate-Pro™) was used for all children admitted with a febrile illness. We used the results to assess the association between hyperlactataemia and mortality in children with and without malaria and suggest how POC lactate results could contribute to clinical decision-making.

Methods

<u>The study site and data collection</u>

The study was conducted in a district hospital in North Eastern Tanzania serving a predominantly rural population with childhood mortality that is typical for Tanzania (165 deaths/1000 person-years under the age of 5 years) [17]. The area is highly endemic for *Plasmodium falciparum* malaria.

Data were collected as part of a study of the cause of febrile illness in children admitted to the pediatric ward and further details are published elsewhere [18]. Over the course of 1 year all daytime pediatric admissions were screened for inclusion and were eligible if aged 2 months to 13 years with a history of fever within the previous 48 hours or axillary temperature $\geq 37.5^0$C. Children with chronic illness (except HIV or malnutrition), or admitted with trauma or a surgical condition were excluded.

Following consenting procedures, a standard clinical history and examination were recorded by a study clinician using WHO guidelines [19]. Pulse oximetry was used on a finger or toe and height and weight were measured. Venous blood was drawn for POC tests of hemoglobin concentration, blood glucose (Hemocue™, Anglholm, Sweden), blood lactate (Lactate-Pro™, Arkray Inc, Kyoto, Japan), and HIV antibody tests (Capillus HIV-1, HIV-2 Test, Trinity Biotech, Ireland and Determine HIV-1/2 Test, Abbott Laboratories, IL, USA) . In addition, an i-STAT™ (Abbott Laboratories, IL, USA) hand-held biochemical analyzer with EC8+ cartridges for serum electrolytes, bicarbonate and base deficit was used in a subset of children with severe malaria enrolled towards the end of the study. Blood was sent to the laboratory for full blood count (Act/Dif™, Beckman-Coulter) and aerobic blood culture (BactAlert™, Biomerieux, France") was undertaken with identification of organisms by standard means as previously described [18]. All POC measures were performed according

to manufacturer's manuals of operation. Blood slides were stained with Giemsa and independently double-read with discordant results resolved by a third reader. Lactate-Pro was purchased on the open market in 2005; the meter cost €315 and test strips €1.92 each.

Data management and analysis.

Data were scanned using Teleforms (Verity software Inc.) into MS-Access (Microsoft Corp, Redmond, Va) and analyzed using Stata-10 (Stata Corp, College Rd, Tx).

Severe malaria was defined as the presence of *P.falciparum* asexual parasitemia and any of: Hb<5g/dL, Blantyre coma scale <4, blood glucose <2.5mmol/L, deep 'acidotic' breathing, blood lactate>5.0 mmol/L, jaundice, 2 or more convulsions in the previous 24 hrs or prostration (inability to sit up or, if <8months of age, inability to drink) with positive final blood slide result for *P.falciparum* [5].

Raised lactate was defined as >5.0 mmol/L, and metabolic acidosis as plasma bicarbonate <15mmol/L. We assessed the sensitivity and specificity of other clinical signs and symptoms for raised lactate. We showed the correlation between simultaneous lactate (Lactate-Pro) and plasma bicarbonate (i-STAT) in a subset of children with simultaneous measures of both. Logistic regression models were used to show crude and adjusted odds ratios (OR) and 95% confidence intervals (95%CI) for associations between raised lactate and clinical features on admission.

Logistic regression was used to explore factors that predict for mortality by showing crude and adjusted OR and 95%CI for associations between admission characteristics of children and subsequent death. We used the receiver operating characteristics (ROC) from the logistic regression to plot the sensitivity and specificity for mortality, for blood lactate

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measures by itself, and as part of a model of factors with significant association with mortality.

Ethics

The study was approved by the Ethics Committees of the National Institute for Medical Research, Tanzania (NIMR/HQ/R.8a/Vol.IX/392) and the London School of Hygiene and Tropical Medicine, UK (LSHTM Ethics # 2087). Witten informed consent to participate was obtained from the parent or guardian of each child in the study.

