White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of York.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/150213/

Version: Published Version

Article:
Maitland, Kathryn, Olupot-Olupot, Peter, Kiguli, Sarah et al. (2019) Transfusion Volume for Children with Severe and LifeThreatening Anaemia. New England Journal of Medicine. pp. 420-431. ISSN: 1533-4406

https://doi.org/10.1056/NEJMoa1900100

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

UNIVERSITY OF LEEDS
University of Sheffield
UNIVERSITY of York

ORIGINAL ARTICLE

Transfusion Volume for Children with Severe Anemia in Africa

K. Maitland, P. Olupot-Olupot, S. Kiguli, G. Chagaluka, F. Alaroker, R.O. Opoka, A. Mpoya, C. Engoru, J. Nteziyaremye, M. Mallewa, N. Kennedy, M. Nakuya, C. Namayanja, J. Kayaga, S. Uyoga, D. Kyeyune Byabazaire, B. M'baya, B. Wabwire, G. Frost, I. Bates, J.A. Evans, T.N. Williams, P. Saramago Goncalves, E.C. George, D.M. Gibb, and A.S. Walker, for the TRACT Group*

ABSTRACT

BACKGROUND

Severe anemia (hemoglobin level, <6 g per deciliter) is a leading cause of hospital admission and death in children in sub-Saharan Africa. The World Health Organization recommends transfusion of 20 ml of whole-blood equivalent per kilogram of body weight for anemia, regardless of hemoglobin level.

METHODS

In this factorial, open-label trial, we randomly assigned Ugandan and Malawian children 2 months to 12 years of age with a hemoglobin level of less than 6 g per deciliter and severity features (e.g., respiratory distress or reduced consciousness) to receive immediate blood transfusion with 20 ml per kilogram or 30 ml per kilogram. Three other randomized analyses investigated immediate as compared with no immediate transfusion, the administration of postdischarge micronutrients, and postdischarge prophylaxis with trimethoprim–sulfamethoxazole. The primary outcome was 28-day mortality.

RESULTS

A total of 3196 eligible children (median age, 37 months; 2050 [64.1%] with malaria) were assigned to receive a transfusion of 30 ml per kilogram (1598 children) or 20 ml per kilogram (1598 children) and were followed for 180 days. A total of 1592 children (99.6%) in the higher-volume group and 1596 (99.9%) in the lower-volume group started transfusion (median, 1.2 hours after randomization). The mean (±SD) volume of total blood transfused per child was 475±385 ml and 353±348 ml, respectively; 197 children (12.3%) and 300 children (18.8%) in the respective groups received additional transfusions. Overall, 55 children (3.4%) in the higher-volume group and 72 (4.5%) in the lower-volume group died before 28 days (hazard ratio, 0.76; 95% confidence interval [CI], 0.54 to 1.08; P=0.12 by log-rank test). This finding masked significant heterogeneity in 28-day mortality according to the presence or absence of fever (>37.5°C) at screening (P=0.001 after Sidak correction). Among the 1943 children (60.8%) without fever, mortality was lower with a transfusion volume of 30 ml per kilogram than with a volume of 20 ml per kilogram (hazard ratio, 0.43; 95% CI, 0.27 to 0.69). Among the 1253 children (39.2%) with fever, mortality was higher with 30 ml per kilogram than with 20 ml per kilogram (hazard ratio, 1.91; 95% CI, 1.04 to 3.49). There was no evidence of differences between the randomized groups in readmissions, serious adverse events, or hemoglobin recovery at 180 days.

CONCLUSIONS

Overall mortality did not differ between the two transfusion strategies. (Funded by the Medical Research Council and Department for International Development, United Kingdom; TRACT Current Controlled Trials number, ISRCTN84086586.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Maitland at the Department of Medicine, Imperial College London, St. Mary's Campus, Norfolk Pl., London W2 1PG, United Kingdom, or at k.maitland@imperial.ac.uk.

*Members of the TRACT group are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Drs. Maitland, Olupot-Olupot, Kiguli, George, Gibb, and Walker contributed equally to this article.

N Engl J Med 2019;381:420-31.
DOI: 10.1056/NEJMoa1900100
Copyright © 2019 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Severe anemia (hemoglobin level, <6 g per deciliter) is a leading cause of hospitalization and death in children in sub-Saharan Africa.[1-4] The demand for blood transfusion is high, with most transfusions administered to young children and women.[5,6] However, blood donation in most African countries is scarcely adequate; most countries collect fewer than 5 units per 1000 population.[7] World Health Organization (WHO) guidelines, therefore, encourage rational blood use, recommending (on the basis of expert opinion) transfusion only for children with profound anemia (hemoglobin level, <4 g per deciliter) or life-threatening severe anemia (4 to 6 g per deciliter) and a uniform transfusion volume of 20 ml of whole blood or its equivalent per kilogram of body weight,[8] irrespective of hemoglobin level. Outcomes remain unsatisfactory, with high reported in-hospital mortality (9 to 10%)[2,3] and 6-month mortality (12%).[4]

If standard formulae for transfusion volume[9,10] are applied, the one-size-fits-all recommendation of 20 ml per kilogram appears to underestimate transfusion requirements by approximately 30%.[11,12] A consensus guideline on transfusion in critically ill children noted a weak global evidence base and specifically highlighted a need to evaluate transfusion volumes and clinical outcomes.[13] In addition to providing superior correction of anemia, higher transfusion volumes may reduce the need for second transfusions,[11,12] thus saving resources and decreasing the risks associated with receiving blood from multiple donors.

