Evaluation of clinical signs to diagnose anaemia in Uganda and Bangladesh, in areas with and without malaria

H.D. Kalter,[1] G. Burnham,[1] P.R. Kolstad,[1] M. Hossain,[2] J.A. Schillinger,[3] N.Z. Khan,[2] S. Saha,[2] V. de Wit,[1] N. Kenya-Mugisha,[4] B. Schwartz,[3] & R.E. Black[1]

The object of this study was to assess the ability of pallor and other clinical signs, including those in the Integrated Management of Childhood Illness (IMCI) guidelines developed by WHO and UNICEF, to identify severe anaemia and some anaemia in developing country settings with and without malaria. A total of 1226 and 668 children aged 2 months to 5 years were prospectively sampled from patients presenting at, respectively, a district hospital in rural Uganda and a children's hospital in Dhaka, Bangladesh. The study physicians obtained a standardized history and carried out a physical examination that included pallor, signs of respiratory distress, and the remaining IMCI referral signs. The haematocrit or haemoglobin level was determined in all children with conjunctival or palmar pallor, and in a sample of the rest. Children with a blood level measurement and assessment of pallor at both sites were included in the anaemia analysis. Using the haematocrit or haemoglobin level as the reference standard, the correctness of assessments using severe and some pallor and other clinical signs in classifying severe and some anaemia was determined.

While the full IMCI process would have referred most of the children in Uganda and nearly all the children in Bangladesh with severe anaemia to hospital, few would have received a diagnosis of severe anaemia. Severe palmar and conjunctival pallor, individually and together, had 10–50% sensitivity and 99% specificity for severe anaemia; the addition of grunting increased the sensitivity to 37–80% while maintaining a reasonable positive predictive value. Palmar pallor did not work as well as conjunctival pallor in Bangladesh for the detection for severe or some anaemia. Combining "conjunctival or palmar pallor" detected 71–87% of moderate anaemia and half or more of mild anaemia. About half the children with no anaemia were incorrectly classified as having "moderate or mild" anaemia. Anaemia was more easily diagnosed in Uganda in children with malaria.

Our results show that simple clinical signs can correctly classify the anaemia status of most children. Grunting may serve as a useful adjunct to pallor in the diagnosis of severe anaemia. Conjunctival pallor should be added to the IMCI anaemia box, or the guidelines need to be adapted in regions where palmar pallor may not readily be detected.

Introduction

Anaemia, which is common in young children in developing countries in areas of both high and low malaria prevalence (*1*, *2*), is most often caused by nutritional iron deficiency, helminth infection or malaria infection in endemic settings. Severe anaemia contributes to an increased risk of death (*3*), while children with milder anaemia have increased susceptibility to infection (*4*), delayed growth (*5*, *6*), impaired cognitive and psychomotor development (*7–9*), and behavioural problems (*10*). Treating children who have severe anaemia and respiratory distress with a blood transfusion can prevent death (*3*), and treating milder anaemia can reverse some of the related ill effects and may often avoid the progression to severe anaemia and the dangers associated with blood transfusion.

The diagnosis of anaemia in a developing country without adequate laboratory facilities is difficult. WHO/UNICEF therefore included the diagnosis of

[1] Department of International Health, Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe St., Suite E8132, Baltimore, MD 21205, USA. Requests for reprints and correspondence should be sent to Dr H.D. Kalter at this address.

[2] Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Dhaka, Bangladesh.

[3] Division of Bacterial Diseases, United States Centers for Disease Control and Prevention, Atlanta, GA, USA.

[4] Director, ARI/CDD Programmes, Ministry of Health, Entebbe, Uganda.

Reprint No. **5825**

anaemia and severe anaemia in children aged 2 months to 5 years in their recent guidelines for the Integrated Management of Childhood Illness (IMCI). The IMCI algorithm, using simple clinical signs and criteria, enables health workers at first-level facilities to diagnose and manage the illnesses that are responsible for about 70% of child deaths in developing countries (*11*). These include pneumonia, diarrhoea, measles, malaria, and malnutrition. Children classified by the algorithm as having a severe condition are referred to hospital after receiving any needed urgent treatment, while those with non-serious illnesses are treated at the first-level facility.

To diagnose severe anaemia, the IMCI algorithm relies on the finding of severe palmar pallor, while anaemia is diagnosed by the finding of some palmar pallor. Studies in Africa (*12*, *13*) and of Whites in the USA (*14*) suggest that the palm and nailbeds are the best sites for assessing pallor. However, palmar pigment may vary in other regions, such as the Indian subcontinent, so there is a need to assess the use of palmar pallor to detect anaemia in developing countries outside of Africa.