Results

During the 1-year study 3,639 children were enrolled, 3,248(89.3%) of whom had a record of lactate measurement and were included in this analysis; 2,299 (70.8%) were over the age of 12 months, and 1,749 (53.8%) were male.

Clinical and laboratory features associated with raised blood lactate

Overall there were 164 (5.0%) deaths among the 3,248 children in the study and the risk of mortality increased with increasing levels of lactate (Figures 1a and 1b); 429 (13.2%) children had serum lactate >5mmol/l and of these 92 (21.4%) died compared to mortality of 72/2819 (2.6%) in the children with lactate ≤5mmol/l. Thus 92/164 (56.1%) of deaths in the study occurred in 429/3,248 (13.2%) children with serum lactate >5mmol/l. Raised lactate was more common in children who were blood slide positive for P.falciparum infection (OR=2.9, p<0.001) while in those with raised lactate, the associated mortality was higher in children with non-malarial illness (OR=3.08, p<0.001); raised lactate was found in 338/1,921 (17.6%)

slide-positive children, 57 (16.9%) of whom died, compared to 91/1,327 (6.9%) slide-negative children, 35 (38.5%) of whom died.

Figure 1a and 1b.

Of the 92 children with raised lactate who died only 47 (51.1%) had the clinical sign of 'deep breathing', while of the 72 children without raised lactate who died only 17 (24%) had deep breathing; using a raised lactate (>5mmol/L) as a reference standard of acidosis, the presence of deep breathing had a sensitivity of 28.2% (95%CI 26.7-29.8), specificity of 96.5% (95%CI 95.9-97.1), positive predictive value of 55.0% (95%CI 53.3-56.7) and negative predictive value of 89.8% (95%CI 88.8-90.9). The correlation coefficient for 115 simultaneous lactate (Lactate-Pro) and bicarbonate (i-STAT) readings was -0.62. Using a reference standard of acidosis defined as plasma bicarbonate <15mol/L, raised lactate (>5.0mmol/L) had a sensitivity of 73.6% (95%CI 65.5-81.6) and specificity of 71.0% (95%CI 62.7-79.3).

Detailed clinical and laboratory factors associated with raised lactate are shown in Table 1. Raised lactate was associated with clinical indicators of poor perfusion ('shock'), reduced tissue oxygenation (hypoxia or severe anemia), and lack of peripheral glucose (malnutrition or hypoglycemia) (Table 1).

The association between raised lactate and mortality differed for children aged under 12 months and those aged 12 months or more (Tables 2a and 2b), with a significant interaction between the 2 age groups (p<0.04). While higher lactate measurements were still significantly associated with death in the younger children, the stronger association was

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seen in the older children. For both older and younger children, after adjustment for other predictors of mortality, raised lactate remained a better predictor than shock or severe anemia.

Table 2a and 2b.

What is an appropriate cutoff for raised lactate?

The sensitivity and specificity of lactate>5.0 mmol/L for predicting mortality in children aged 12months or more were 64% and 90% respectively (Figure 2a). Figure 2b shows the predicted probability of mortality from a logistic regression model including age, *P.falciparum* infection, invasive bacterial disease, severe anemia, altered consciousness, severe malnutrition (weight for age z-score <-3), hypoglycemia, lactate acid and deep breathing, which improved the sensitivity to 86%, while keeping the specificity for mortality to 90% (Fig 2b). The best performance in the prediction of mortality is seen when both the sensitivity and specificity are around 86%, which is when the predicted probability of death in these children was 2.8%. In the absence of other factors in the model, a raised lactate of 6 mmol/L would predict 86% of deaths with 86% specificity, but if we do not know whether a child has or does not have any other risk factor for mortality, then a lactate of 2.8 mmol/L would predict 86% of deaths, but with a specificity of 65%.

Figures 2a and 2b.

