
Plasmodium falciparum (*Pf*), Coevolutionary Balance, and Therapeutically-Rational Exchange Transfusion (T-REX): Nearly All *Pf* Genomes Allow HbAS Hemoglobin to Promote Human Survival

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Review

***Plasmodium falciparum* (Pf), Coevolutionary Balance, and Therapeutically-Rational Exchange Transfusion (T-REX): Nearly All Pf Genomes Allow HbAS Hemoglobin to Promote Human Survival**

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Abstract

Background: While *Plasmodium falciparum* (Pf) genomes are constantly evolving to counter new antimalarial drugs, Pf parasites currently allow ancient Pf-malaria-combating red blood cell (RBC) genetic variants to markedly protect humans against onset of severe Pf disease and death. The prevalences of sickle-trait hemoglobin (HbAS) RBCs and “dual-gene protection” type-O HbAS RBCs are substantial in Pf-endemic regions thousands of years after the “sickle” HbS hemoglobin allele (HBB gene variant) and the type-O ABO blood group first emerged. Do Pf-human coevolution data and growing interest in transfusion services in Africa suggest rescue exchanges of “evolution-engineered” RBCs warrant evaluation? **Methods:** We reviewed transfusion-related publications and data regarding Pf-combating RBC genetic variants and a worrisome Pf genotype (Pfsa⁺⁺⁺) that completely eliminates HbAS survival-promotion. **Results:** Clinicians in Africa are eager to advance transfusion therapies and exploit automated continuous-flow apheresis machines for RBC exchange. There is no evidence the low prevalence of Pfsa⁺⁺⁺ is increasing or the combination of the survival-promoting effects of HbAS hemoglobin and type-O blood group provides less than an additive increase in protection. **Conclusions:** Geneticists can support evaluating therapeutic use of HbAS RBCs by explaining how the prevalence of the worrisome Pfsa⁺⁺⁺ genotype might be low and unchanging due to an equilibrium between competing selection pressures and “fitness costs.” Since HbAS hemoglobin alone provides 90% protection against death, conceivably, no human with type-O HbAS RBCs has ever died from Pf malaria. So, it seems prudent to evaluate converting children with life-threatening Pf infections into type-O HbAS patients via exchange transfusion – now.

Keywords: malaria; evolutionary biology; exchange transfusion; T-REX; parasite-human coevolution; red blood cell genetic variants

1. Preface

Evaluating Type-O HbAS Exchange: Patient Exclusions and African Perspectives

Given current data and knowledge gaps [1], evaluation of adjunctive exchange transfusion of “dual-protection” type-O sickle-trait hemoglobin (HbAS) red blood cells (RBCs) for the rescue of patients with life-threatening *Plasmodium falciparum* (Pf) infections should not involve (1) women who are pregnant or have placental malaria [2,3], (2) neonates and infants [4,5], and (3) any patients who have been taking drugs, or have medical conditions, healthcare providers feel might promote sickling

of HbAS RBCs or thrombosis [6,7]. Fortunately, these exclusions mean nearly all young children dying with cerebral malaria (CM) or severe *Pf*-induced anemia are eligible for adjunctive type-O HbAS RBC exchange transfusion. Regarding potential safety concerns, case-reports in 1963 and 1981 suggest transfusions of HbAS-hemoglobin whole blood possibly contributed to the deaths of 2 neonates who were, notably, premature neonates [4,5]. Regarding full-term neonates, a 1981 study in Nigeria found that HbAS RBC exchange transfusions were both safe and effective for the treatment of hyperbilirubinemia [8]. Despite this demonstration of HbAS safety in neonates, initially excluding neonates and infants from evaluations of type-O HbAS exchange seems prudent. No reports of adverse reactions attributable to transfusion of HbAS RBCs in children or adults could be found. Kaufman et al. reported no adverse reactions in 13 patients transfused HbAS RBCs [9]. Some blood centers allow healthy (qualifying) individuals with thalassemic trait, glucose-6-phosphate dehydrogenase deficiency (G6PD) trait, and sickle cell trait (SCT) to donate blood [10]. Also notable, Aneke et al. reported that, after suspending the testing of donor blood for sickle trait HbAS hemoglobin, there were no reports of adverse effects [11].