The Transfusion and Treatment of Severe Anemia in African Children Trial (TRACT) investigated four interventions in African children with hemoglobin levels of less than 6 g per deciliter.[14] Here, we report the results comparing the transfusion of 20 ml of whole-blood equivalent per kilogram with the transfusion of 30 ml per kilogram; a companion article from the trial about immediate as compared with no immediate transfusion also appears in this issue of the *Journal*.[15]

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted an open-label, multicenter, factorial, randomized trial at three hospitals in Uganda and one in Malawi. Children 2 months to 12 years of age who had been admitted with severe anemia (hemoglobin level, <6 g per deciliter) were eligible to participate. Children who had known chronic disease (kidney or liver failure, malignant conditions, heart failure, or congenital heart disease) or who had been admitted for burns, trauma, or surgery were excluded, as were children who had already received a transfusion during the primary hospitalization and infants who had been exclusively breast-fed.[14] (For details, see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

In the first stratum, children with complicated severe anemia (a hemoglobin level <4 g per deciliter, reduced consciousness, respiratory distress, acute hemoglobinuria,[16] disclosed sickle cell disease, or a combination of these severity features) were randomly assigned in a 1:1 ratio to receive 30 ml of whole blood per kilogram (15 ml of packed or settled cells per kilogram) or 20 ml of whole blood per kilogram (10 ml of packed or settled cells per kilogram). In the second stratum, children with uncomplicated severe anemia (4 to 6 g per deciliter without signs of severity) were randomly assigned in a 1:1 ratio to immediate transfusion of whole-blood equivalent or no immediate transfusion (until or unless severity criteria were met). The patients in the immediate-transfusion group were then assigned, with the use of a factorial design, to receive either 30 ml per kilogram or 20 ml per kilogram.[15] The groups that were assigned to immediate or no immediate transfusion are reported separately.[15] Here, we do not report the results of randomized analyses of 3 months of postdischarge adjunctive micronutrient supplementation or prophylaxis with trimethoprim–sulfamethoxazole.

Ethics committees at Imperial College London, Makerere University (Kampala, Uganda), and the College of Medicine (Blantyre, Malawi) approved the protocol, which is available at NEJM.org. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol; all the authors contributed to the writing of the manuscript. There was no commercial support for the trial.

SCREENING AND RANDOMIZATION

Children with suspected severe anemia (severe pallor[17]) had hemoglobin measured (with the use of a HemoCue[18] system) and were clinically assessed for severity. Either oral assent with delayed written informed consent[19] or written in-

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

formed consent from the children's parents or guardians was obtained before randomization, which was stratified according to center and severity stratum. Details are provided in the accompanying article by Maitland et al.[15] and in the Methods section in the Supplementary Appendix.

TRIAL PROCEDURES

General clinical management, timing of observation, and blinding are described in Maitland et al.[15] Units of blood were weighed before and after transfusion and administered in burettes with volume markers to ensure an accurate volume.[20] Whole-blood cells were transfused over a period of 3 to 4 hours, and packed or settled cells were transfused over a period of 2 to 3 hours. Blood was not specifically reserved for the trial; enrollment was temporarily suspended if blood became unavailable. Additional transfusions were permitted for new or persistent hemoglobin levels of less than 4 g per deciliter or severity features (see above) if the hemoglobin level remained below 6 g per deciliter. Second transfusions followed the initial randomized volume; children who continued to fulfill the trial criteria received further transfusions of 20 ml of whole-blood equivalent per kilogram.

OUTCOMES

The primary outcome was mortality at 28 days after randomization. Secondary outcomes were mortality at 48 hours, 90 days, and 180 days; the development of new profound anemia (hemoglobin level, <4 g per deciliter) during the primary hospitalization or development of severe anemia (<6 g per deciliter) after discharge; hospital readmission; the percentage of patients with anemia correction (>9 g per deciliter, on the basis of WHO guidelines); suspected transfusion reactions (febrile reactions and transfusion-related acute lung injury); serious adverse events; and cost and cost-effectiveness. Details are provided in the article by Maitland et al.[15]

STATISTICAL ANALYSIS

We determined that the randomization of 2977 children would provide the trial with 80% power to detect a 30% relative difference in 28-day mortality (13.7% in the group receiving 20 ml per kilogram and 9.6% in the group receiving 30 ml per kilogram), assuming that 6% of the children would be lost to follow-up by 6 months (allowing for different primary-outcome timing in other randomizations) and a two-sided alpha level of 0.013 (four comparisons across randomizations). (For details, see the Methods section in the Supplementary Appendix.) Randomized groups were compared on an intention-to-treat basis with the use of log-rank tests or competing-risks methods for time-to-event outcomes, Fisher's exact test for binary outcomes, and generalized estimating equations for repeated measures. Confidence intervals and P values were not adjusted for multiple testing, except for unadjusted heterogeneity P values of less than 0.05 for subgroup analyses, which are reported as Sidak-adjusted values; 16 subgroup analyses were performed. For details regarding meetings of the data monitoring committee and further details of the statistical analysis, see Maitland et al.[15] and the Methods section in the Supplementary Appendix.