Potential for a POC lactate measure to guide treatment and/or nursing care

Presence of one or more of the WHO criteria for severe malaria on admission included 78/83 (93.1%) of malaria deaths of which 57 (73.1%) had a raised lactate. The commonest qualifying criteria for severe malaria were Hb<5g/dL (344/724, 47.5%) followed by blood lactate>5.0mmol/L (338/724, 46.7%) and 'prostration' (270/724, 37.3%). Of these, 91/724 (12.5%) had the single criterion of raised lactate among whom 5 (5.5%) died and these accounted for 5/78 (6.4%) of the deaths in children with severe malaria.

To illustrate the contribution of lactate results to predicting mortality among children with non-malarial illness, we assessed the association between raised lactate and severity of pneumonia. Children with a cough or breathing difficulty and raised respiratory rate for age meet WHO criteria for non-severe pneumonia, and the addition of 'low chest wall indrawing' defines criteria for severe pneumonia. Among children with non-severe pneumonia 9/335 (2.7%) had raised lactate and these included 2/8 (25.0%) of the deaths in these children. By contrast, in children with severe pneumonia 50/323 (15.5%) had raised lactate, among whom 27/51 (52.9%) of the deaths from severe pneumonia occurred.

Discussion

The results demonstrate that a POC measure of blood lactate (Lactate-Pro) was strongly predictive of mortality in children with severe febrile illness. In children with WHO criteria of severe malaria almost three-quarters of fatal cases had a raised lactate on admission although more than 9 out of 10 of these had at least one other feature of severe malaria. In children with non-malarial illness standard criteria defining severity do not include raised lactate but more than half of the deaths associated with severe pneumonia occurred in children who had a raised lactate.

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Our findings, similar to those of Newton et al, suggest that the large majority of malaria fatalities can be identified on admission by a high standard of clinical assessment such as is available in research centres [3]. Unfortunately this standard is rarely reached in routine practice [20-21] and, while the use of POC devices should not be used as an alternative to clinical examination, they can encourage and complement routine clinical assessments. In addition, the feasibility of lactate measurement in these settings is greatly enhanced by the availability of a low-cost POC device. A similar case can be made for the use of other POC devices for measurement of hemoglobin, oxygen saturation, acute phase proteins and blood sugar although rigorous assessment of their contribution to care requires some level of randomization, a requirement that raises complex ethical and logistic challenges.

Although it was not possible to validate Lactate-Pro or i-STAT results against a laboratory-based gold standard, the two measures were reasonably well correlated with each other and this is consistent with another study that compared four POC lactate meters [22]. More importantly, blood lactate values on admission strongly predicted mortality and this is consistent with other studies [1, 7]. Use of the clinical sign of deep breathing identified a group of children at high risk of death but almost half of the children who died with a raised lactate were judged not to have abnormally deep breathing on admission. Conversely, a smaller number of children were judged to be positive for 'deep breathing' but with a normal blood lactate, a finding that could be due to non-lactate acidosis, poor specificity of the sign or to inter-observer variability that has been described in detecting 'deep breathing' [14-15].

As far as we are aware, this is the first study of the use of a POC measure of lactate in children admitted for both malaria and non-malarial febrile illness. Raised blood lactate was more strongly associated with malaria than invasive bacterial disease and this may relate to

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the pathophysiology of malaria that includes a number of processes known to result in tissue hypoxia (e.g. parasite sequestration) or hypoglycemia resulting in altered cellular metabolism [8]. The results of multiple logistic regression suggested that the association between malaria and lactic acidosis persisted after allowance for the contribution of the other clinical and laboratory measures that were included in the model. This suggests additional factors causing a raised lactate for which this study had no direct measure; parasite sequestration in small blood vessels could be one such factor and this interpretation is consistent with the finding that increasing blood lactate values were associated with increasing *P.falciparum* parasite densities. ~~Conversely, f~~For non-malarial illness the clinical and laboratory factors that were included in the model were fully explained~~sufficient to account for~~ the association between bacterial infection and raised lactate, suggesting that the extra knowledge of bacterial infections added nothing more to the presence or absence of raised lactate. Studies with more detailed measures of acidosis and tissue respiration are better suited to explore these associations.