Of note, the transfusion-related perspectives of front-line clinicians in sub-Saharan Africa (SSA) warrant consideration: They feel (1) modern, automated, continuous-flow apheresis machines help them control and optimize critical exchange-related hemodynamic parameters, such as blood volume and post-exchange hematocrit [12,13] and (2) HbAS RBCs (that are prevalent in many *Pf*-endemic regions) can safely be used for exchange transfusions and HbAS blood donations may help address blood-bank shortages [8,14]. Regarding concerns of clinicians in SSA that HbAS RBCs can sickle or promote thrombosis in special situations, it may seem counter-intuitive that, compared to *Pf*-infected HbAA children, the hematologic parameters of *Pf*-infected HbAS children are markedly better, including a substantially lower erythrocyte sedimentation rate [15]. Conceivably, in the context of severe *Pf*-malaria infections, HbAS RBCs, might markedly promote perfusion via anti-adhesive molecular mechanisms that might include therapeutic competitive binding involving the extracellular vesicles (EVs) secreted by donor HbAS RBCs.

Managing transfusion-related uncertainties responsibly: Prudence and clinical opportunities

When and where possible in SSA, it seems prudent to evaluate the clinical impact of type-O HbAS RBC exchange transfusions because prevalence data and case-reports suggest (1) it is very likely type-O HbAS RBC exchanges are already being used periodically, but unknowingly [3,16][17] and data suggest (2) type-O HbAS exchange might substantially reduce mortality [18,19] [20–25]. Given this highly unusual medical context (along with the unacceptably high death toll of *Pf*-infected children), this ambiguity should be replaced by clinical data that can be used to optimize patient care. Of note, adjunctive exchange transfusions have been used for more than 40 years to rescue dying *Pf*-infected patients [26,27], and we know donor HbAS RBCs are – unknowingly – being transfused as documented in case-reports that describe surprising, retrospective discoveries of transfusion-acquired HbAS hemoglobinopathy [16]. Given the emergency use of type-O “universal-donor” RBCs and the substantial prevalence of HbAS RBCs and even of type-O HbAS RBCs in some *Pf*-endemic regions [3,17] simple and exchange transfusions of type-O HbAS RBCs will surely continue to be used unknowingly to treat *Pf*-infected patients. In general, it seems prudent to evaluate, and publish, the clinical impact and treatment details of any therapy being used unknowingly to rescue patients with life-threatening conditions. Also, it seems “evolution-engineered” survival-promoting strategies warrant investigation given that “human-engineered” therapies are driving the emergence of drug-resistant genes [28–30]. Unfortunately, studies specifically designed to assess the impact of exchanging special *Pf*-disease-combating RBCs have never been conducted. Given that the vast majority of patients dying with severe *Pf* infections carry *Pf*-disease-promoting non-O normal hemoglobin HbAA RBCs, clinicians trying to rescue patients with life-threatening *Pf* infections should, when possible, try to convert these patients into quantitatively substantial carriers of *Pf*-combating RBCs via exchange transfusion [31]. Conceivably, if citizens who carry *Pf*-disease-

combating RBCs are told their special blood might save the lives of young children suffering gruesomely with CM, they might be motivated to register as contactable donors.