While pallor in various anatomical sites has been the principal clinical sign studied to diagnose anaemia (*12–16*), attention has recently been focused on the usefulness of signs of respiratory distress to help identify children with severe anaemia who require blood transfusion (*3*, *12*). However, because this diagnosis could be complicated by concurrent pneumonia or malaria, which often present with fever, cough and difficult breathing, many children without severe anaemia might needlessly be referred for this condition, and referred children with pallor might not receive treatment needed for a lesser degree of anaemia. The IMCI algorithm avoids these potential complications by placing the signs for respiratory distress, fever, and nutrition problems in separate boxes or sections. Thus, children with both pallor and respiratory distress, with or without fever, can be appropriately treated for their anaemia as well as referred for any suspected severe illnesses. A potential difficulty remains with this approach. The IMCI algorithm does not identify which children without severe pallor who are referred for respiratory problems have severe anaemia, and the care of these children might be delayed or the diagnosis might also be missed at the referral centre.

Some prior studies have examined the validity of clinical signs for diagnosing severe and moderate anaemia, but have not determined how well the signs differentiate these conditions from each other (*12*, *13*). With this approach, severe pallor may indicate severe anaemia, while moderate anaemia may be diagnosed by any degree of pallor, including severe. It is important, however, to diagnose and appropriately treat both severe and lesser degrees of anaemia. This approach, adopted by the IMCI algorithm, requires that diagnostic criteria should be restricted to specific categories.

We undertook our study to assess how well pallor and signs of respiratory distress perform in identifying severe anaemia, and in differentiating severe from milder anaemia in the context of the IMCI guidelines. We did this both in an African setting with a high prevalence of malaria and in Dhaka, Bangladesh, where there is no malaria and the performance of palmar pallor in detecting anaemia could be evaluated in a developing country outside of Africa.

Patients and methods

We carried out a prospective study of children aged 2 months to 5 years who presented at the outpatient department of Kabarole District Hospital in Fort Portal, Uganda, and the outpatient or emergency department of the Dhaka Shishu (Children's) Hospital in Dhaka, Bangladesh. Each enrolled child's anaemia status was evaluated in the context of a standardized medical history and physical examination that included the signs included in the IMCI protocol, as of August 1994, plus several additional clinical signs. Because we sought to validate the content of the IMCI guidelines, rather than the ability of health auxiliaries to use the instructions, all clinical data were collected by study physicians. The Ugandan study physicians were general medical officers in practice for 7–13 years and the Bangladeshi physicians were experienced paediatricians.

In Uganda, conjunctival, palmar, nailbed and tongue pallor were rated as none, mild, moderate, or severe; "mild" and "moderate" pallor were combined as "some" pallor for the analysis. In Bangladesh, only the conjunctivae and palms were examined, and pallor was rated as none, some, or severe. Conjunctival pallor was evaluated by everting the lower eyelid and examining the palpebral conjunctiva. Palmar pallor was assessed over the thenar eminence without extending the fingers. The nailbeds were examined for pallor without compressing the nails. The superior surface of the tongue was examined for pallor by natural light. The Ugandan medical officers were provided with written guidelines for the assessment of these and other clinical signs, while the physical examination by the Bangladeshi paediatricians was standardized in clinical sessions conducted by one of the investigators (*J.A.S.*), who is a paediatrician.

Systematic samples of children presenting for sick child care were selected for enrolment in Uganda from August 1994 through January 1995 and in Bangladesh from September 1994 through February 1995. Children presenting for immunizations, well-child care, and scheduled or referred visits were excluded. In Bangladesh, the study population included cases of more severe illness by preferentially selecting children who were referred to the emergency room and by taking all patients with a chief complaint of fever and a measured rectal temperature >38 °C.

After obtaining informed consent, patients enrolled in Uganda were evaluated by a study physician. A blood film for malaria was obtained in children with a history of fever or an axillary temperature >37.5 °C. A spun haematocrit (hct) was determined for any child with pallor of the conjunctivae or palms or who was having blood drawn for another reason. In Bangladesh, patients were seen first by a nurse who measured the height, weight and vital signs, and then by a study paediatrician. The HemoCue method (*17*) was used to measure the haemoglobin (hgb) level of children with conjunctival or palmar pallor, or who were having blood drawn for another reason, or had a weight-for-age *Z*-score <–3 (compared with the National Center for Health Statistics reference population (*18*)), or were included in a systematic sample of every fifth child not meeting one of the other criteria. Other laboratory tests and chest radiographs were ordered by the study physicians at both locations, as clinically indicated and specified by the study criteria.

The data from the two study locations were analysed separately. Only those children who were assessed for both conjunctival and palmar pallor and who had a haematocrit or haemoglobin measurement were included in the anaemia analysis. Mean haematocrit and haemoglobin levels were compared through an analysis of variance. The performance (sensitivity, specificity, and positive predictive value) of the IMCI guidelines and other clinical signs in identifying children with severe (hct <15% or hgb <5 g/dl) and "moderate or mild" (hct 15–32% or hgb 5–10 g/dl) anaemia was determined by comparison with the haematocrit or haemoglobin level. Because the IMCI algorithm may refer some children with severe anaemia for other concomitant conditions, the clinical signs of children with severe anaemia but without severe pallor were also examined. Epi Info software (*19*) was used for computer entry and analysis of the data.