RESULTS

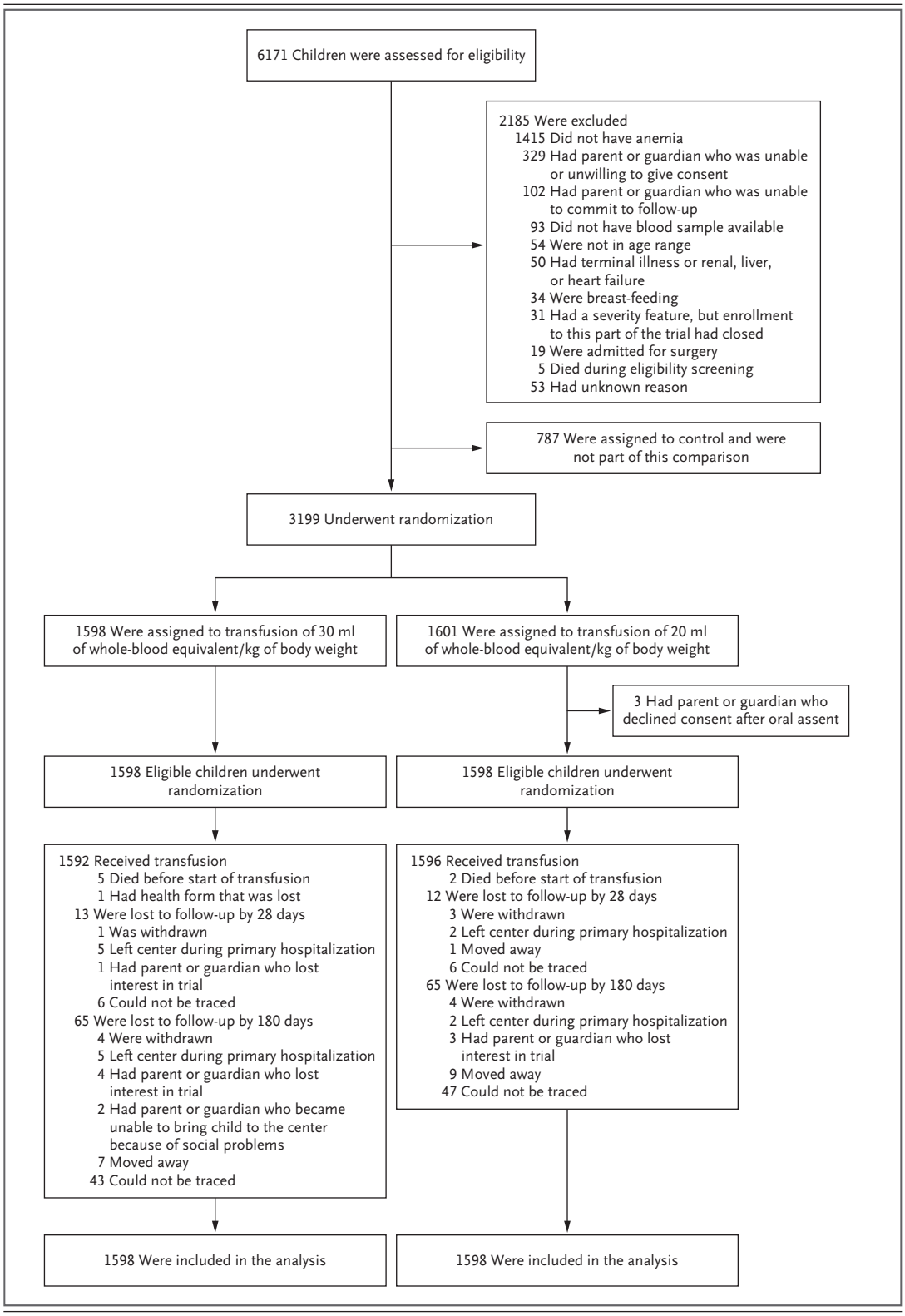
PARTICIPATING CHILDREN

From September 2014 through May 2017, a total of 3199 children with hemoglobin levels of less than 6 g per deciliter were randomly assigned to receive 30 ml of whole-blood equivalent per kilogram or 20 ml of whole-blood equivalent per kilogram; consent was declined for 3 children after oral assent had been obtained, and they were excluded (Fig. 1). Of the 3196 included children, 2418 (75.7%) had a hemoglobin level of less than 4 g per deciliter or severity features; 1137 (35.6%) had two or more severity features. Baseline characteristics were balanced between the randomized groups (Table 1, and Table S1 in

Figure 1 (facing page). Screening, Randomization, and Follow-up.

Severity features of anemia were a hemoglobin level of less than 4 g per deciliter, reduced consciousness, respiratory distress, acute hemoglobinuria, or disclosed sickle cell disease. Data regarding loss to follow-up are presented for 0 to 28 days and 0 to 180 days (i.e., data that were lost by 28 days are a subset of the data lost by 180 days). No screening took place on days when no blood was available for transfusion.

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.



The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Table 1. Characteristics of the Children at Baseline.*

Characteristic	Lower Volume: 20 ml/kg (N=1598)	Higher Volume: 30 ml/kg (N=1598)	Total (N=3196)
Median age (IQR) — mo	37 (18–64)	37 (18–63)	37 (18–64)
Male sex — no. (%)	913 (57.1)	900 (56.3)	1813 (56.7)
Median hemoglobin (IQR) — g/dl	4.3 (3.4–5.2)	4.2 (3.3–5.2)	4.2 (3.4–5.2)
Median weight (IQR) — kg	12 (9–16)	12 (9.2–15.8)	12 (9.1–16.0)
Median heart rate (IQR) — beats/min	147 (131–162)	146 (131–161)	146 (131–161)
Median circumference of mid upper arm (IQR) — cm	14.5 (13.5–15.5)	14.5 (13.5–15.5)	14.5 (13.5–15.5)
History of fever in current illness — no. (%)	1540 (96.4)	1566 (98.0)	3106 (97.2)
Median axillary temperature at screening (IQR) — °C†	37.3 (36.7–38.0)	37.3 (36.7–38.0)	37.3 (36.7–38.0)
Fever — no. (%)	618 (38.7)	635 (39.7)	1253 (39.2)
Hypothermia — no. (%)	67 (4.2)	55 (3.4)	122 (3.8)
Median blood pressure (IQR) — mm Hg			
Systolic	91 (84–98)	92 (83–99)	91 (83–99)
Diastolic	54 (47–61)	54 (47–62)	54 (47–62)
Median oxygen saturation (IQR) — %	97 (95–99)	97 (95–99)	97 (95–99)
Median respiratory rate (IQR) — breaths/min	42 (33–51)	41 (34–52)	41 (34–52)
Shock — no. (%)‡	527 (33.0)	531 (33.2)	1058 (33.1)
Severe dehydration — no. (%)§	120 (7.5)	120 (7.5)	240 (7.5)
HIV positivity — no./total no. (%)	49/1526 (3.2)	49/1520 (3.2)	98/3046 (3.2)
Malaria slide or RDT positivity — no. (%)	1025 (64.1)	1025 (64.1)	2050 (64.1)
Positive blood culture — no./total no. (%)	54/1374 (3.9)	38/1377 (2.8)	92/2751 (3.3)
Median C-reactive protein (IQR) — mg/dl	61.2 (23.3–112.3)	62.4 (24.1–119.5)	61.6 (23.8–114.4)
Median lactate (IQR) — mmol/liter	3.0 (2–4.7)	2.8 (1.9–4.6)	2.9 (1.9–4.7)
Previous blood transfusion in current illness — no. (%)	32 (2.0)	32 (2.0)	64 (2.0)
Blood transfusion ever — no./total no. (%)	586/1583 (37.0)	573/1590 (36.0)	1159/3173 (36.5)
Severity features — no. (%)¶			
Any	1208 (75.6)	1210 (75.7)	2418 (75.7)
Impaired consciousness	373 (23.3)	385 (24.1)	758 (23.7)
Respiratory distress	436 (27.3)	424 (26.5)	860 (26.9)
Hemoglobinuria	300 (18.8)	290 (18.1)	590 (18.5)
Profound anemia	660 (41.3)	682 (42.7)	1342 (42.0)
Reported sickle cell disease	237 (14.8)	226 (14.1)	463 (14.5)
Sickle cell disease ascertained by genotyping — no./total no. (%)‖	440/1579 (27.9)	446/1588 (28.1)	886/3167 (28.0)

* There was no evidence of imbalances in baseline characteristics between the randomized groups (P≥0.06). HIV denotes human immunodeficiency virus, IQR interquartile range, and RDT rapid diagnostic test.
† Axillary temperature was measured with a digital thermometer. Fever was defined as a temperature of more than 37.5°C. Hypothermia was defined as a temperature of less than 36.0°C.
‡ Shock was defined by any of the following: a capillary refill time of more than 2 seconds, temperature gradient, or weak pulse.
§ Severe dehydration was defined as decreased skin turgor, sunken eyes, or both.
¶ Profound anemia was defined as a hemoglobin level of less than 4 g per deciliter. Reported sickle cell disease was defined according to a parental statement at screening.
‖ Sickle cell disease was ascertained by the presence of hemoglobin SS in batch genotyping at Kilifi, Kenya. For detailed results, see Table S1 in the Supplementary Appendix.