2. Introduction

2.1. Terms and Potential Confusions

Regarding the term “extracellular vesicles” (EVs), Sadallah and colleagues note, “A major problem in the microvesicle literature is the somewhat confusing nomenclature. Various names have been used, including particles, microparticles, vesicles, microvesicles, nanovesicles, exosomes, dexosomes, argosomes, ectosomes, etc.” [32] For clarification, they noted “Whereas their formation, size and biological function may be different, one common point between all vesicles is the fact that they bud from a membrane, whether this occurs at the cell surface or in a vesicular compartment inside the cell.” Since RBC ectosomes **are EVs formed by budding out of the RBC surface** membrane, donor type-O HbAS RBC ectosomes delivered by exchange transfusion secrete EVs expressing specific type-O HbAS RBC surface antigens that have unique immuno-modulating effects, such as inhibiting release of the pro-inflammatory TNF- α , IL-10, and IL-8 cytokines [33]. Because cerebral malaria (CM) involves brain inflammation, it is notable **that RBC ectosomes (EVs that bud directly from the RBC’s surface) express** phosphatidylserine (PS) and are, therefore, anti-inflammatory and immunosuppressive [32]. Regarding the therapeutic potential RBC EVs, **Sekar et al. found that RBC EVs injected into mice with retinal degeneration were anti-inflammatory and neuroprotective by modulating the release of the pro-inflammatory cytokines involved in neurodegenerative-disease pathways** [34]. **RBC ectosome EVs, that bud from the RBC surface, are anti-inflammatory and immunosuppressive because they express** phosphatidylserine [32].

“*Pfsa+++*” refers to the rare *Pf* genotype (that is associated with the human HbS hemoglobin-gene variant) is characterized by the simultaneous presence of 3 special alleles in the *Pf* genome (*Pfsa1*, *Pfsa2*, and *Pfsa3*) [35]. From the perspective of evolutionary biology and human survival, *Pfsa+++* parasites are worrisome – as are life-threatening drug-resistant *Pf* genotypes – because they are able to cause severe *Pf*-malaria disease in sickle-trait HbAS hemoglobin humans as easily as the (very common) non-*Pfsa+++* parasite strains cause severe disease (and death) in normal-hemoglobin HbAA humans [35]. *Pfsa+++* parasites can be viewed as “HbAS-protection-nullifying *Pf* parasites.” Regarding potential confusion, *Pfsa+++* parasites are only more lethal to HbAS individuals: *Pfsa+++* parasites completely eliminate the survival-protection HbAS patients enjoy when infected with non-*Pfsa+++* parasites.

The term “linkage disequilibrium” (LD) – that refers to the non-random relationship between the *Pfsa1*, *Pfsa2*, and *Pfsa3* alleles (*Pfsa*-gene variants) that can be present in some *Pf* genomes (in different combinations) – can also be confusing [35]. Slatkin warns “Linkage disequilibrium (LD) is one of those unfortunate terms that does not reveal its meaning [36]. As every instructor of population genetics knows, the term is a barrier not an aid to understanding. LD means simply a nonrandom association of alleles at two or more loci, and detecting LD does not ensure either linkage or a lack of equilibrium” [36]. Unfortunately, LD has the potential to discourage clinicians who might consider using type-O HbAS RBC exchange transfusions (“type-O HbAS T-REX”) to rescue dying *Pf*-infected patients. The word “disequilibrium” in the term LD may cause clinicians to worry that *Pf*-human coevolution cannot maintain the (favorable) equilibrium that seems to currently exist in which the prevalence of the human HbAS hemoglobin genotype is very substantial (about 15%) coexists with a low prevalence (unknown but must be <3%) of the HbAS-protection-nullifying *Pfsa+++* genotype. That is, the prevalence of the sickle-trait HbAS human genotype does not seem to be decreasing, and the prevalence of the *Pfsa+++* parasite strain does seem to be increasing. Unfortunately, clinicians might not want to consider evaluating type-O HbAS RBC exchange as a rescue adjunct if they think LD among the *Pfsa* alleles means there is a destabilizing selection pressure that will increase the prevalence of the worrisome *Pfsa+++* genotype.