The study was approved by the ethical review committees of the Kabarole District Hospital, the Dhaka Shishu Hospital, the Johns Hopkins School of Hygiene and Public Health, and the U.S. Centers for Disease Control and Prevention.

Results

In Uganda and Bangladesh, respectively, a total of 1226 and 668 children aged 2 months up to 5 years were enrolled in the study. In Uganda, 1192 (97%) of the children were evaluated for conjunctival and palmar pallor, and 691 (58%) had at least mild pallor of one or both sites. The haematocrit level was determined in 544 (79%) of these children, and in an additional 291 children without pallor who had blood drawn for another reason. In Bangladesh, pallor was assessed in 666 (99.7%) of the children, of whom 311 (47%) had pallor of at least one site. The haemoglobin level was measured in 274 (88%) of these children, and in 208 other children without pallor who were severely malnourished, or had blood drawn for another medical reason or study criterion, or were part of the systematic sample of haemoglobin measurements. Thus, the anaemia analysis presented in this paper included the 835 and 482 children, respectively, in Uganda and Bangladesh who were both assessed for conjunctival and palmar pallor and whose haematocrit or haemoglobin level was measured.

The median ages of the children in Uganda and Bangladesh were, respectively, 18 and 14 months; 50% and 62%, respectively, were male. Children included in the anaemia analysis at both locations did not differ in sex from the excluded children, and in Uganda their median ages were also similar. In Bangladesh, however, children included in the anaemia analysis were older (14 vs. 9 months, $P < 0.001$) than those without pallor and/or a haemoglobin measurement.

The mean haematocrit level of the children in Uganda was 30.7% (SD = 7.3; range, 7.0–55.0). Children with malaria (≥5000 parasites per high-power field *plus* a history of fever in the past 24 hours or measured temperature ≥37.5°C) had a lower mean haematocrit level than those without malaria (26.8% vs. 31.7%, $P < 0.001$). In Bangladesh, the mean haemoglobin level was 9.5 g/dl (SD = 1.9; range, 2.3–14.6). In Uganda and Bangladesh, 2% (19/835) and 2% (10/482) of the children, respectively, had severe anaemia (hct <15% or hgb <5 g/dl); 111 (13%) and 80 (17%), respectively, of the children in Uganda and Bangladesh had moderate anaemia (hct 15–23% or hgb 5–7 g/dl); and 347 (42%) and 301 (62%), respectively, had mild anaemia (hct 24–32% or hgb 8–10 g/dl).

Detecting severe anaemia

Although the study physicians' findings of pallor correlated with the children's haematocrit and haemoglobin levels (Table 1), the sensitivity of severe conjunctival and palmar pallor, alone or together, for severe anaemia was low in both study locations. This was somewhat variable in Bangladesh, where the sensitivity of severe conjunctival pallor approached an acceptable level while the sensitivity of severe palmar pallor was very low (Table 2). The specificity of these signs for severe anaemia was high in both locations, and combining severe conjunctival and palmar pallor with an "or" statement did not improve the detection of severe anaemia over that of conjunctival pallor alone. In Uganda, the sensitivity and specificity for severe anaemia of severe nailbed pallor (16% and 99%), severe tongue pallor (21% and 99%), and severe conjunctival, palmar, nailbed or tongue pallor (21% and 99%) were similar to the sensitivity and specificity of severe conjunctival and palmar pallor.

Adding respiratory signs to severe conjunctival and palmar pallor with an "and" statement reduced the sensitivity for severe anaemia to an unacceptable level (Table 2). Adding respiratory signs with an "or" statement increased the sensitivity over that of pallor alone, but at some cost to specificity and, owing to the low prevalence of severe anaemia, to the positive predictive value. Only grunting in Bangladesh increased the sensitivity while maintaining a viable predictive value. While these sign combinations are not part of the IMCI algorithm, they could be obtained by adding them to the anaemia box. The current IMCI algorithm would have referred most (in Uganda) or nearly all (in Bangladesh) of the children with severe anaemia to hospital, though because the IMCI anaemia box includes only pallor, most would have lacked a diagnosis of severe anaemia (Table 2).

The eight children in Uganda with severe anaemia who were missed by severe pallor, but detected by other IMCI referral sings were most often picked up by signs of malnutrition. Five had visible severe wasting (three also had a general danger sign and one had chest indrawing) and three had bipedal oedema (one also had chest indrawing). Seven children in Uganda had severe anaemia, but were missed by severe pallor and all other IMCI referral signs. Of the five children in Bangladesh with severe anaemia who were missed by severe pallor, four would have been referred for chest indrawing (two also had a danger sign), and one had bipedal oedema and a danger sign.