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

the Supplementary Appendix). The median age was 37 months (interquartile range, 18 to 64). A history of fever was very common (3106 of 3196 children [97.2%]), and a documented temperature of more than 37.5°C (1253 of 3196 [39.2%]) and shock (1058 of 3196 [33.1%]) at screening were common. *Plasmodium falciparum* malaria was present in 2050 children (64.1%), but human immunodeficiency virus (HIV) infection, culture-proven bacteremia, and severe malnutrition were found in less than 4% of the children. The number of children with sickle cell disease increased from 463 (14.5%) (reported) to 886 (27.7%) (actual) after batch genotyping.

RANDOMIZED INTERVENTIONS

A total of 1592 children (99.6%) who were assigned to receive 30 ml per kilogram and 1596 (99.9%) who were assigned to 20 ml per kilogram started transfusion, both at a median of 1.2 hours (interquartile range, 0.9 to 1.7) after randomization. First transfusions were within 3 ml per kilogram of the randomized volume in 1525 of 1592 children (95.8%) in the higher-volume group and in 1551 of 1596 (97.2%) in the lower-volume group and were infused over a median of 2.9 hours (interquartile range, 2.1 to 4.0) and 2.6 hours (interquartile range, 2.1 to 3.9), respectively. First transfusions were stopped for reactions in 17 of 1592 children (1.1%) in the higher-volume group and in 10 of 1596 (0.6%) in the lower-volume group. First transfusions were whole blood in 700 of 1592 children (44.0%) in the higher-volume group and in 703 of 1596 (44.0%) in the lower-volume group; the median hemoglobin level of the donor unit was 16.4 g per deciliter (interquartile range, 13.8 to 19.2), and the median blood storage time was 12 days (interquartile range, 6 to 19) (Table S2 and Fig. S1 in the Supplementary Appendix).

A further transfusion or transfusions occurred in 197 of 1592 children (12.4%) in the higher-volume group and in 300 of 1596 (18.8%) in the lower-volume group (absolute difference, 6.4 percentage points; 95% confidence interval [CI], 3.9 to 8.9) (Fig. S2 in the Supplementary Appendix); the randomized volume strategy was followed in 1841 of 1914 transfusions (96.2%) in the higher-volume group and in 2024 of 2074 (97.6%) in the lower-volume group. During the primary hospitalization, the mean (±SD) volume of whole-blood equivalent was 475±385 ml in the higher-volume group and 353±348 ml in the lower-volume group. Overall, similar numbers of units of blood were used (mean units, 1.47±1.03 in the higher-volume group and 1.46±1.12 in the lower-volume group) (Table S3 in the Supplementary Appendix).

HEMOGLOBIN RECOVERY

The hemoglobin level increased more at 48 hours among children receiving 30 ml per kilogram than among those receiving 20 ml per kilogram (mean difference, 0.99 g per deciliter; 95% CI, 0.80 to 1.18) (Fig. S3A in the Supplementary Appendix). Similarly, hemoglobin recovery to more than 9 g per deciliter occurred faster with 30 ml per kilogram, and a new hemoglobin level of less than 4 g per deciliter occurred less frequently (Table 2, and Fig. S3B through S3E in the Supplementary Appendix). However, from day 28 through day 180, there was no evidence of differences in hemoglobin level between the two groups (Fig. S3A and S3B in the Supplementary Appendix).

MORTALITY

Vital status at day 28 (primary outcome) was unknown for 13 children (0.8%) assigned to receive 30 ml per kilogram and 12 (0.8%) assigned to receive 20 ml per kilogram and at day 180 for 65 children (4.1%) in each group. There was no evidence of differences in mortality between the two groups at day 28 — at which time 55 children (3.4%) in the higher-volume group and 72 (4.5%) in the lower-volume group had died (hazard ratio, 0.76; 95% CI, 0.54 to 1.08; P=0.12 by log-rank test) (Fig. 2A) — or at day 180 (Table 2). There was no evidence of interaction with other factorial randomizations to postdischarge micronutrients (unadjusted P=0.73) or trimethoprim–sulfamethoxazole (P=0.12) or with severity strata (P=0.09). No cause could be assigned in 145 of 288 deaths, primarily because these deaths occurred outside the hospital or insufficient information was available (Table S4 in the Supplementary Appendix). Specific infections were the most commonly assigned primary cause of death (in 51 children [17.7%]), followed by hematologic conditions (in 45 [15.6%]) and pneumonia (in 22 [7.6%]).

Of the 10 subgroup analyses that were prespecified in the protocol and 6 additional analyses that were prespecified in the statistical analysis plan (available with the protocol at

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Higher Volume: 30 ml/kg (N=1598)	Lower Volume: 20 ml/kg (N=1598)	Total (N=3196)	Hazard Ratio (95% CI)†	P Value
Death — no. (%)					
At 48 hr‡	32 (2.0)	34 (2.1)	66 (2.1)	0.94 (0.58–1.52)	
At 28 days: primary outcome	55 (3.4)	72 (4.5)	127 (4.0)	0.76 (0.54–1.08)	0.12
At 90 days‡	93 (5.8)	114 (7.1)	207 (6.5)	0.81 (0.61–1.06)	
At 180 days‡	134 (8.4)	154 (9.6)	288 (9.0)	0.86 (0.68–1.08)	
Correction of anemia during the primary hospitalization — no. (%)‡	678 (42.4)	349 (21.8)	1027 (32.1)	2.13 (1.89–2.41)§	
Development of new profound anemia during the primary hospitalization — no. (%)‡	40 (2.5)	85 (5.3)	125 (3.9)	0.47 (0.32–0.68)§	
Development of severe anemia after discharge — no. (%)‡	338 (21.2)	303 (19.0)	641 (20.1)	1.10 (0.94–1.28)§	
Readmission to hospital — no. (%)‡	301 (18.8)	278 (17.4)	579 (18.1)	1.08 (0.92–1.27)§	
Serious adverse event					
At least one event — no. of patients (%)‡	431 (27.0)	416 (26.0)	847 (26.5)	1.03 (0.90–1.18)	0.63
No. of events	608	544	1152		
Type of serious adverse event					
Anemia¶					
At least one event — no. of patients (%)	230 (14.4)	224 (14.0)	454 (14.2)		0.80‖
No. of events	323	292	615		
Malaria					
At least one event — no. of patients (%)	129 (8.1)	108 (6.8)	237 (7.4)		0.18‖
No. of events	149	119	268		
Sepsis					
At least one event — no. of patients (%)	67 (4.2)	78 (4.9)	145 (4.5)		0.40‖
No. of events	85	95	180		
Hemoglobinuria					
At least one event — no. of patients (%)	52 (3.3)	44 (2.8)	96 (3.0)		0.39‖
No. of events	64	51	115		
Suspected allergic reaction — no. (%)‡**	25 (1.6)	20 (1.3)	45 (1.4)		0.55‖
Suspected transfusion-related lung injury — no. (%)‡**	2 (0.1)	3 (0.2)	5 (0.2)		1.00‖
Suspected raised intracranial pressure — no. (%)**	1 (0.1)	0	1 (<0.1)		