The terms “*Pf*-resistant RBCs” and “*Pf*-combating RBCs” are used interchangeably and refer to death-combating RBC genetic variants that resist onset of severe *Pf*-malaria infection (and, thereby, death). Regarding potential confusion, these terms do not mean these RBCs necessarily reduce *Pf* invasion, *Pf* growth, or *Pf* transmission. *Pf*-combating RBCs are not *Pf*-killing agents like the antimalarial drug chloroquine. *Pf*-resistant RBCs promote human survival by altering the life-threatening molecular mechanisms triggered by *Pf* infections, such as the cytoadhesive ligand-receptor binding that can, for example, obstruct cerebral blood flow.

“Therapeutically-rational exchange transfusion” (T-REX) refers to an exchange transfusion that removes a patient’s *Pf*-infected RBCs and replaces them with special *Pf*-combating donor RBCs such as HbAS RBCs or type-O (ABO blood group O) RBCs or “dual protection” type-O HbAS RBCs, etc. So, trying to rescue a dying *Pf*-infected patient using adjunctive exchange of type-O HbAS RBCs, for example, could be called “type-O HbAS T-REX.” Of note, modern automated, continuous-flow exchange transfusions markedly differ from simple transfusions due to increased safety and control. Clinicians in sub-Saharan Africa (SSA) highly value exchange because critically important hematologic parameters can be controlled, including the ability to determine in advance (1) the extent to which a patient is converted to a new survival-promoting RBC status (perhaps almost completely converting a dying type-A HbAA patient into a type-O HbAS patient) and (2) the critically important post-exchange hematocrit that is considered optimal for the patient. Interested healthcare providers should not hesitate to ask transfusion-medicine and blood-bank specialists to explain other advantages of advanced exchange procedures.

The term “fitness cost” refers to a survival disadvantage associated with a specific genotype, such as the *Pf* parasite’s rare *Pf*sa+++ genotype. Within the “survival of the fittest” conceptual framework, while *Pf*sa+++ might promote *Pf* survival by being able to cause severe *Pf* disease when infecting sickle-trait HbAS humans, the *Pf*sa+++ strain might pay a “fitness cost,” for example, by being less able to cause severe *Pf* disease in normal-hemoglobin HbAA humans. And so, a survival-promoting selection pressure driving an increase in the prevalence of a specific *Pf* genotype in one environmental context might be opposed by a survival-reducing “fitness cost” paid by that same *Pf* genotype in a different context. Fortunately, a relatively stable equilibrium of pathogen-genotype and human-genotype prevalences can emerge despite “linkage disequilibrium” among some pathogen alleles [36,37] – that is, equilibrium despite the word “disequilibrium.”

2.2. Goals and Objectives

One of our aims is to encourage geneticists and transfusion-medicine and blood-bank specialists to support front-line clinicians in Africa who are responsible for rescuing children dying with CM and severe anemia caused by *Pf* infections. Clinicians should be reminded that although drug-resistance alleles can emerge relatively rapidly in *Pf*-parasite genomes, in the 21st century, both type-O and HbAS RBCs (and other “evolution-engineered” *Pf*-combating RBCs) provide substantial protection against the onset of severe *Pf*-malaria infections thousands of years after the sickle-hemoglobin HbS allele, for example, first emerged [38]. And so, clinicians should be reminded that *Pf*-infected patients born with death-promoting RBCs can be converted into patients with survival-promoting RBCs. Until proven otherwise, it seems most prudent to assume converting young, small-volume children dying with *Pf* infections into patients with *Pf*-combating RBCs can substantially reduce mortality. Regarding wording, when epidemiologists report that type-O and HbAS RBCs markedly reduce onset of severe *Pf* disease and death, this is equivalent to saying the vast majority of children who are dying from *Pf*-malaria infections carry non-O, normal-hemoglobin HbAA RBCs. That is, carrying non-O or normal HbAA hemoglobin RBCs are 2 key risk factors for *Pf*-induced death. Unfortunately, *Pf*-genome evolution can foster a sense of futility among clinicians given that drug-resistant *Pf* strains can emerge within decades. Also unfortunate, regarding *Pf*-human coevolution, geneticists often use the “arms race” analogy to describe *Pf*-genome and human-genome coevolution. This pessimistic, adversarial conflict suggests *Pf*-genome evolution that promotes *Pf* survival might always conflict with human-genome evolution that promotes human survival. Also