The performance of the signs in detecting severe anaemia was not appreciably different in children with and without malaria. For example, the sensitivity/specificity of palmar pallor in Uganda were 14%/97% and 17%/99%, respectively, in children with and without malaria. However, the sample sizes were small (seven and six children, respectively, with and without malaria who had severe anaemia), and there was no difference in the mean haematocrit levels of the two groups (10.7% and 11.3%, $P = 0.64$). Adding respiratory signs to pallor increased the sensitivity only for "*or* grunting," respectively, to 29% and 33% in children with and without malaria, but this also decreased the specificity, respectively, to 85% and 90%.

Table 1: **Haematocrit and haemoglobin levels in 835 and 482 children (aged 2 months to 5 years), respectively, in Uganda and Bangladesh, according to the level of conjunctival and/or palmar pallor, as assessed by a study physician**

Pallor	Mean haematocrit level (%) ± S.D.		
	Conjunctiva[a]	Palm[a]	Conjunctiva or palm[a]
Uganda			
Severe	18.1 ± 7.9	16.1 ± 7.1	18.1 ± 7.9
Some	30.2 ± 7.5	30.3 ± 7.4	30.2 ± 7.4
None	32.0 ± 6.3	31.7 ± 6.5	32.0 ± 6.3
	Mean haemoglobin level (g/dl) ± S.D.		
	Conjunctiva[a]	Palm[a]	Conjunctiva or palm[a]
Bangladesh			
Severe	4.1 ± 1.8	6.4 ± 4.1	5.1 ± 2.6
Some	8.8 ± 2.1	8.7 ± 2.1	9.0 ± 2.0
None	10.1 ± 1.4	9.9 ± 1.6	10.3 ± 1.3

[a] $P < 0.001$.

Detecting moderate or mild anaemia

The sensitivity and specificity of some conjunctival and palmar pallor for "moderate or mild" anaemia were low to moderate in both study locations (Table 2). In Bangladesh, as was true for severe pallor and severe anaemia, the sensitivity of some palmar pallor for "moderate or mild" anaemia was somewhat lower than that of some conjunctival pallor ($P = 0.09$). Also, while the sensitivity of some pallor was low at both anatomical sites, the sensitivity for moderate anaemia was much greater than for mild anaemia (Table 3). As a result, 88% (210/239) and 90% (197/218) of "moderate or mild" anaemia cases not detected in Bangladesh, respectively, by "some palmar pallor" and "some conjunctival pallor" had mild anaemia. This pattern also held true in Uganda, but to a lesser degree.

Combining conjunctival and palmar pallor with

Table 2: **Sensitivity, specificity and positive predictive value for severe anaemia or severe pallor at two anatomical sites, without and with the addition of particular respiratory signs; and of some pallor at the same anatomical sites for moderate or mild anaemia, among 835 and 482 children (aged 2 months to 5 years), respectively, in Uganda and Bangladesh**

	No. of children	Conjunctiva			Palm			Conjunctiva or palm		
		Sens.[a]	Spec.[b]	PPV[c]	Sens.[a]	Spec.[b]	PPV[c]	Sens.[a]	Spec.[b]	PPV[c]
Uganda										
Severe anaemia (hct <15%)	19 (2%)									
Severe pallor		21	99	36	21	99	44	21	99	36
and grunting[d]		0	99	0	0	99	0	0	99	0
or grunting[e]		37	89	8	37	90	8	37	89	8
or some pallor and grunting[f]		37	92	10	37	92	10	37	92	10
or lower chest indrawing[g]		32	91	8	32	91	8	32	91	8
or some pallor and indrawing[h]		32	92	9	32	93	9	32	92	9
or cough or d.b. *plus* c.i.[i]		32			32			32		
or any IMCI referral sign[j]		68			68			68		
Moderate or mild anaemia (hct 15–32%)	458 (55%)									
Some pallor		65	42	58	63	43	57	67	40	57
or severe pallor and no grunting[d]		66	41	58	64	42	57	68	38	57
and no grunting[e,f]		57	47	57	55	49	56	58	45	56
and no lower chest indrawing[g,h]		57	47	57	55	48	56	59	45	56
Bangladesh										
Severe anaemia (hgb <5 g/dl)	10 (2%)									
Severe pallor		50	99	71	10	99	33	50	99	56
and grunting[d]		20	100	100	0	100	—	20	100	100
or grunting[e]		80	93	20	60	93	15	80	93	19
or some pallor and grunting[f]		80	96	30	50	96	22	80	94	23
or lower chest indrawing[g]		90	72	6	70	72	5	90	71	6
or some pallor and indrawing[h]		90	87	13	60	90	11	90	83	10
or cough or d.b. *plus* c.i.[i]		90			70			90		
or any IMCI referral sign[j]		100			90			100		
Moderate or mild anaemia (hgb 5–10 g/dl)	381 (79%)									
Some pallor		43	69	84	37	72	84	58	55	83
or severe pallor and no grunting[d]		43	66	83	38	71	83	59	52	82
and no grunting[e,f]		39	73	84	33	76	84	52	59	83
and no lower chest indrawing[g,h]		29	77	83	26	78	82	39	64	80