* Correction of anemia was defined as a hemoglobin level of more than 9 g per deciliter. Profound anemia was defined as a hemoglobin level of less than 4 g per deciliter. Severe anemia was defined as a hemoglobin level of less than 6 g per deciliter. Suspected transfusion-related lung injury refers to suspected pulmonary overload, transfusion-related acute lung injury, or transfusion-related cardiac overload. CI denotes confidence interval.

† Hazard ratios are for the higher-volume group as compared with the lower-volume group. Confidence intervals have not been adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible.

‡ This is a secondary outcome that was prespecified in the protocol. The P value is not reported except for adverse events.

§ This hazard ratio was estimated from competing-risks subhazard regression.

¶ The diagnosis of the serious adverse event of anemia (including anemia-related death) was made by the attending clinician (during the primary hospitalization and after discharge). There was no formal hemoglobin threshold required.

‖ This P value was calculated with Fisher's exact test.

** Grades of adverse events are shown in Table S9 in the Supplementary Appendix.

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

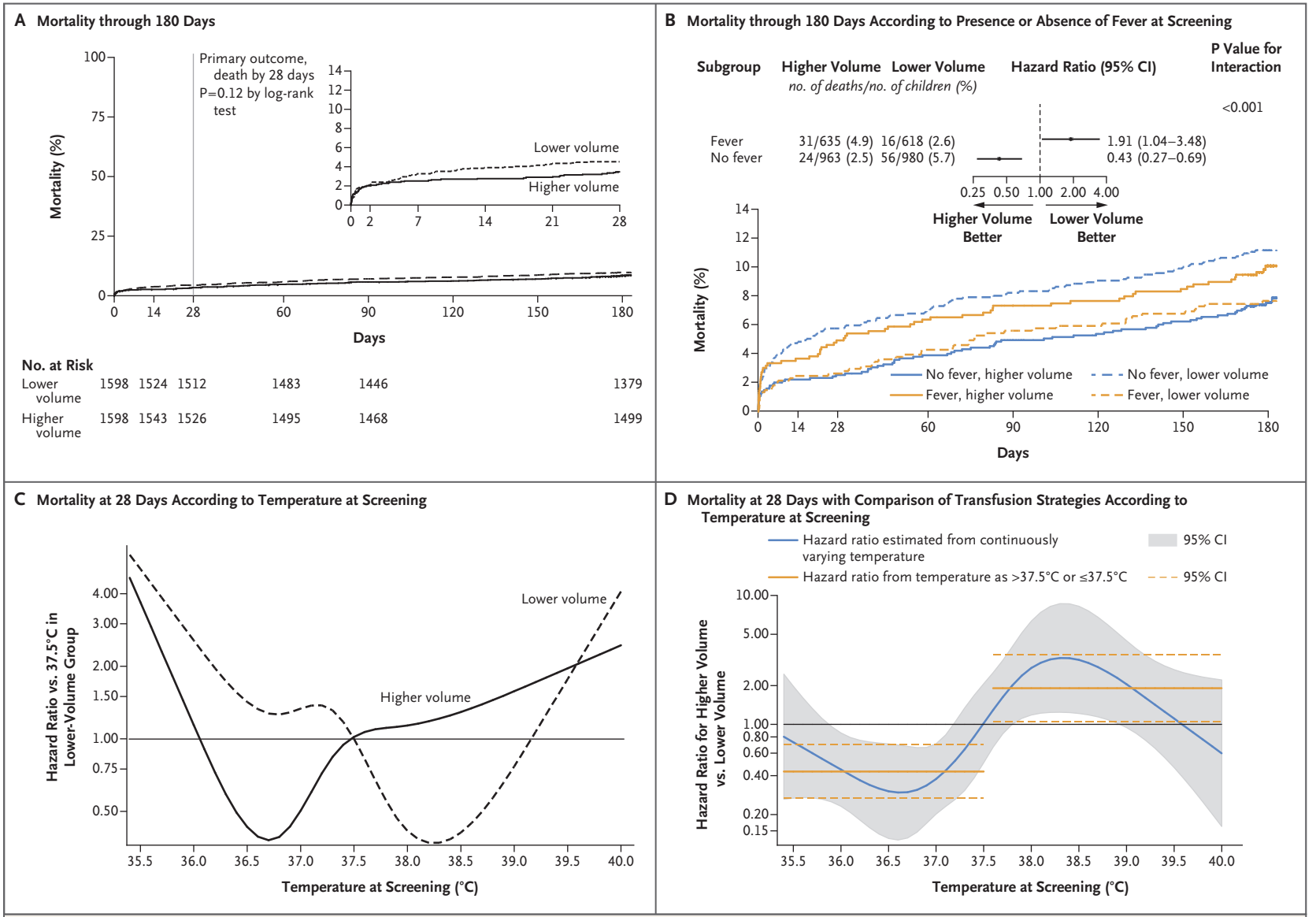


Figure 2. Mortality through 180 Days and at 28 Days.

The lower-volume group was assigned to receive 20 ml of whole-blood equivalent per kilogram, and the higher-volume group was assigned to receive 30 ml of whole-blood equivalent per kilogram. The window for the 180-day visit was defined as 120 to 240 days after randomization.