worrisome for clinicians, researchers have discovered a *Pf* genotype called “*Pf*sa+++” that can completely nullify the human-survival-promotion of sickle-trait HbAS hemoglobin RBCs [35]. To counter a sense of futility among clinicians, we discuss recent findings that, ideally, will (1) encourage front-line clinicians to convert, when possible (and with the help of transfusion-medicine specialists), dying children into type-O HbAS RBC patients, (2) reduce anxiety about the worrisome *Pf*sa+++ *Pf*-parasite strain, and (3) explain that, after thousands of years of *Pf*-human coevolution, a relatively stable coevolutionary balance can exist that provides extraordinary human-survival-promoting therapeutic opportunities.

For clinicians who feel human evolution will inevitably lose the “arms race” with the highly adaptable *Pf* genome, we describe possible “fitness costs” that might be paid by the worrisome *Pf*sa+++ strain that might explain why ancient HbAS RBCs continue to promote human survival despite robust evolution of *Pf* drug-resistance alleles [21,28] [29,30,38–41].

We hope to increase interest in advancing transfusion-medicine services in SSA and in exploiting T-REX studies to gain insights into the kinetics, distribution, and impact of the nano-sized extracellular vesicles (EVs) secreted by donor RBCs. In an attempt to generate interest in evaluating special exchange transfusions for the rescue of dying children, we pose the simple question: Has any human with type-O HbAS blood ever died from a *Pf*-malaria infection?

2.3. Context and Challenges

Currently, *Pf*-malaria infections – caused by the growth and replication of *Pf* parasites inside RBCs – kill hundreds of thousands of children annually [42,43]. Interestingly, although Ebel et al. noted that (1) “Over one-third of healthy donors unknowingly carried alleles for G6PD deficiency or hemoglobinopathies” (which can be substantially *Pf*-resistant) and (2) “a better understanding of how *P. falciparum* biology is impacted by natural RBC variation could help lead to new therapies,” their article ignored adjunctive transfusion [42]. Similarly, Riggle et al. neglected to discuss optimization of transfusion while stressing the “desperate” need to develop better rescue adjuncts [43]. Regarding the critical importance of RBC transfusions, the majority of children treated for *Pf*-malaria infections in the AQUAMAT study were transfused [44]. And, since *Pf* malaria is a RBC disorder, it is not surprising that in, Malawi, the majority of all transfusions delivered in a regional hospital were used to treat *Pf*-infected children [45]. Perhaps lack of interest in transfusing *Pf*-combating RBCs is the result of assuming (1) *Pf* genomes will soon nullify the survival-promoting effects of *Pf*-combating RBCs, (2) the prevalence of type-O HbAS RBCs, for example, is very low, (3) carriers of *Pf*-combating RBCs will not be willing to become contactable donors, or (4) the number of life-threatening *Pf* infections is so overwhelming, rescuing some patients via exchange transfusion will not make a meaningful difference. Fortunately, new vaccines should markedly reduce onset of severe *Pf* infections in young children (and even suggest *Pf* malaria eradication is possible) [46]. Ideally, with vaccine-related successes, more attention can be directed to evaluating the impact of exchanging special *Pf*-combating RBCs to rescue the smaller number of children who still develop life-threatening disease.