[a] Sensitivity (%).
[b] Specificity (%).
[c] Positive predictive value (%).
[d–h] These signs designate corresponding levels of sensitivity, specificity and positive predictive value for severe anaemia and some anaemia (these combinations of signs do not exist in the IMCI guidelines, but they could by adding the respiratory signs to the anaemia box).
[i] Cough or difficult breathing (d.b.) *plus* chest indrawing (c.i.); these signs exist in the IMCI guidelines by combining the anaemia and cough boxes. They do not affect the specificity and predictive value of the IMCI diagnosis because they are not part of the anaemia box.
[j] These signs exist in the IMCI guidelines by combining the anaemia and all other boxes. They do not affect the specificity and predictive value of the IMCI diagnosis because they are not part of the anaemia box.

an "or" statement (some pallor of one or both sites, and no severe pallor) had little impact on the diagnosis of "moderate or mild" anaemia in Uganda, but in Bangladesh this increased the sensitivity and lowered the specificity (Table 2). The overall effect was to improve the performance of the signs in diagnosing anaemia. The increase in the correct identification of moderate and mild anaemia more than offset the increased false positive diagnosis of no anaemia as anaemia (Table 3). In areas of high malaria risk, the IMCI algorithm calls for treating children with a severe illness classification and "moderate or mild" anaemia with an oral antimalarial prior to referral to hospital. Using the combined anatomical sites, 153/267 children with a severe illness would have been treated for "moderate or mild" anaemia (132 correctly) before being referred to hospital; while 114 (99 correctly)/266 and 102 (88 correctly)/265, respectively, would have been treated for "moderate or mild" anaemia using conjunctival and palmar pallor alone.

Adding respiratory signs to severe pallor for the detection of severe anaemia often had a negative impact on these gains in the overall diagnosis of anaemia achieved by combining the anatomical sites (Table 2). For example, using "severe conjunctival or palmar pallor *or* lower chest indrawing" to identify severe anaemia changed the sensitivity/

Table 3: **Distribution of children aged 2 months to 5 years in Uganda and Bangladesh with correct and incorrect sign-based classification of their anaemia status, using severe pallor to diagnose severe anaemia and some pallor to diagnose moderate or mild anaemia**

		Sign-based diagnosis			
			% incorrectly classified as:		
Anaemia status	No.	% correctly classified (sensitivity)	Severe anaemia	Anaemia	No anaemia
Uganda					
Sign-based diagnosis (palmar pallor)					
Severe (hct <15%)[a]	19	21	—	58	21
Moderate (hct 15–23%)	111	69	4	—	27
Mild (hct 24–32%)	347	61	<1	—	39
None (hct ≥33%)	358	43	0	57	—
Total	835	53	<1	26	20
Sign-based diagnosis (conjunctival pallor)					
Severe (hct <15%)	19	21	—	68	11
Moderate (hct 15–23%)	111	71	5	—	24
Mild (hct 24–32%)	347	63	<1	—	36
None (hct ≥33%)	358	42	0	58	—
Total	835	54	<1	26	19
Bangladesh					
Sign-based diagnosis (palmar pallor)					
Severe (hgb <5 g/dl)[a]	10	10	—	70	20
Moderate (hgb 5–7 g/dl)	80	65	1	—	34
Mild (hgb 8–10 g/dl)	301	30	<1	—	70
None (hgb ≥11 g/dl)	91	77	0	23	—
Total	482	48	<1	6	45
Sign-based diagnosis (conjunctival pallor)					
Severe (hgb <5 g/dl)	10	50	—	50	0
Moderate (hgb 5–7 g/dl)	80	74	2	—	24
Mild (hgb 8–10 g/dl)	301	35	0	—	65
None (hgb ≥11 g/dl)	91	71	0	29	—
Total	482	48	<1	6	45
Sign-based diagnosis (conjunctival or palmar pallor)					
Severe (hgb <5 g/dl)	10	50	—	50	0
Moderate (hgb 5–7 g/dl)	80	87	4	—	9
Mild (hgb 8–10 g/dl)	301	50	<1	—	50
None (hgb ≥11 g/dl)	91	56	0	44	—
Total	482	57	<1	9	33

[a] hct = haematocrit; hgb = haemoglobin.

specificity of "some conjunctival or palmar pallor" for "moderate or mild" anaemia from 58%/55% to 39%/64%. This was lower than the sensitivity and specificity of "some conjunctival pallor" alone.