The study identified an increase in odds of death for children with blood lactates in the upper 'normal' range by WHO standards compared to children in the low 'normal' range. The analysis of sensitivity and specificity identified the most efficient cutoff defining raised lactate (i.e. the cutoff that resulted in the optimum combination of sensitivity and specificity) to be below the 5.0mmol/L currently recommended by WHO although given lack of evidence on the cost and efficacy of treatment the current cut-off seems appropriate.[8, 23-24].

Limitations of this study include the lack of comparison with laboratory measures of blood lactate and the inclusion of only one POC lactate test on admission to the ward. In addition,

a comparison of clinical outcomes under conditions where POC lactate results were and were not available is required to fully assess their contribution to care.

This study demonstrates that the use of lactate meters in these settings creates possibilities for improved clinical assessment of severely ill children. In addition, POC measurement of lactate provides an opportunity for pragmatic clinical trials for the treatment of acidosis. In particular, the indications for the use of blood, fluids and antibiotics could all be modified by the availability of lactate POC resulting in improved use of these basic interventions to reduce mortality in severely ill children.

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Conflict of interest

None of the authors or those listed in acknowledgements has a conflict.

Author contributions

GM was responsible for clinical data collection and drafting the MS

BN was responsible for all the clinical data collection, contributed to the data analysis and

provided critical review of the MS.

BA was responsible for the laboratory analysis, drafted sections of the methods and

provided critical review of the MS.

IH contributed to the design and data collection and provided critical review of the MS.

JT was responsible for the data analysis, and contributed to the writing of the paper.

References

1.   Taylor T, Olola C, Valim C, et al. Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network. Trans R Soc Trop Med Hyg **2006** Jul;100(7):615-22.
2.   Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. N Engl J Med **1995** May 25;332(21):1399-404.

3. Newton CR, Valim C, Krishna S, et al. The prognostic value of measures of acid/base balance in pediatric falciparum malaria, compared with other clinical and laboratory parameters. Clin Infect Dis **2005** Oct 1;41(7):948-57.

4. WHO. Guidelines for the treatment of malaria. **2006**.

5. WHO. Guidlines for the treatment of malaria. **2010**.

6. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. Ann Surg **1996** Jul;224(1):97-102.

7. English M, Sauerwein R, Waruiru C, et al. Acidosis in severe childhood malaria. QJM **1997** Apr;90(4):263-70.

8. Maitland K, Newton CR. Acidosis of severe falciparum malaria: heading for a shock? Trends Parasitol **2005** Jan;21(1):11-6.

9. Marsh K, English M, Crawley J, Peshu N. The pathogenesis of severe malaria in African children. Ann Trop Med Parasitol **1996** Aug;90(4):395-402.

10. Krishna S, Waller DW, ter Kuile F, et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophysiological and prognostic significance. Trans R Soc Trop Med Hyg **1994** Jan-Feb;88(1):67-73.

11. Day NP, Phu NH, Mai NT, et al. The pathophysiologic and prognostic significance of acidosis in severe adult malaria. Crit Care Med **2000** Jun;28(6):1833-40.

12. Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory medicine in Africa: a barrier to effective health care. Clin Infect Dis **2006** Feb 1;42(3):377-82.

13. English M, Waruiru C, Amukoye E, et al. Deep breathing in children with severe malaria: indicator of metabolic acidosis and poor outcome. Am J Trop Med Hyg **1996** Nov;55(5):521-4.

14. Kahigwa E, Schellenberg D, Schellenberg JA, Aponte JJ, Alonso PL, Menendez C. Inter-observer variation in the assessment of clinical signs in sick Tanzanian children. Transactions of the Royal Society of Tropical Medicine and Hygiene **2002** Mar-Apr;96(2):162-6.

15. Nadjm B, Jeffs B, Mtove G, et al. Inter-observer variation in paediatric clinical signs between different grades of staff examining children admitted to hospital in Tanzania. Trop Med Int Health **2008** Sep;13(9):1213-9.

16. Moore CC, Jacob ST, Pinkerton R, et al. Point-of-care lactate testing predicts mortality of severe sepsis in a predominantly HIV type 1-infected patient population in Uganda. Clin Infect Dis **2008** Jan 15;46(2):215-22.

