International Journal of Infectious Diseases (2008) 12, 62—70

http://intl.elsevierhealth.com/journals/ijid

Diarrhea and fever as risk factors for anemia among children under age five living in urban slum areas of Indonesia

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Received 7 February 2007; accepted 10 April 2007
Corresponding Editor: William Cameron, Ottawa, Canada

KEYWORDS
Anemia;
Children;
Diarrhea;
Fever;
Hemoglobin;
Indonesia

Summary
Objectives: To characterize diarrhea and fever as risk factors for anemia among children in developing countries.
Methods: We characterized risk factors for anemia in a sample of 32 873 children, aged 6—59 months, from poor families in urban slum areas of Indonesia from 2000 to 2003.
Results: The prevalence of anemia was 58.7%. In separate multivariate models, after adjusting for age, sex, stunting, maternal age and education, and weekly per capita household expenditure, current diarrhea (OR 1.20, 95% CI 1.07—1.35, $p = 0.002$), current fever (OR 1.44, 95% CI 1.18—1.75, $p < 0.0001$), and a history of diarrhea in the previous seven days (OR 1.12, 95% CI 1.03—1.23, $p = 0.024$) were associated with an increased risk of anemia.
Conclusions: Diarrhea and fever are important risk factors for anemia among young children living in urban slum communities in Indonesia.
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Introduction

Anemia is highly prevalent among children in developing countries, affecting approximately two-thirds of children in Southeast Asia.[1] Southeast Asia has the highest prevalence of anemia in children compared with all other regions of the world.[1] Although iron deficiency anemia accounts for a large proportion of anemia,[1] the anemia of chronic inflammation (which also includes the anemia of infection) may account for a substantial proportion of anemia among children.[2] In comparison with iron deficiency anemia, the anemia of chronic inflammation has received less attention in epidemiological studies and has been relatively neglected except for anemia due to malaria.[3] In areas where malaria is uncommon, less is

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1201-9712/$32.00 © 2007 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.
doi:10.1016/j.ijid.2007.04.011

known about how infections may contribute to anemia in children. The relationship between diarrhea, fever, and anemia has not been well characterized among young children living in the community. We hypothesized that diarrhea and fever were associated with anemia in young children. To address this hypothesis, we examined the relationship between risk factors for anemia among children aged 6—59 months from families in urban slum communities in Indonesia.

Material and methods

The study subjects consisted of households that participated in a major nutritional surveillance system (NSS) in Indonesia that was established by the Ministry of Health, Government of Indonesia and Helen Keller International (HKI) in 1995.[4] The NSS was based upon UNICEF's conceptual framework on the causes of malnutrition[5] with the underlying principle to monitor public health problems and guide policy decisions.[6] The NSS was based upon stratified multistage cluster sampling of households in sub-districts of administrative divisions of the country and purposive sampling to target poor households in slum areas of large cities.[4] The NSS in Indonesia involved the collection of data from approximately 10 000 randomly selected slum households every quarter. The NSS involved five major urban slum areas in the cities of Jakarta, Surabaya, Makassar, Semarang, and Padang. New households were selected every round. Data were collected by two-person field teams. A structured coded questionnaire was used to record data on children aged 0—59 months, including anthropometric measurements, date of birth, and sex. The mother of the child or other adult member of the household was asked to provide information on the household's composition, parental education, and weekly household expenditures, along with other socioeconomic, environmental sanitation, and health indicators. The questionnaire inquired about whether the child had diarrhea in the previous week and whether the child currently had diarrhea.

The field teams measured and recorded the weight of each child aged 0—59 months to a precision of 0.1 kg and the length/height to a precision of 0.1 cm. Axillary temperature was recorded for each child. Hemoglobin was measured using a HemoCue instrument (HemoCue AB, Angelholm, Sweden). Birth dates of the children were estimated using a calendar of local and national events and converted to the Gregorian calendar. Z-scores of weight-for-height (wasting), weight-for-age (underweight), and height-for-age (stunting) were calculated using EpiInfo software (Centers for Disease Control and Prevention, Atlanta, GA), which uses the reference population of the US National Center for Health Statistics. Children with Z-scores less than −2 standard deviations (SD) for weight-for-height, weight-for-age, or height-for-age were considered wasted, underweight, or stunted.[7] Severe wasting, underweight, and stunting were defined by respective Z scores less than −3 SD.