In Uganda, the signs performed better in detecting "moderate or mild" anaemia in children with malaria than in those without malaria. For example, the sensitivity of conjunctival pallor in children with and without malaria was, respectively, 75% and 63% ($P = 0.04$). This correlated with the mean haematocrit levels, which were, respectively, 25.1% and 27.1% ($P < 0.001$) in children with and without malaria who had "moderate or mild" anaemia (hct 15–32%).

Discussion

Our data revealed a high prevalence of both severe and some anaemia in Uganda and Bangladesh, demonstrating the importance of identifying and appropriately managing children with these conditions both in and outside of malaria endemic areas. In both locations, 2% of the children included in the anaemia analysis had severe anaemia; 13% and 17%, respectively, in Uganda and Bangladesh had moderate anaemia, and 42% and 62%, respectively, had mild anaemia. The levels for severe and moderate anaemia were in the mid-range of those found by previous health facility-based studies conducted in

malarious areas (*3*, *12*, *13*, *20*, *21*), while mild anaemia was more common in Bangladesh, where there was no malaria, than in these other studies.

The study physicians were able to use clinical signs to identify most cases of severe and "moderate or mild" anaemia, and were usually able to differentiate these levels of anaemia from each other and from no anaemia. Previous studies (*12*, *13*) have used overlapping pallor grades to identify severe and moderate anaemia, while our study used severe pallor to classify severe anaemia and some pallor to classify "moderate or mild" anaemia. This distinction is necessary if both degrees of anaemia are to be detected and appropriately managed.

Severe pallor alone had low to moderate sensitivity and high specificity for severe anaemia. Adding signs of respiratory distress with an "or" statement increased the detection of severe anaemia, but this had a negative effect on the specificity and positive predictive value of severe pallor for severe anaemia, as well as on the diagnosis of "moderate or mild" anaemia. Only grunting in Bangladesh maintained a reasonable predictive value for severe anaemia, while also minimizing any negative impact on the diagnosis of "moderate or mild" anaemia. This suggests that grunting could be added to the IMCI anaemia box for the diagnosis of severe anaemia requiring referral to hospital. In Uganda, the greater loss in predictive value when adding grunting to the signs was due to the lower baseline sensitivity of severe pallor.

The current IMCI guidelines would have referred 68–90% of the children with severe anaemia, but as respiratory signs appear only in the cough box, few referred children with severe anaemia would have received this diagnosis. First-level health facilities with poor access to a hospital might wish to prioritize their referrals by disease classification, since some conditions may be more readily managed in the periphery than others. Such facilities could use grunting to detect most of the children who require immediate referral for a potentially life-saving blood transfusion, while retarding less urgent referrals. For example, only 39 of the 267 children referred by the full IMCI process in Bangladesh had severe conjunctival or palmar pallor *or* grunting, yet this combination of signs identified 8 of the 10 children with severe anaemia. First-level facilities with good access to a hospital could use grunting to identify children who should receive high-priority referral slips for presentation at hospital.

While some pallor had only low to moderate sensitivity for "moderate or mild" anaemia, the sensitivity for moderate anaemia was reasonably high (72% in Uganda and 88% in Bangladesh for "some palmar or conjunctival pallor"). Moderate anaemia is associated with complications and is more likely to progress to severe anaemia, and therefore is more important to detect and treat than mild anaemia. The higher sensitivity for moderate anaemia will also provide a boost in positive predictive value in settings with a higher prevalence of moderate than mild anaemia. While the modest specificity of pallor for "moderate or mild" anaemia resulted in a third or more of children with no anaemia being classified as having some anaemia, this should not present a major problem since treating these children with iron is not a harmful practice, particularly in populations with a high prevalence of anaemia.

In Bangladesh, the combination "some conjunctival *or* palmar pallor" decreased the specificity, but increased the sensitivity and improved the overall performance of the signs in diagnosing moderate and mild anaemia. Combining pallor at different anatomical sites with an "or" statement will almost always increase the sensitivity and decrease the specificity, and this will often improve the diagnosis of "moderate or mild" anaemia. That this was not true in Uganda was due to the similar values for sensitivity and specificity at the various anatomical sites, suggesting that the findings at the sites are highly correlated or that the study physicians may not have independently assessed the sign at each site. This serves to highlight that, if clinical guidelines are to benefit from including the rating of pallor at more than one anatomical site, health worker training must stress the importance of evaluating these sites independently.