17. Tanzanian National Census. National Bureau of Statistics United Republic of Tanzania **2002**.

18. Nadjm B, Amos B, Mtove G, et al. WHO guidelines for antimicrobial treatment in children admitted to hospital in an area of intense Plasmodium falciparum transmission: prospective study. BMJ **2010**;340:c1350.

19. WHO. Management of the child with a serious infection or severe malnutrition. ISBN 9241545313 Vol. WHO Geneva, **2000**.

20. English M, Esamai F, Wasunna A, et al. Assessment of inpatient paediatric care in first referral level hospitals in 13 districts in Kenya. Lancet **2004** Jun 12;363(9425):1948-53.

21. Reyburn H, Mwakasungula E, Chonya S, et al. Clinical assessment and treatment in paediatric wards in the north-east of the United Republic of Tanzania. Bull World Health Organ **2008** Feb;86(2):132-9.

22. Acierno MJ, Mitchell MA. Evaluation of four point-of-care meters for rapid determination of blood lactate concentrations in dogs. Journal of the American Veterinary Medical Association **2007** May 1;230(9):1315-8.

23. Molyneux EM, Maitland K. Intravenous fluids--getting the balance right. N Engl J Med **2005** Sep 1;353(9):941-4.

24. Krishna S, Supanaranond W, Pukrittayakamee S, et al. Dichloroacetate for lactic acidosis in severe malaria: a pharmacokinetic and pharmacodynamic assessment. Metabolism **1994** Aug;43(8):974-81.

Figure 1. Case fatality (%) by blood lactate level in children with positive (1a) and negative (1b) blood slide results for malaria.