HKI provided training to new field teams, field supervisors, and assistant field officers, and refresher training prior to each new round of data collection. During each round, a monitoring team from HKI made unannounced visits to all field sites to check and calibrate the equipment and supervise data collection. A quality control team from HKI revisited 10% of households without prior warning within two days of data collection by the field teams and recollected data on selected indicators, including anthropometric measurements. Data collected by these quality control teams were later compared with the data collected by the field teams to check the accuracy of the data collection. Expenditure and price variables were collected in Indonesian rupiah. For this analysis, expenditures are presented in US $ to control for the fluctuation of the rupiah. Monthly exchange rates from 2000—2003 were established using historic data publicly available through the Bank of Canada.[8] Average exchange rates by data collection round were calculated in Excel (Microsoft Corporation, Seattle, WA, USA) based upon the months in which data were collected for each round. Expenditure and price variables in US $ per round were created and calculated within SPSS using the appropriate exchange rates by round.

The study protocol complied with the principles enunciated in the Helsinki Declaration.[9] The field teams were instructed to explain the purpose of the NSS and data collection to each child's mother or caretaker, and, if present, the father and/or household head; data collection and phlebotomy proceeded only after written informed consent. Participation was voluntary and all subjects were free to withdraw at any stage of the interview. The protocol was approved by the Medical Ethical Committee of the Ministry of Health, Government of Indonesia, and the plan for secondary data analysis was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

This study was limited to children aged 6—59 months of age because the interpretation of low hemoglobin and loose stools in children under age 6 months may be difficult. The physiological anemia of newborns extends through the first three months of life.[10] The interpretation of diarrhea may be questionable in exclusively breastfed infants under six months of age, since these infants have loose stools. Malnutrition in children was defined using criteria of the World Health Organization (WHO) for stunting, underweight, and wasting.[7] Anemia was defined as hemoglobin $<$11 g/dl, according to WHO criteria.[11] In analyses where child malnutrition was the outcome and there was more than one child in the household, the youngest child in the household was used as the index of child malnutrition for that particular household (i.e., households were not counted more than once). Maternal and paternal age was divided into quartiles. Maternal and paternal education was categorized as 0, 1—6 (primary), 7—9 (junior high), and $\geq$10 years (high school or higher). The proportion of mothers and fathers who had achieved more than 12 years (high school graduate) was small and was thus included in the category $\geq$10 years.

Univariate and multivariate logistic regression models were used to examine the relationship between concurrent diarrhea, concurrent fever, and history of diarrhea in the preceding seven days, and the risk of anemia in children in the youngest 6—59 month-old child in the household. Simple and multiple analyses of covariance using linear regression were used to examine the relationship of risk factors with hemoglobin. A value of $p < 0.05$ was considered significant.

Results

The prevalence of anemia among 32 873 children aged 6—59 months was 58.7%. The relationship between hemoglo-

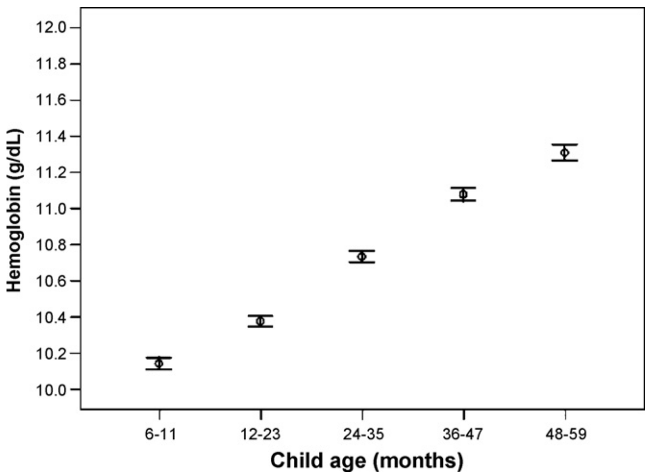

Figure 1 Mean hemoglobin (SE) by age category among children aged 6—59 months in urban slum areas of Indonesia.