In Bangladesh, the lower sensitivity values of palmar than conjunctival pallor (for both severe and some anaemia) suggest that increased palmar pigment may be present and complicate the diagnosis at this anatomical site. In a study in Pakistan (*15*), it was found that conjunctival pallor had the highest sensitivity of all sites for detecting anaemia (hgb <11 g/dl) in young children. Studies in Africa (*12*, *13*) and of Whites in the USA (*14*) have shown that the nailbeds and palm are the best sites for assessing pallor. Our data suggest that the use of palmar pallor alone for detecting anaemia needs to be further assessed in developing countries outside of Africa, using a larger sample size of children with severe anaemia.

In Uganda, the performance of pallor in detecting anaemia in children, with and without malaria, corresponded to the children's haematocrit levels. It has previously been shown that children with malaria have lower mean haematocrit levels than children without malaria (*20*, *22*). Since we and others (*13*, *16*) have demonstrated a correlation between haemoglobin or haematocrit levels and the clinical assessment of pallor, it is to be expected that, all other things being equal, the sign-based diagnosis of

anaemia should work better in settings with a higher prevalence of malaria.

In summary, our data confirm the high prevalence of anaemia in developing country settings with and without malaria, and show that a careful evaluation of clinical signs can correctly classify half or more of young children with anaemia. Severe and some pallor alone, respectively, identified many children with severe anaemia and most with some anaemia, and differentiated almost all the less than severe from severe anaemia and about half to two thirds of no anaemia from some anaemia. Palmar pallor did not perform as well as conjunctival pallor in Bangladesh, and combining "conjunctival *or* palmar pallor" improved the overall diagnosis of anaemia, suggesting that the IMCI algorithm should include conjunctival pallor or should be locally adapted. While the full IMCI process would have referred most of the children with severe anaemia to hospital, few would have received a diagnosis of severe anaemia. Adding grunting to pallor with an "or" statement identified most of these cases of severe anaemia, with minimal impact on the diagnosis of "moderate or mild" anaemia. This sign should therefore be considered for addition to the IMCI anaemia box.

Acknowledgements

The authors acknowledge the contributions of the following individuals and organizations: in Bangladesh — the study paediatricians, Dr Asgar Hossain and Dr Humaira Begum, and Dr Mohammad Hanif of the Dhaka Shishu Hospital; in Uganda — the study's physicians, Dr John Keeri, Dr Paul Mainuka, Dr Monday-Araali, and Dr John Ruhweza, the Basic Health Services Project in Fort Portal, Dr Walter Kipp and the German Agency for Technical Cooperation (GTZ) in Fort Portal and GTZ/PAS in Kampala; and in the United States — Dr Bradley Perkins of the U.S. Centers for Disease Control and Prevention. Financial support was provided by the United States Agency for International Development through the Johns Hopkins Family Health and Child Survival Cooperative Agreement.

Résumé

Evaluation des signes cliniques pour le diagnostic d'anémie, en Ouganda et au Bangladesh, en secteur impaludé et non impaludé

L'objet de cette étude était d'évaluer la capacité de la pâleur et de divers signes cliniques, notamment ceux qui figurent dans les recommandations pour la prise en charge intégrée des maladies de l'enfant (IMCI) mises au point par l'OMS et l'UNICEF, à dépister l'anémie sévère et divers degrés d'anémie, dans le contexte des pays en développement, impaludés ou non. Un échantillon prospectif comptant 1226 et 668 enfants de 2 mois à 5 ans a été recruté parmi les patients qui se sont présentés respectivement dans un hôpital de district rural en Ouganda et dans un hôpital pour enfants de Dacca au Bangladesh. Les médecins de l'étude ont procédé à une anamnèse standardisée et à un examen physique pour rechercher une pâleur, des signes de détresse respiratoire, ainsi que les autres signes inclus dans l'IMCI indiquant la nécessité d'un transfert. L'hématocrite ou le taux d'hémoglobine ont été déterminés chez tous les enfants ayant une pâleur conjonctivale ou palmaire, ainsi que dans un échantillon des autres enfants. Les enfants des deux sites d'étude ayant eu une évaluation hématologique et de la pâleur ont été inclus dans l'étude sur l'anémie. En utilisant l'hématocrite ou le taux d'hémoglobine comme référence, on a déterminé l'exactitude des classifications de divers degrés d'anémie, y compris l'anémie sévère, qui s'appuient sur la pâleur et d'autres indicateurs cliniques.

En appliquant toutes les recommandations de l'IMCI, la plupart des enfants en Ouganda ou presque tous les enfants au Bangladesh, atteints d'anémie sévère auraient été hospitalisés, mais peu auraient été considérés comme sévèrement anémiés. Prises individuellement ou ensemble, la forte pâleur des conjonctives et celle des paumes avaient une sensibilité de 10–50% et une spécificité de 99% pour l'anémie sévère; le geignement ajouté à la pâleur a porté la sensibilité à 37–80%, tout en permettant de conserver une valeur prédictive positive raisonnable. Au Bangladesh, la pâleur palmaire n'a pas donné d'aussi bons résultats que la pâleur conjonctivale pour le dépistage de l'anémie, sévère ou autre. L'association des deux indicateurs, à savoir «pâleur conjonctivale ou palmaire» a permis de dépister 71–87% des cas d'anémie modérée, et au moins la moitié des anémies légères. Près de la moitié des enfants dépourvus d'anémie ont été classés par erreur dans la catégorie «anémie modérée ou légère». L'anémie a été plus facilement diagnostiquée en Ouganda chez l'enfant impaludé.