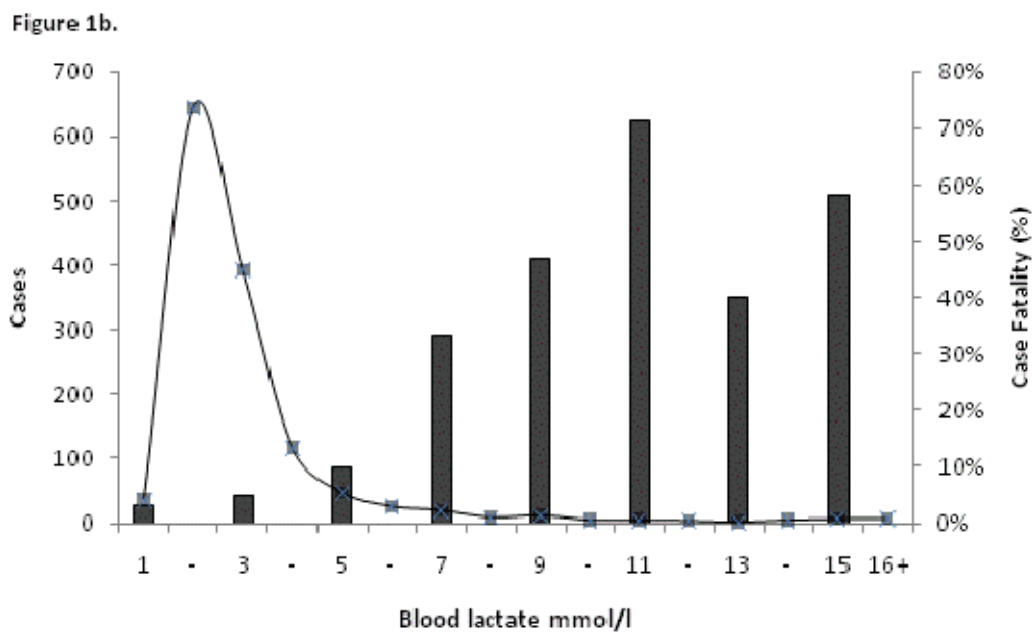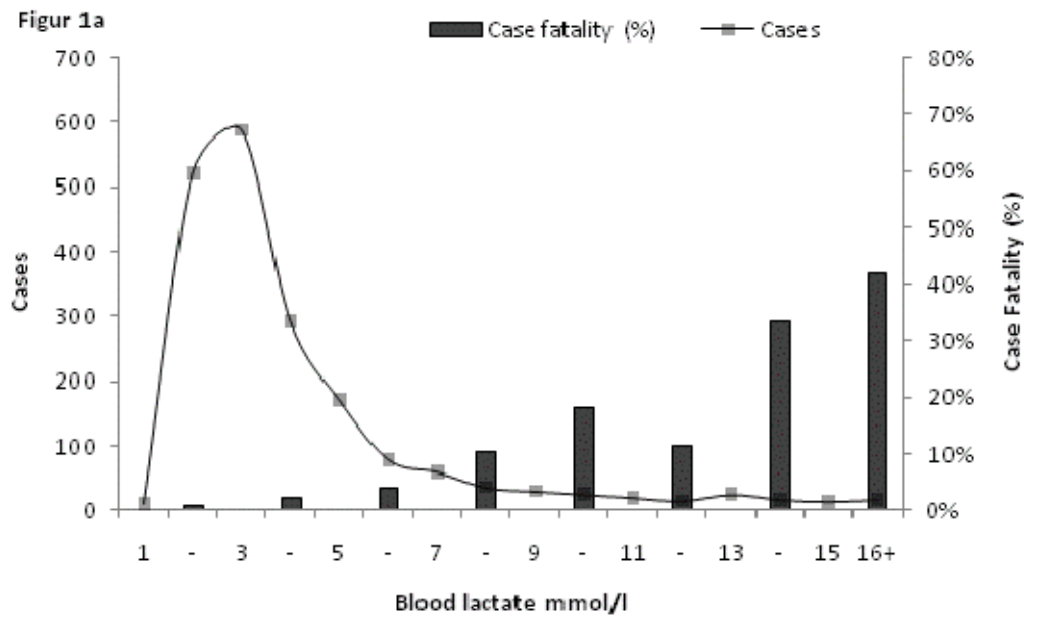Figure 2. The receiver operator characteristics (ROC) curves for mortality in children aged 12 months of more admitted to hospital: a) using lactate measurement alone, b) using the predicted probability of death from the logistic regression model shown in Table 1.
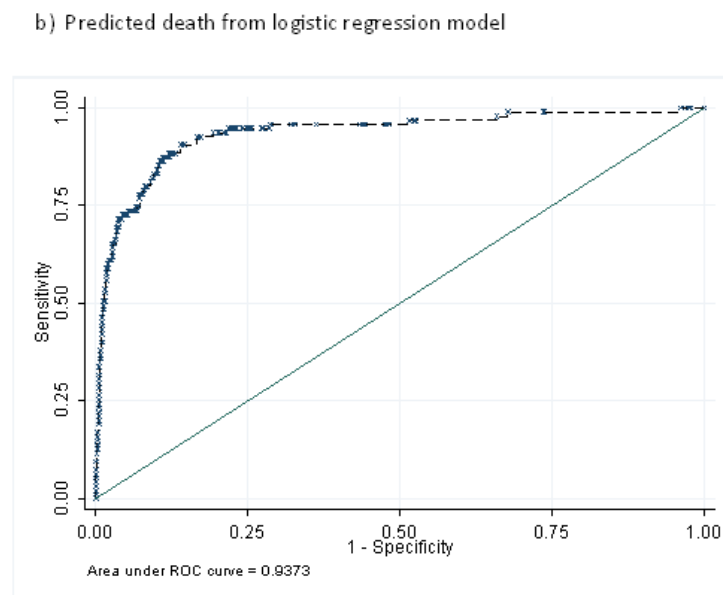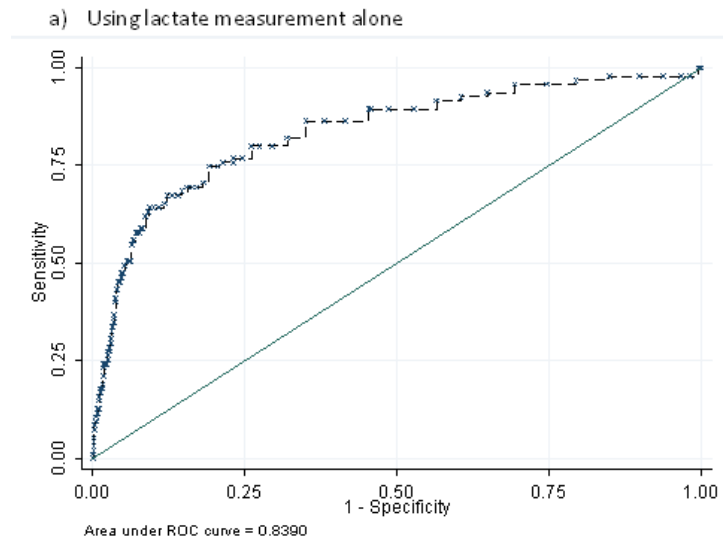