bin and age category is shown in Figure 1. In univariate analyses, risk factors that were associated with anemia included younger age, male gender, younger maternal age, lower maternal education, lower paternal education, wasting, underweight, stunting, current diarrhea, current fever, a history of diarrhea in the previous week, and more than four people eating from the same kitchen (Table 1). Mean weekly per capita household expenditure was significantly lower among households with an anemic child than a household without an anemic child.

As shown in Table 2, in a univariate logistic regression model (model 1), current diarrhea was significantly associated with anemia. In a model adjusting for child age, gender, stunting, and mother's age and education (model 2), current diarrhea was significantly associated with anemia. In a final model that adjusted for the previous factors and weekly per capita household expenditure, current diarrhea was associated with anemia (OR 1.20, 95% CI 1.07—1.35, $p = 0.002$). Similar stepwise models were conducted to examine the relationship between current fever and anemia (Table 3). After adjusting for child age, gender, stunting, mother's age and education, and weekly per capita household expenditure, current fever was associated with anemia (OR 1.44, 95% CI 1.18—1.75, $p < 0.0001$). Stepwise models were conducted to examine the relationship between a history of diarrhea the previous week and anemia (Table 4). After adjusting for child age, gender, stunting, mother's age and education, and weekly per capita household expenditure, a history of diarrhea in the previous week

Table 1 Demographic and disease characteristics of children by anemia status

Characteristic	Anemic		Non-anemic		*p*
	n	%	*n*	%	
Child age in months (%)					
6—11	4543	23.5	1646	12.1	0.0001
12—23	6749	35.0	3463	25.5	
24—35	4374	22.7	3503	25.8	
36—47	2468	12.8	3060	22.5	
48—59	1157	6.0	1911	14.1	
Child gender (%)					
Male	10 361	53.7	6793	50.0	0.0001
Female	8930	46.3	6789	50.0	
Maternal age in years (%)					
$\leq$24	5304	27.6	2962	21.8	0.0001
25—28	5140	26.7	3564	26.3	
29—32	4115	21.4	3167	23.3	
33+	4675	24.3	3871	28.5	
Maternal education in years (%)					
0	892	4.6	518	3.8	0.0001
1—6	9030	47.0	5811	42.9	
7—9	4588	23.9	3223	23.8	
$\geq$10	4722	24.6	3987	29.4	
Paternal education in years (%)					
0	405	2.2	200	1.5	0.0001
1—6	6829	36.3	4457	33.6	
7—9	4895	26.0	3319	25.0	
$\geq$10	6679	35.5	5283	39.8	
Weight-for-height Z (WHZ) score (%)					
≥-2	16 713	87.4	12 308	91.7	0.0001
<-2	2410	12.6	1119	8.3	
≥-3	18 892	98.8	13 340	99.3	0.0001
<-3	230	1.2	88	0.7	

Table 1 (*Continued*)

Characteristic	Anemic		Non-anemic		*p*
	n	%	*n*	%	
Weight-for-age Z (WAZ) score (%)					
≥−2	11 215	58.5	8675	64.5	0.0001
<−2	7947	41.5	4780	35.5	
≥−3	17 542	91.6	12 694	94.3	0.0001
<−3	1619	8.4	761	5.7	
Height-for-age Z (HAZ) score (%)					
≥−2	12 639	66.4	9227	68.8	0.0001
<−2	6399	33.6	4180	31.2	
≥−3	17 339	91.1	12 301	91.8	0.03
<−3	1699	8.9	1105	8.2	
Current diarrhea (%)					
No	17 800	92.9	12 832	94.6	0.0001
Yes	1367	7.1	738	5.4	
Current fever (%)					
No	18 454	97.3	13 102	98.3	0.0001
Yes	514	2.7	227	1.7	
History of diarrhea last week (%)					
No	17 006	88.6	12 381	91.3	0.0001
Yes	2183	11.4	1181	8.7	
Weekly per capita household expenditure (US $)[a]	12 485	2.75 (2.71—2.77)	7905	2.86 (2.84—2.89)	0.0001
Number of household members eating from same kitchen (%)					
1—4 people	10 333	53.8	7467	55.3	0.006
>4	8888	46.2	6037	44.7	