Regarding risk factors for death from *Pf* infections, the RBCs carried by most patients who develop severe *Pf* infections (1) have normal HbAA hemoglobin [25,47–49], (2) are non-O ABO blood group (are not type-O) [50], (3) have normal RBC enzyme levels [51], and (4) have normal membrane structures [52]. Thus, it is disappointing that Rowe and her colleagues seem to have been ignored after they suggested transfusing *Pf*-disease-resistant type-O RBCs for the rescue patients with severe *Pf* infections [41]. Given the substantial mortality rate reported in the AQUAMAT study despite use of IV artesunate and simple transfusions [44], we have been recommending that, in hospitals that have acquired automated, continuous-flow apheresis machines, clinicians ask blood-bank or transfusion-medicine specialists to help them evaluate therapeutically-rational exchange transfusion (T-REX) options. The rationale being (1) exchange (in contrast to simple transfusion) can substantially convert (to the extent desired) patients carrying *Pf*-disease-promoting RBCs into patients carrying special *Pf*-combating RBCs, (2) modern apheresis machines help clinicians monitor a patient’s status

and can be set to provide the post-exchange hematocrit that is considered optimal, and (3) regarding safety, transfusions of *Pf*-combating hemoglobin-variant RBCs are already been used, but unknowingly, without any reports of adverse effects [16]. Also reassuring, exchange transfusions of *Pf*-combating HbAS RBCs and G6PD-deficient RBCs were found to be safe in SSA [8].

Regarding the challenge posed by the continual evolution of drug-resistant *Pf*-parasite genomes [28–30], it seems prudent for global-health specialists to consider how exchange of *Pf*-combating donor RBCs (T-REX) as a non-drug adjunctive therapy might slow the emergence of drug-resistant *Pf* strains as well as save lives. To reassure worried clinicians, geneticists should explain how the interaction of diverse pathogen and human survival-related selection pressures and “fitness costs” can result in a balance of *Pf* and human genotype prevalences that provide extraordinary human-cell therapeutic opportunities.

2.4. Coevolution of Human and *Pf* Genomes

Regarding *Pf*-human coevolution, in 2005, Kwiatkowski noted, “malaria is the most powerful known force for recent selection of human genetic variants” [53]. Regarding the evolution of special *Pf*-combating RBCs, Goheen and colleagues noted, “humans and *Plasmodium* parasites have been at war for centuries, and one of the key evolutionary battlegrounds is indisputably the human RBC. Better understanding of malaria pathogenesis in the face of altered RBC physiology will ultimately help improve our strategies to combat the disease” [38]. Given that highly adaptable *Pf* genomes can evolve to very effectively nullify the survival-promoting effects of antimalarial drugs within just decades [28–30] it seems prudent to consider why *Pf* parasites have not yet evolved to nullify – to a meaningful extent – the survival-promoting mechanisms of ancient *Pf*-disease-combating RBCs that markedly promote human survival in the 21st century. Understanding how ancient *Pf*-combating RBCs reduce onset of CM, severe anemia, and death thousands of years after they emerged is likely to help us develop new rescue adjuncts [19,38,54,55]. Conceivably, adjunctive T-REX options might slow the emergence of drug-resistant *Pf* parasites as well as reduce deaths from CM and severe anemia.

Regarding the very challenging task of researching RBC-driven evolution of *Pf* parasites, Band and his colleagues have studied how the *Pf* genome has been impacted by the human survival-promoting HbS sickle-hemoglobin allele [35]. Given that the vast majority (about 90%) of patients who are dying with severe *Pf* infections carry normal-hemoglobin HbAA RBCs, it seems prudent to consider how the HbAS-protection-nullifying *Pf*sa+++ parasite affects HbAA humans. Because the *Pf*sa+++ parasite strain can completely nullify the human survival-promotion of HbAS RBCs, exploiting donor RBCs with multiple *Pf*-disease-combating characteristics (like type-O HbAS RBCs) seems most prudent.