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

NEJM.org), one (fever [>35°C] vs. no fever at screening, prespecified in the protocol) showed substantial heterogeneity with respect to 28-day mortality (Sidak-adjusted P=0.001; unadjusted P>0.08 for other comparisons) (Fig. 2B, and Figs. S4 and S5 in the Supplementary Appendix). In 1943 children (60.8%) with a body temperature of 37.5°C or less at screening, 24 of 963 (2.5%) in the higher-volume group and 56 of 980 (5.7%) in the lower-volume group died by 28 days (hazard ratio, 0.43; 95% CI, 0.27 to 0.69). In contrast, in 1253 children (39.2%) with fever at screening, 31 of 635 (4.9%) in the higher-volume group and 16 of 618 (2.6%) in the lower-volume group died by 28 days (hazard ratio, 1.91; 95% CI, 1.04 to 3.49).

With respect to the actual temperature at screening (rather than the prespecified dichotomization at 37.5°C), the risk of death was high in both groups at very low and very high temperatures (Fig. 2C). However, in the higher-volume group, the risk of death dropped more quickly as the temperature increased to 37.5°C before rising substantially, which led to almost equal and opposite benefits and risks from the two strategies, depending on the temperature being above or no more than 37.5°C (Fig. 2D). As expected, there were some modest differences between children with fever and those without fever at screening in baseline characteristics (Table S5 in the Supplementary Appendix), but the receipt of other interventions was similar (Table S6 in the Supplementary Appendix). There was no evidence of heterogeneity in five additional exploratory subgroup analyses (unadjusted P>0.2 for all comparisons) (Fig. S6 in the Supplementary Appendix), nor was there heterogeneity according to the temperature 30 minutes after transfusion, when other treatments (including antipyretics) had also been initiated (unadjusted P=0.10). When temperature at screening and 30 minutes after transfusion were considered, higher temperatures at screening drove different treatment effects (Table S7 in the Supplementary Appendix). Heterogeneity according to the presence or absence of fever persisted even after adjustment for a weak interaction with C-reactive protein levels (see the Results section in the Supplementary Appendix).

Heterogeneity according to the presence or absence of fever was already evident in mortality at 48 hours (Sidak-adjusted P=0.05) and persisted through day 180 (Sidak-adjusted P=0.06), with no strong evidence implicating any specific cause (Fig. S7 in the Supplementary Appendix). Temperatures differed substantially between children with fever and those without fever at screening for 8 hours after randomization (Fig. S8 in the Supplementary Appendix). Recovery of hemoglobin level, heart rate, and respiratory rate occurred similarly in children with fever and those without fever (Fig. S9 in the Supplementary Appendix).

SECONDARY CLINICAL OUTCOMES TO 180 DAYS

Children spent a median of 4 days (interquartile range, 3 to 5) in the hospital in the two groups, but the time until discharge was shorter in the group receiving 30 ml per kilogram than in the group receiving 20 ml per kilogram (hazard ratio, 1.12; 95% CI, 1.04 to 1.20) (Fig. S10 in the Supplementary Appendix), with a mean length of stay of 4.7 days in the higher-volume group and 4.9 days in the lower-volume group. Readmission within 180 days occurred in 301 children (18.8%) in the higher-volume group and in 278 (17.4%) in the lower-volume group (hazard ratio, 1.08; 95% CI, 0.92 to 1.27) (Fig. S11 in the Supplementary Appendix), with no evidence of heterogeneity according to the presence or absence of fever at screening (unadjusted P=0.78) (Fig. S7 in the Supplementary Appendix).

One or more serious adverse events occurred in 431 children (27.0%) in the higher-volume group and in 416 (26.0%) in the lower-volume group (P=0.63) (Table 2, and Table S8 in the Supplementary Appendix), with no evidence of differences between the two groups in serious adverse events related to anemia, malaria, sepsis, or hemoglobinuria (P>0.15 for all comparisons). Allergic reactions occurred in 25 children (1.6%) in the higher-volume group and in 20 (1.3%) in the lower-volume group (P=0.55); there were no fatal reactions (Table S9 in the Supplementary Appendix). Suspected pulmonary or cardiovascular serious adverse events occurred in 2 children (0.1%) in the higher-volume group and in 3 (0.2%) in the lower-volume group (P=1.00); there were 2 deaths from pulmonary or cardiovascular causes. A neurologic (grade 3) serious adverse event occurred in 1 child in the higher-volume group.

COSTS AND COST-EFFECTIVENESS

The main cost drivers were hospital length of stay (mean, $33.38 [U.S. dollars] in children re-

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

ceiving 30 ml per kilogram and $32.59 in children receiving 20 ml per kilogram), blood transfusions (mean, $25.18 and $27.26, respectively), and hemoglobin tests (mean, $8.53 and $8.46, respectively), resulting in total costs per child of $80.62 in the higher-volume group and $81.97 in the lower-volume group (Tables S10 through S12 in the Supplementary Appendix). Life-years gained over a period of 180 days were slightly higher in the group receiving 30 ml (0.473) than in the group receiving 20 ml per kilogram (0.466). Overall, a transfusion volume of 30 ml per kilogram appeared to offer additional benefits, at an increased cost of $87 per life-year gained through 180 days (adjusted model) (Table S13 in the Supplementary Appendix). However, for the subgroup without fever at screening, costs per life-year gained were reduced to $20 per life-year gained, whereas for the subgroup with fever at screening, a transfusion volume of 30 ml per kilogram was less costly but also less effective than a volume of 20 ml per kilogram. (Results of regression and sensitivity analyses are provided in the Results section in the Supplementary Appendix.)

28-DAY MORTALITY

Key predictors of death by 28 days were clinical severity features, including the Blantyre coma score and convulsions (Table 3). A lower oxygen saturation, a higher respiratory rate, and a higher lactate level were also associated with increased mortality. Malaria infection reduced the risk of death, whereas HIV infection and AB blood group increased the risk. There was no evidence of association between 28-day mortality and the characteristics of the blood used (the hemoglobin level of the donor unit, the type of blood unit transfused [hazard ratio for whole blood vs. packed or settled cells, 1.18; 95% CI, 0.78 to 1.78], or the duration of storage) or the presence of sickle cell disease. Results were broadly similar at 180 days (see the Results section and Table S14 in the Supplementary Appendix).

Table 3. Predictors of Death at 28 Days after Blood Transfusion in Children with a Hemoglobin Level of Less Than 6 g per Deciliter.