[a] Geometric mean (95% CI).

was associated with anemia (OR 1.12, 95% CI 1.03—1.23, $p = 0.024$). Current fever and current diarrhea were also entered in the same multivariate model. After adjusting for child age, gender, stunting, mother's age and education, and weekly per capita household expenditure, current fever (OR 1.42, 95% CI 1.17—1.74, $p = 0.001$) and current diarrhea (OR 1.19, 95% CI 1.06—1.34, $p = 0.004$) were associated with anemia.

Table 2 Univariate and multivariate logistic regression models of current diarrhea as a risk factor for anemia

Variable	OR	95% CI	*p*
Model 1			
Current diarrhea	1.33	1.21—1.46	0.0001
Model 2			
Current diarrhea	1.12	1.02—1.23	0.025
Child age category (months)			
6—11	5.02	4.56—5.52	0.0001
12—23	3.27	3.00—3.56	0.0001
24—35	2.07	1.90—2.25	0.0001
36—47	1.33	1.22—1.46	0.0001
48—59	1.00	—	—
Male gender	1.17	1.12—1.23	0.0001
HAZ <−2	1.31	1.24—1.37	0.0001
Mother's age (years)			
≤24	1.21	1.13—1.29	0.0001
25—28	1.18	1.10—1.26	0.0001
29—32	1.06	0.98—1.13	0.11
33+	1.00	—	—

Table 2 (*Continued*)

Variable	OR	95% CI	*p*
Mother's education (years)			
0	1.65	1.46–1.87	0.0001
1–6	1.44	1.36–1.53	0.0001
7–9	1.23	1.15–1.31	0.0001
10+	1.00	–	–
Model 3			
Current diarrhea	1.20	1.07–1.35	0.002
Child age category (months)			
6–11	4.79	4.28–5.36	0.0001
12–23	3.23	2.91–3.57	0.0001
24–35	2.03	1.83–2.24	0.0001
36–47	1.32	1.17–1.45	0.0001
48–59	1.00	–	–
Male gender	1.17	1.11–1.24	0.0001
HAZ <-2	1.38	1.30–1.46	0.0001
Mother's age (years)			
$\leq$24	1.23	1.14–1.33	0.0001
25–28	1.17	1.08–1.26	0.0001
29–32	1.07	0.99–1.16	0.077
33+	1.00	–	–
Mother's education (years)			
0	1.66	1.43–1.91	0.0001
1–6	1.38	1.29–1.48	0.0001
7–9	1.20	1.11–1.29	0.0001
10+	1.00	–	–
Weekly per capita household expenditure (US $)	0.99	0.99–1.01	0.85

OR, odds ratio; CI, confidence interval; HAZ, height for age Z score.

Discussion

This study demonstrates that current diarrhea, current fever, and a history of diarrhea in the previous week are associated with anemia among children under age five in urban slum areas of Indonesia after controlling for other factors that underlie both diarrhea and fever as well as anemia, such as socioeconomic status and weekly expenditures. These findings suggest that diarrhea and fever may contribute substantially to anemia among young children in developing

Table 3 Univariate and multivariate logistic regression models of current fever as a risk factor for anemia

Variable	OR	95% CI	*p*
Model 1			
Current fever	1.60	1.37–1.88	0.0001
Model 2			
Current fever	1.52	1.28–1.79	0.0001
Child age category (months)			
6–11	4.96	4.50–5.47	0.0001
12–23	3.23	2.96–3.52	0.0001
24–35	2.07	1.89–2.26	0.0001
36–47	1.32	1.15–1.45	0.0001
48–59	1.00	–	–
Male gender	1.18	1.12–1.23	0.0001
HAZ <-2	1.30	1.24–1.37	0.0001
Mother's age (years)			
$\leq$24	4.96	1.13–1.29	0.0001
25–28	1.17	1.09–1.25	0.0001
29–32	1.04	0.98–1.12	0.21
33+	1.00	–	–

