Twenty-thousand adults with hemorrhage from blunt or penetrating injury were enrolled; 15% died and there was slightly lower all-cause mortality and death from bleeding in the intervention group. In both treatment groups, about 50% of participants received at least one blood transfusion, receiving a mean of 6 units of blood. Trauma resuscitation may be another indication where the transfusion of whole blood is acceptable when this is the only product available. Studies are ongoing into the benefits of tranexamic acid to reduce transfusion needs after trauma, and of course, prevention of these injuries through road safety campaigns and violence prevention are paramount.

### Transfusion Thresholds

An additional approach to reducing transfusion utilization overall is to ensure transfusions are administered only when absolutely necessary. Transfusion thresholds recommended by WHO are lower than commonly used in HICs: less than 7 g/dL in symptomatic adults, including pregnant women, and less than 4 g/dL in children. In children with hypoxia, acidosis, or impaired consciousness, transfusion is considered at slightly higher hemoglobin levels, between 4 and 6 g/dL.[29] Adhering to these guidelines, however, assumes a hemoglobin level is checked before a transfusion rather than relying on pallor or other components of the history and physical exam, which are often unreliable. A retrospective review of pediatric wards in Uganda found that hemoglobin was not checked before 38% of transfusions.[30] This may reflect provider differences in knowledge of or trust in the guidelines, clinical severity necessitating immediate transfusion, or shortage of reagents to check a hemoglobin level or complete blood count.

## Blood Transfusions for Sickle Cell Disease

In addition to malaria and iron deficiency, SCD may be a third significant contributor to severe childhood anemia, and one that is currently unrecognized and largely unaddressed. People with SCD must be identified and treated to decrease mortality and to decrease the demand for preventable transfusions across sub-Saharan Africa.

## Mechanisms of Anemia

SCD refers to a group of inherited disorders of red cells in which the hemoglobin molecules polymerize to create erythrocytes that become sickle-shaped under deoxygenated conditions. This leads to rigid erythrocytes that are prone to intravascular and extravascular hemolysis; accordingly, chronic anemia is a common feature of SCD, especially the most common and severe form, homozygous hemoglobin SS (HbSS). Affected individuals do not require transfusions while in their steady state of partially compensated hemolytic anemia, but develop worsening anemia through several major mechanisms, including 1) acute splenic sequestration, a hemodynamically significant event in which blood enters the spleen but is unable to exit because of obstruction of splenic venules, causing severe anemia, thrombocytopenia, and hypovolemic shock; 2) transient aplastic crisis, caused by abrupt erythrocyte aplasia in the setting of parvovirus or other viral infections, with progressive anemia due to lack of compensatory reticulocytosis; and 3) hyperhemolysis due to infections, including malaria, and worsened by dehydration, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other triggers that tip these already anemic patients into an uncompensated hemodynamic state.

## SCD Transfusion Utilization

According to the United Nations, of the estimated 25 million people worldwide living with SCD, 12 to 15 million of them live in sub-Saharan Africa and contribute significantly to transfusion utilization in this region.[31,32] In one systematic review, 18% of blood transfusion recipients of all ages in sub-Saharan Africa had known SCD.[6] In addition, emerging evidence confirms that a significant proportion of blood transfusions are given to children with undiagnosed SCD. As a result of a lack of newborn or universal screening for SCD, many children with SCD in sub-Saharan Africa can live years without being diagnosed properly and may die without an established diagnosis. The Transfusion and Treatment of Severe Anemia in African Children Trial (TRACT; ISRCTN84086586) was a randomized controlled trial evaluating transfusion volumes and timing in children with severe anemia in Uganda and Malawi.[4,20] Children with known SCD were excluded from one arm of the study, and their enrollment was capped at 25% in another arm. Nonetheless, 20% of anemic children

requiring blood transfusions in the study were subsequently found to have previously undiagnosed SCD, in addition to 12% with known SCD.[18] It is substantial that about 1% of children born in Uganda have SCD, yet they account for at least 30% of pediatric blood transfusions (Fig 4-1). Transfusion utilization in older children and adults with SCD in Uganda and other countries across the region must be evaluated.

Because of the lack of accessible disease-modifying therapy, there is a high utilization of acute, unscheduled blood transfusions for anemia and acute vaso-occlusive complications for patients with SCD in developing countries in contrast to the scheduled, chronic transfusions used for stroke prophylaxis or organ failure in HICs.[33] In the Realizing Effectiveness Across Continents with Hydroxyurea (REACH; ClinicalTrials.gov number NCT01966731) trial, over 600 children with HbSS from Uganda, Kenya, Angola, and the Democratic Republic of Congo received open-label hydroxyurea treatment. At enrollment, the participants in the REACH cohort were moderately anemic with a baseline average hemoglobin of 7.3 ± 1.1 g/dL. During a 2-month pretreatment screening period, 43 children (6.7%) required 48 blood transfusions at a rate of 43.3 transfusions per 100 patient-years.[34] The most common indications for these transfusions were anemia (62.5%) and malaria (16.7%), along with splenic sequestration (2.4%) and other SCD-related complications, such as stroke or acute chest syndrome (6.3%).[35]

These patients are not only more likely to need a transfusion than other children, but also are more likely to require multiple transfusions. A case-control study of children under 5 years old with severe anemia in Uganda assessed for risk factors for recurrent transfusion within 6 months. Again, children with known SCD were excluded, yet on subsequent genotype testing, SCD (HbSS) was a leading risk factor for recurrent transfusion, with an adjusted odds ratio of 20 compared to children without SCD.[5] Undoubtedly, including SCD in studies on severe anemia and recurrent transfusions would reveal an excessive burden of untreated SCD on blood transfusion utilization. Children with SCD across sub-Saharan Africa currently rely on sporadic blood transfusions as the only “treatment” for their disease despite the availability of alternative medication that is safer, is more effective, and uses fewer scarce resources.