Nos résultats montrent que des signes cliniques simples permettent de classer correctement l'anémie de la plupart des enfants. Le geignement peut s'ajouter utilement à la pâleur pour le diagnostic de l'anémie sévère. Il est souhaitable que la pâleur conjonctivale soit ajoutée dans l'encadré «anémie» des recommandations de l'IMCI ou que

celles-ci aient besoin d'être adaptées dans les régions ou la pâleur palmaire n'est parfois pas facile à déceler.

References

1. **Blot I, Vovor A.** Anemia in Third World children. *Revue du Praticien*, 1989, **39**: 2125–2127.
2. **Kasili EG.** Malnutrition and infections as causes of childhood anemia in tropical Africa. *American journal of pediatric hematology/oncology*, 1990, **12**: 375–377.
3. **Lackritz EM et al.** Effect of blood transfusion on survival among children in a Kenyan hospital. *Lancet*, 1992, **340**: 524–528.
4. **Masawe AE.** Nutritional anaemias. Part 1: Tropical Africa. *Clinical haematology*, 1981, **10**: 815–842.
5. **Bhatia D, Seshadri S.** Growth performance in anemia and following iron supplementation. *Indian pediatrics*, 1993, **30**: 195–200.
6. **Aukett MA et al.** Treatment with iron increases weight gain and psychomotor development. *Archives of disease in childhood*, 1986, **61**: 849–857.
7. **Walter T.** Effect of iron-deficiency anaemia on cognitive skills in infancy and childhood. *Bailliere's clinical haematology*, 1994, **7**: 815–827.
8. **Cook JD, Skikne BS, Baynes RD.** Iron deficiency: the global perspective. *Advances in experimental medicine & biology*, 1994, **356**: 219–228.
9. **Walter T et al.** Iron-deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics*, 1989, **84**: 7–17.
10. **Johnson SR et al.** The association between hemoglobin and behavior problems in a sample of low-income Hispanic preschool children. *Journal of developmental and behavioral pediatrics*, 1992, **13**: 209–214.
11. **World Health Organization, Division of Diarrhoeal and Acute Respiratory Disease Control.** Integrated management of the sick child. *Bulletin of the World Health Organization*, 1995, **73**: 735–740.
12. **Zucker JR et al.** Clinical signs for the recognition of children with moderate or severe anaemia in western Kenya. *Bulletin of the World Health Organization*, 1997, **75** (Suppl. 1): 97–102.
13. **Luby SP et al.** Using clinical signs to diagnose anaemia in African children. *Bulletin of the World Health Organization*, 1995, **73**: 477–482.
14. **Nardone DA et al.** Usefulness of physical examination in detecting the presence or absence of anaemia. *Archives of internal medicine*, 1990, **150**: 201–204.
15. **Thaver IH, Baig L.** Anaemia in children. Part I. Can simple observations by primary care provider help in diagnosis? *Journal of the Pakistan Medical Association*, 1994, **44**: 282–284.
16. **Strobach RS et al.** The value of the physical examination in the diagnosis of anaemia. Correlation of the physical findings and the hemoglobin concentration. *Archives of internal medicine*, 1988, **148**: 831–832.
17. **von Schenck H, Falkensson M, Lundberg B.** Evaluation of "HemoCue," a new device for determining hemoglobin. *Clinical chemistry*, 1986, **32**: 526–529.
18. **United States Public Health Service, Health Resources Administration.** *NCHS growth charts.* Rockville, MD, 1976 (HRA 76-1120, 25, 3).
19. **Dean AG et al.** *Epi Info, Version 6: a word processing, database, and statistics program for epidemiology on microcomputers.* Atlanta, GA, Centers for Disease Control and Prevention, 1994.
20. **Hedberg K et al.** *Plasmodium falciparum*-associated anaemia in children at a large urban hospital in Zaire. *American journal of tropical medicine and hygiene*, 1993, **48**: 365–371
21. **Olaleye B et al.** *Clinical signs of malaria — Farafenni 93/94.* Presentation at the U.S. Centers for Disease Control and Prevention, Atlanta, 1995.
22. **Renaudin P, Lombart JP.** Anaemia in infants under one year of age in Moundou, Chad: prevalence and etiology. *Medecine tropicale*, 1994, **54**: 337–342 (in French, summary in English).