Table 3 (*Continued*)

Variable	OR	95% CI	*p*
Mother's education (years)			
0	1.62	1.43–1.83	0.0001
1–6	1.44	1.36–1.52	0.0001
7–9	1.23	1.15–1.31	0.0001
10+	1.00	–	–
Model 3			
Current fever	1.44	1.18–1.75	0.0001
Child age category (months)			
6–11	4.82	4.29–5.41	0.0001
12–23	3.22	2.91–3.57	0.0001
24–35	2.03	1.89–2.25	0.0001
36–47	1.30	1.21–1.45	0.0001
48–59	1.00	–	–
Male gender	1.18	1.12–1.23	0.0001
HAZ <-2	1.30	1.24–1.37	0.0001
Mother's age (years)			
$\leq$24	1.24	1.14–1.34	0.0001
25–28	1.17	1.08–1.26	0.0001
29–32	1.07	0.99–1.15	0.10
33+	1.00	–	–
Mother's education (years)			
0	1.63	1.41–1.89	0.0001
1–6	1.38	1.29–1.47	0.0001
7–9	1.20	1.11–1.29	0.0001
10+	1.00	–	–
Weekly per capita household expenditure (US $)	1.00	0.99–1.01	0.71

OR, odds ratio; CI, confidence interval; HAZ, height for age Z score.

Table 4 Univariate and multivariate logistic regression models of a history of diarrhea in the previous week as a risk factor for anemia

Variable	OR	95% CI	*p*
Model 1			
History of diarrhea	1.35	1.25–1.45	0.0001
Model 2			
History of diarrhea	1.17	1.07–1.27	0.0001
Child age category (months)			
6–11	4.99	4.53–5.50	0.0001
12–23	3.24	2.97–3.53	0.0001
24–35	2.06	1.88–2.24	0.0001
36–47	1.32	1.21–1.46	0.0001
48–59	1.00	–	–
Male gender	1.17	1.12–1.22	0.0001
HAZ <-2	1.31	1.24–1.37	0.0001
Mother's age (years)			
$\leq$24	1.22	1.14–1.30	0.0001
25–28	1.19	1.11–1.27	0.0001
29–32	1.06	0.99–1.13	0.09
33+	1.00	–	–
Mother's education (years)			
0	1.66	1.47–1.88	0.0001
1–6	1.46	1.37–1.54	0.0001
7–9	1.24	1.16–1.32	0.0001

Table 4 (*Continued*)

Variable	OR	95% CI	p
10+	1.00	—	—
Model 3			
History of diarrhea	1.12	1.03—1.23	0.024
Child age category (months)			
6—11	4.80	4.28—5.38	0.0001
12—23	3.22	2.91—3.56	0.0001
24—35	2.01	1.81—2.23	0.0001
36—47	1.30	1.17—1.44	0.0001
48—59	1.00	—	—
Male gender	1.17	1.11—1.23	0.0001
HAZ <-2	1.38	1.30—1.46	0.0001
Mother's age (years)			
$\leq$24	1.24	1.14—1.34	0.0001
25—28	1.18	1.18—1.28	0.0001
29—32	1.08	0.99—1.17	0.06
33+	1.00	—	—
Mother's education (years)			
0	1.67	1.45—1.93	0.0001
1—6	1.40	1.31—1.49	0.0001
7—9	1.21	1.13—1.30	0.0001
10+	1.00	—	—
Weekly per capita household expenditure (US $)	1.00	0.99—1.01	0.89

OR, odds ratio; CI, confidence interval; HAZ, height for age Z score.

countries where malaria is not endemic. Anemia of chronic inflammation has not been well characterized among young children in developing countries, as most studies have focused on iron deficiency anemia[12] or anemia in malaria holoendemic areas.[3] Although iron deficiency accounts for a large proportion of anemia among children, it is notable that supplementation with iron or iron in combination with other micronutrients may reduce only 40—60% of the anemia,[13—15] and a large proportion of the anemia is not responsive to supplementation. It has been unclear in these trials whether or not the anemia that is not responsive to iron or multiple micronutrient supplementation is caused by the anemia of chronic inflammation.