Factor at Randomization	Hazard Ratio (95% CI) from Multivariable Model*
Malaria	0.52 (0.34–0.78)
Higher oxygen saturation	0.91 (0.88–0.94)†
Higher respiratory rate	1.03 (1.01–1.04)‡
Higher lactate level	1.09 (1.04–1.15)§
HIV positivity	2.58 (1.32–5.05)
Convulsions in current illness	1.87 (1.05–3.33)
Blantyre coma score¶	
5	1.00
4	0.83 (0.31–2.17)
3	2.19 (0.97–4.95)
2	2.48 (1.22–5.05)
1	3.29 (0.97–12.5)
0	3.21 (1.04–9.89)
Blood type	
O	1.00
A	1.03 (0.64–1.68)
B	0.74 (0.43–1.27)
AB	2.59 (1.41–4.78)

* Estimates were adjusted for randomized comparison, continuous variation in temperature, and the interaction between the two with the use of natural cubic splines (details in the Supplementary Appendix).
† Shown is the hazard ratio for each increment of 1% in oxygen saturation.
‡ Shown is the hazard ratio for each increment of 1 breath per minute in the respiratory rate.
§ Shown is the hazard ratio for each increment of 1 mmol per liter in the lactate level.
¶ The Blantyre coma scale is used to assess malarial coma in children. Scores range from 0 to 5, with lower scores indicating lower levels of consciousness.

DISCUSSION

In this large, multicenter trial involving children with severe anemia, we observed no overall evidence of differences in mortality at 48 hours, 28 days, or 180 days between those receiving a transfusion volume approximately one third higher than recommended (30 ml per kilogram) and those receiving the recommended volume (20 ml per kilogram). By 48 hours, the higher-volume group had superior correction of anemia (to >9 g per deciliter), less development or redevelopment of profound anemia, and fewer additional transfusions. Nevertheless, by day 28, hemoglobin levels were similar in the two groups, and the two strategies used similar numbers of units of blood per child overall.

The overall results obscure an important and potentially unusually strong interaction with fever, which meets six of nine relevant criteria proposed to assess credibility of subgroup findings.[21] Among the majority of children who did not have fever at admission, 28-day mortality with a transfusion volume of 30 ml per kilogram was less than half that with a transfusion volume

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

of 20 ml per kilogram, a finding consistent with the hypothesis of the trial. This difference occurred soon after randomization and persisted, at a cost of $20 per life-year gained, falling well within recently published cost-effectiveness thresholds for Uganda and Malawi.[22] Because 6 to 15% of children who are admitted to African hospitals have severe anemia,[2,3] a transfusion strategy of 30 ml per kilogram may have substantial implications for improving outcome for the two thirds who are hospitalized with anemia but without documented fever.

Conversely, among the one third of children with fever (>37.5°C) at screening, 28-day mortality with a transfusion volume of 30 ml per kilogram was nearly twice as high as that with a transfusion volume of 20 ml per kilogram. In contrast, underlying disease (e.g., malaria and sickle cell disease) and physiological characteristics (e.g., shock, oxygen saturation, heart rate, and lactate level) did not affect differences between the two groups, nor did differences in these characteristics or in C-reactive protein levels explain the differential effect according to the presence or absence of fever. Although 97.2% of the children had a history of fever, children who were febrile at screening remained febrile through 8 hours, whereas nonfebrile children remained afebrile, which indicates that this measurement was not an isolated one.

One explanation for this finding could be the time course of intercurrent illness. Neither the length of illness nor referral from another health facility affected the response to the transfusion volume. However, in a post hoc analysis, effects of 30 ml per kilogram were strongest in children who received a transfusion within 2.5 hours after admission (Table S15 in the Supplementary Appendix). Alterations in the hemoglobin dissociation curve with fever could alter the balance between risks and benefits from 30 ml as compared with 20 ml per kilogram; however, the mechanism for harm with a higher transfusion volume in children with fever remains unclear. We are exploring several hypotheses related to infection, including altered iron metabolism. Further research is needed to understand how temperature might affect the risk–benefit ratio of transfusion volume. We observed few transfusion-related adverse events nor cases of pulmonary or cardiovascular overload with 30 ml per kilogram.

It is important that neither the use of whole blood (44% of units transfused) nor longer storage age of (non–leukocyte-reduced) donor blood adversely affected 28-day or 180-day mortality. Thus, component preparation, recently introduced to blood-transfusion services in sub-Saharan Africa at substantial cost, does not appear to be essential for safe transfusion practice.

Strengths of the trial include broad eligibility criteria, which enhance generalizability, and high adherence to the randomized strategy and follow-up (>95%). The enrollment of large subgroups of children with malaria and sickle cell disease should ensure relevance across Africa. An important limitation is that mortality was lower than anticipated, probably because of the consistent standard of care provided by trial staff and the pausing of recruitment when blood was unavailable. However, the trial retained high power to identify effects on hospital readmissions (18% by day 180). The trial was open-label, by necessity; although adherence to thresholds for retransfusion was high, we cannot rule out the possibility that knowledge of group assignment influenced retransfusion for some children. Substantial uncertainty exists regarding costs of units of blood (which vary according to country), unit size and type, and hemoglobin testing and monitoring during the hospitalization. The economic analysis does not capture longer-term mortality benefits, which could increase the cost-effectiveness (value for money) of 30 ml per kilogram in children without fever. Further implementation research is required to estimate cost savings from providing whole blood rather than packed or settled cells and to evaluate practical approaches to giving 30 ml per kilogram to children without fever and 20 ml per kilogram to children with fever in real-world settings.

In conclusion, overall mortality did not differ between the two transfusion strategies. Among afebrile children, a transfusion volume of 30 ml of whole-blood equivalent per kilogram resulted in lower mortality and lower rates of re-transfusion than current recommendations of 20 ml per kilogram. However, higher transfusion volume was associated with higher mortality among febrile children.

The views expressed are those of the authors and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Supported by a grant (MR/J012483/1) from the U.K. Medical Research Council (MRC) through a concordat with the Department for International Development. Cipla donated the trimethoprim–sulfamethoxazole for the trial. The MRC Clinical Trials Unit at University College London receives core support from the MRC (MC_UU_12023/26) through a concordat with the Department for International Development. Dr. Williams holds a Wellcome Senior Research Fellowship (202800/Z/16/Z). Dr. Walker is a National Institute for Health Research Senior Investigator.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the children and staff members from all the centers who participated in the trial.