a) Using lactate measurement alone

Area under ROC curve = 0.8390

b) Predicted death from logistic regression model

Area under ROC curve = 0.9373

Table 1. Logistic regression model of clinical and laboratory factors associated with blood lactate >5.0mmol/L in 3,211 children* in the study.

	No of children	No with High lactate (%)	Unadjusted Odds				Adjusted Odds[‖]			
			OR	95% CI		p	OR	95% CI		p
Age 2-11m (baseline group)	936	147 (16)	1				1			
Age 12-59m	1999	255 (13)	0.78	0.63	0.98	0.048	0.60	0.45	0.78	<0.001
Age 60+m	276	16 (6)	0.33	0.19	0.56	<0.001	0.45	0.25	0.83	0.01
No P.falciparum seen (baseline)	1317	89 (7)	1				1			
P.falciparum 1-4,999/mcl	359	39 (11)	1.68	1.13	2.50	0.015	1.43	0.90	2.27	0.1
P.falciparum 5,000-50,000/mcl	786	102 (13)	2.06	1.53	2.78	<0.001	2.08	1.44	2.99	<0.001
P.falciparum >50,000/mcl	749	188 (25)	4.62	3.53	6.06	<0.001	6.67	4.77	9.34	<0.001
†Invasive bacterial disease	316	55 (17)	147	1.08	2.01	0.01	1.49	1.01	2.22	0.05
Hb<5g/dl	483	198 (41)	7.92	6.31	9.95	<0.001	8.25	6.27	10.85	<0.001
Oxygen sat.<90%	70	25 (36)	3.88	2.36	6.41	<0.001	1.96	0.98	3.90	0.06
Blood sugar<2.5mmol/L	103	53 (52)	7.97	5.33	11.90	<0.001	5.54	3.20	9.59	<0.001
‡Severe malnutrition	99	15 (15)	1.20	0.69	2.10	0.562	2.35	1.20	4.57	0.012
§Shock	835	182 (22)	2.53	2.04	3.13	<0.001	1.89	1.46	2.46	<0.001
Deep breathing	213	115 (54)	10.44	7.78	14.0	<0.001	6.21	4.29	9.00	<0.001

Table 1 footnote.

*   37 children excluded due to missing data on oxygen saturation (34) and deep breathing (3)

†   Bacterial pathogen isolated from blood or cerebrospinal fluid

‡   Height-for-weight Z score<-3 or visible severe wasting.

§   Limb-core palpable temperature gradient, capillary refill>3 seconds or heart rate>180/min.

‖   Adjusted for age, *P.falciparum* density, invasive bacterial disease, Hb, Oxygen saturation, blood sugar, severe malnutrition, shock, and deep breathing.

Table 2a. Logistic regression model of clinical and laboratory factors associate with mortality among 949 children aged less than 12 months in the study.