The strengths of this analysis are that it was done using data from a large population-based sample that is representative of households in urban slum areas of Indonesia. The temperature of the children was directly measured. The prevalence of anemia was similar to that reported for children under five years of age of 65% in the Southeast Asia region.[1] The prevalence of anemia among children under five years of age is more than three times higher in Southeast Asia than in the Americas and Europe.[1] A limitation of the data is that indicators of iron status were not measured, and it is possible that some children with fever and diarrhea also had underlying iron deficiency.

Although diarrhea and fever were associated with anemia, the direction of the association cannot be determined in this cross-sectional study. However, a history of diarrhea in the previous week was associated with anemia, and there was at least a temporal placement of an episode of diarrhea prior to the measurement of hemoglobin. However, it cannot be ascertained whether anemia may have preceded or accompanied the episode of diarrhea that was reported in the previous week. A cross-sectional study among Palestinian refugee children showed that a current episode of fever or diarrhea was associated with an increased risk of anemia.[16] One longitudinal study from Israel suggests that anemia is an independent predictor of diarrheal disease.[17] It is also possible that the relationship is circular, with diarrhea increasing the subsequent risk of anemia, and anemia increasing the subsequent risk of diarrhea, in a similar way to the relationship between vitamin A deficiency and diarrheal disease.[18,19]

The anemia of chronic inflammation, also known as the anemia of chronic disease, is commonly associated with infections.[20] The anemia occurs due to underlying inflammation, alterations in iron homeostasis, impaired proliferation of erythroid progenitor cells, blunted erythropoietin response, and decreased erythrocyte half-life.[20] Several proinflammatory cytokines have been implicated in the anemia of chronic inflammation, including interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), and IL-6. Mild viral illness, such as that following immunization with live attenuated measles virus, has been shown to be associated with a decrease in hemoglobin.[21,22] Diarrheal disease is associated with an increase in TNF-α and IL-6, two cytokines that play a role in the anemia of chronic inflammation.[23]

Hepcidin, a peptide hormone, has emerged as the principal regulator of iron metabolism during the anemia of inflammation.[24] Hepcidin is a cysteine-rich peptide found in human plasma and urine[25,26] that is synthesized primarily in the liver.[25—27] Hepcidin regulates iron metabolism by inhibiting duodenal iron absorption at the level of intestinal epithelium.[28] Hepcidin binds to the iron exporter, ferroportin, inducing its internalization and degradation.[29] The synthesis of hepcidin is regulated by iron status, erythropoiesis, hypoxia, and inflammation.[27,30,31] Although it is possible that hepcidin mediates anemia in children with diarrhea and fever, the role of hepcidin in the anemia of inflammation in young children has not been characterized.

Vitamin A deficiency and zinc deficiency could potentially contribute to the anemia of chronic inflammation because of the role these two micronutrients play in maintaining immunity to infectious diseases.[32,33] Diarrheal disease is more common among children with vitamin A deficiency[32] and zinc deficiency,[34] and both micronutrient deficiencies are common in Indonesia.[14]

In conclusion, diarrhea and fever are independently associated with anemia in children under five years of age living in the community in urban slum areas of Indonesia. Further studies are needed to characterize the relative contribution of anemia of chronic inflammation to the overall anemia that occurs among young children. Such studies may provide further insight into anemia among children in Southeast Asia, a region with the highest prevalence of anemia in the world.

Acknowledgements

The NSS was supported by the United States Agency for International Development. This paper was conceived and written independently of the funding agency; the funding agency had no role in the study design, data collection, analysis, interpretation, writing, or decision to submit the manuscript for publication.

Conflict of interest: No conflict of interest to declare.

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