APPENDIX

The authors' full names and academic degrees are as follows: Kathryn Maitland, M.D., Ph.D., Peter Olupot-Olupot, M.B., Ch.B., Ph.D., Sarah Kiguli, M.B., Ch.B., M.Med., George Chagaluka, M.D., Florence Alaroker, M.B., Ch.B., M.Med., Robert O. Opoka, M.B., Ch.B., M.Med., Ayub Mpoya, M.Sc., Charles Engoru, M.B., Ch.B., M.Med., Julius Nteziyaremye, M.B., Ch.B., Macpherson Mallewa, M.R.C.P.C.H., Ph.D., Neil Kennedy, M.D., Margaret Nakuya, M.B., Ch.B., Cate Namayanja, M.B., Ch.B., Julianna Kayaga, M.B., Ch.B., Sophie Uyoga, Ph.D., Dorothy Kyeyune Byabazaire, M.B., Ch.B., D.T.M., Bridon M'baya, M.P.H., Benjamin Wabwire, M.B., Ch.B., D.T.M., Gary Frost, Ph.D., R.D., Imelda Bates, M.D., Ph.D., Jennifer A. Evans, M.D., Thomas N. Williams, M.D., Ph.D., Pedro Saramago Goncalves, Ph.D., Elizabeth C. George, Ph.D., Diana M. Gibb, M.D., and A. Sarah Walker, Ph.D.

The authors' affiliations are as follows: the Department of Medicine (K.M., T.N.W.) and Nutrition Research Section (G.F.), Imperial College London, and the Medical Research Council Clinical Trials Unit at University College London (E.C.G., D.M.G., A.S.W.), London, the School of Medicine, Dentistry, and Biomedical Science, Queen's University, Belfast (N.K.), the Liverpool School of Tropical Medicine and Hygiene, Liverpool (I.B.), the Department of Pediatrics, University Hospital of Wales, Cardiff (J.A.E.), and the Centre for Health Economics, University of York, York (P.S.G.) — all in the United Kingdom; Busitema University Faculty of Health Sciences, Mbale Campus, Mbale Regional Referral Hospital (P.O.-O., J.N., C.N.), and the Mbale Blood Transfusion Services (B.W.), Mbale, the Department of Pediatrics, Makerere University and Mulago Hospital (S.K., R.O.O., J.K.), and the Uganda Blood Transfusion Services, National Blood Transfusion Services (D.K.B.), Kampala, and Soroti Regional Referral Hospital, Soroti (F.A., C.E., M.N.) — all in Uganda; the Kenya Medical Research Institute–Wellcome Trust Research Program, Kilifi (K.M., A.M., S.U., T.N.W.); and the College of Medicine and the Malawi–Liverpool–Wellcome Trust Clinical Research Program (G.C., M.M., N.K.) and the Malawi Blood Transfusion Services (B.M.) — all in Blantyre, Malawi.

REFERENCES

1. Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Glob Health 2013;1(1):e16-e25.
2. Pedro R, Akech S, Fegan G, Maitland K. Changing trends in blood transfusion in children and neonates admitted in Kilifi District Hospital, Kenya. Malar J 2010;9:307.
3. Calis JC, Phiri KS, Faragher EB, et al. Severe anemia in Malawian children. N Engl J Med 2008;358:888-99.
4. Phiri KS, Calis JC, Faragher B, et al. Long term outcome of severe anaemia in Malawian children. PLoS One 2008;3(8):e2903.
5. Ala F, Allain JP, Bates I, et al. External financial aid to blood transfusion services in sub-Saharan Africa: a need for reflection. PLoS Med 2012;9(9):e1001309.
6. Bates I, Chapotera GK, McKew S, van den Broek N. Maternal mortality in sub-Saharan Africa: the contribution of ineffective blood transfusion services. BJOG 2008;115:1331-9.
7. Global status report on blood safety and availability 2016. Geneva: World Health Organization, 2017 (https://apps.who.int/iris/bitstream/handle/10665/254987/1/9789241565431-eng.pdf).
8. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. 2nd ed. Geneva: World Health Organization, 2013 (https://apps.who.int/iris/bitstream/handle/10665/81170/1/9789241548373_eng.pdf).
9. Walker RH. Mathematical calculations in transfusion medicine. Clin Lab Med 1996;16:895-906.
10. Morris KP, Naqvi N, Davies P, Smith M, Lee PW. A new formula for blood transfusion volume in the critically ill. Arch Dis Child 2005;90:724-8.
11. Olupot-Olupot P, Engoru C, Thompson J, et al. Phase II trial of standard versus increased transfusion volume in Ugandan children with acute severe anemia. BMC Med 2014;12:67.
12. Kiguli S, Maitland K, George EC, et al. Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness. BMC Med 2015;13:21.
13. Doctor A, Cholette JM, Remy KE, et al. Recommendations on RBC transfusion in general critically ill children based on hemoglobin and/or physiologic thresholds from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatr Crit Care Med 2018;19:Suppl 1:S98-S113.
14. Mpoya A, Kiguli S, Olupot-Olupot P, et al. Transfusion and treatment of severe anaemia in African children (TRACT): a study protocol for a randomised controlled trial. Trials 2015;16:593.
15. Maitland K, Kiguli S, Olupot-Olupot P, et al. Immediate transfusion in African children with uncomplicated severe anemia. N Engl J Med 2019;381:407-19.
16. Olupot-Olupot P, Engoru C, Uyoga S, et al. High frequency of blackwater fever among children presenting to hospital with severe febrile illnesses in eastern Uganda. Clin Infect Dis 2017;64:939-46.
17. Olupot-Olupot P, Prevatt N, Engoru C, et al. Evaluation of the diagnostic accuracy and cost of different methods for the assessment of severe anaemia in hospitalised children in eastern Uganda. Wellcome Open Res 2019;3:130.
18. Medina Lara A, Mundy C, Kandulu J, Chisuwo L, Bates I. Evaluation and costs of different haemoglobin methods for use in district hospitals in Malawi. J Clin Pathol 2005;58:56-60.
19. Maitland K, Molyneux S, Boga M, Kiguli S, Lang T. Use of deferred consent for severely ill children in a multi-centre phase III trial. Trials 2011;12:90.
20. Uyoga S, Mpoya A, Olupot-Olupot P, et al. Haematological quality and age of donor blood issued for paediatric transfusion to four hospitals in sub-Saharan Africa. Vox Sang 2019;114:340-8.
21. Sun X, Briel M, Busse JW, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. BMJ 2012;344:e1553.
22. Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. Value Health 2016;19:929-35.

Copyright © 2019 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org by Lucy Cook on August 29, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.