	No of children	No (%) of deaths	Unadjusted Odds			Adjusted Odds [‖]		
			OR	95%CI	P	OR	95%CI	P
Age 2-11m (baseline)	949	69 (7.3)						
P.falciparum positive	427	23 (5.4)	0.59	0.35 0.99	0.045	0.36	0.18 0.73	0.005
Invasive bacterial disease	111	23 (20.7)	4.50	2.60 7.78	<0.001	2.96	1.53 5.73	0.001
Severe anemia	142	21 (14.8)	2.74	1.59 4.74	<0.001	0.76	0.34 1.73	0.5
Shock	339	33 (9.7)	1.72	1.05 2.81	0.03	0.94	0.51 1.73	0.8
Altered consciousness	71	27 (38.0)	12.21	6.90 21.61	<0.001	4.87	2.36 10.0	<0.001
Severe malnutrition	23	6 (26.1)	4.83	1.84 12.69	0.001	5.31	1.80 15.6	0.002
Hypoglycemia	16	8 (50)	14.30	5.19 39.40	<0.001	2.58	0.67 10.0	0.17
Lactate >=3.0 mmol/L (baseline)	602	25 (4.2)	1			1		
Lactate 3.1-5.0 mmol/L	197	13 (6.6)	1.63	0.82 3.25	0.165	1.81	0.84 3.91	0.13
Lactate 5.1-8.0 mmol/L	71	9 (12.7)	3.35	1.50 7.50	0.003	2.62	0.90 7.56	0.076
Lactate 8.1+ mmol/L	79	22 (27.9)	8.91	4.72 16.80	<0.001	5.65	1.96 16.26	0.001
Deep breathing *	80	26 (32.5)	9.24	5.28 16.16	<0.001	3.05	1.45 6.44	0.003

Footnotes to Table 2a:

* One missing value for deep breathing

[‖]Adjusted for density of *P.falciparum* parasites, severe anemia, shock, altered consciousness, severe malnutrition, hypoglycemia, deep breathing and lactate measurements

Definitions as in Table 1.

Table 2b. Logistic regression model of clinical and laboratory factors associate with mortality among 2299 children aged ≥12 months in the study.

	No of children	No (%) of deaths	Unadjusted Odds				Adjusted Odds [‖]			
			OR	95%CI		P	OR	95%CI		P
Age 2-11m Age 12-59m (baseline)	2,022	82 (4.1)	1				1			
Age 60+m	277	13 (4.7)	1.17	0.64	2.12	0.6	2.38	1.10	5.16	0.03
P.falciparum positive	1494	60 (4.0)	0.92	0.60	1.41	0.7	0.70	0.36	1.35	0.28
Invasive bacterial disease	208	30 (14.4)	5.25	3.32	8.31	<0.001	5.60	2.89	10.85	<0.001
Severe anemia	351	26 (7.4)	2.18	1.37	3.47	0.001	0.44	0.22	0.86	0.017
Shock	516	41 (8.0)	2.76	1.82	4.20	<0.001	1.17	0.65	2.09	0.6
Altered consciousness	215	62 (28.8)	25.19	16.01	39.62	<0.001	7.93	4.43	14.20	<0.001
Severe malnutrition	76	11 (14.5)	4.31	2.19	8.47	<0.001	4.54	1.81	11.39	0.001
Hypoglycemia	91	35 (38.5)	22.38	13.65	36.67	<0.001	5.06	2.57	9.96	<0.001
Lactate >=3.0 mmol/L (baseline)	1,517	17 (1.1)	1				1			
Lactate 3.1-5.0 mmol/L	482	17 (3.5)	3.23	1.63	6.37	<0.001	3.17	1.44	6.97	0.004
Lactate 5.1-8.0 mmol/L	173	20 (11.6)	11.53	5.92	22.49	<0.001	9.14	4.02	20.77	<0.001
Lactate 8.1+ mmol/L	127	41 (32.3)	42.07	22.95	77.09	<0.001	15.73	6.60	37.50	<0.001
Deep breathing *	140	38 (27.1)	13.73	8.70	21.66	<0.001	2.68	1.39	5.20	0.003

Footnotes to Table 2b.

* Two missing values for deep breathing.

[‖]Adjusted for age, *P.falciparum* positive, invasive bacterial disease, severe anemia, shock, altered consciousness, severe malnutrition, hypoglycemia, deep breathing and lactate measurements

Definitions as in Table 1.