Adjunctive exchange transfusion, post-exchange rebound parasitemia, and “time to speak”

In 2020, Riggle et al. noted that because thousands of children are gruesomely suffering and dying from CM (brain swelling, seizures, and/or coma) each year, researchers are “desperately seeking therapies for cerebral malaria” [43]. Regarding context, in 2000, Weir et al. had already noted that “automated RBC exchange transfusion can rapidly reduce the level of parasitemia and restore neurologic functioning in patients with cerebral malaria” [56]. Regarding immunopathogenesis, Riggle et al. noted “CM in children is consistently linked to excessive inflammatory responses,” that includes involvement of the proinflammatory cytokine TNF- α [43]. Unfortunately, in discussing the rationale for developing immunologic adjunct treatments for CM, they conspicuously ignored RBC-transfusion therapies despite numerous case-reports suggesting the existence of a (yet-to-be-characterized) subset of exchange transfusions that trigger dramatically rapid coma-resolution [31]. The markedly reduced “time-to-speak” values are consistent with the secretion of rapid-acting nano-sized extracellular vesicles (EVs) secreted by special donor *Pf*-combating RBCs. Of note, EVs secreted by donor RBCs may (1) reduce brain inflammation in CM patients by reducing levels of TNF- α [33] and (2) compete with the pathogenic binding of *Pf*-infected RBCs [31]. Regarding the life-saving

protection provided by sickle-trait HbAS RBCs, Riggle et al. noted “the induction of pro- and anti-inflammatory cytokines may play roles” [43]. Immune cells may also be pathogenic, and Riggle et al. noted, “CM is associated with cerebrovascular engagement of CD3+CD8+ T cells . . . Thus, CD3+CD8+ T cells are highly promising targets for CM adjunctive therapy [57]. Interestingly, Ferreira et al. Previously noted that sickle-trait HbAS RBCs inhibit activation and/or expansion of pathogenic CD8+ T cells that recognize *Pf* antigens [58]. Regarding therapeutic delivery of microparticles (MPs) via transfusion, Pinheiro et al. noted “Packed red blood cell (pRBC) transfusion has been reported to induce immunomodulations independently of residual leukocytes and cytokines” and concluded “MPs from blood donors thus have immunoregulatory functions” [59]. Regarding the potential antibody-related immuno-therapeutic benefits **directed against, for example, pathogenic *Pf*-derived variant** surface antigens (VSAs) expressed on the membranes of *Pf*-infected RBCs, **Cabrera et al. found that children with HbAS RBCs have significantly enhanced IgG anti-VSA antibody activity that protects against severe malaria** [60]. Unfortunately, juxtaposing immunology-related articles about malaria, HbAS-RBC, and RBC-EVs reveals that transfusion of *Pf*-combating RBC genetic variants – that includes delivery of EV nanoparticles, some of which express the special immuno-modulating surface antigens of the parent RBCs – is rarely viewed as an immunotherapy that affects cytokines, antibodies, and immune cells.

Of note, *Pf*-malaria researchers might be impressed by some of the transfusion-related successes unique to SSA. In 1892, a dying cerebral malaria patient with blackwater fever was successfully rescued in East Africa via an adjunctive transfusion that may have been an interracial transfusion intentionally: The physician may have previously concluded that the blood from certain donors could be especially therapeutic [61]. In 1981, Nigerian physicians reported that exchange transfusions of *Pf*-combating HbAS RBCs were safe, and implied the substantial prevalence of HbAS RBCs in *Pf*-endemic regions might help reduce blood shortages [8]. Also notable, clinicians in SSA found that the properties of non-O HbAS blood differ from type-O HbAS blood [62]. Fortunately, given current interest in SSA in exchange transfusion and modern apheresis machines, it seems feasible to (1) advance transfusion services in SSA and (2) conduct the first-ever exchange-transfusion study to specifically evaluate exchange of *Pf*-combating RBCs [12,13]. Regarding generating interest in advancing transfusion services, citizens who carry special “evolution-engineered” *Pf*-resistant RBCs should be told their blood might rescue dying children – a realization that might motivate them to register as “contactable special-blood donors.”

Since some exchange transfusions have triggered remarkably rapid coma-recoveries compared to intravenous (IV) artesunate, T-REX studies may identify associations between post-exchange “rebound parasitemia,” coma-recovery “time-to-speak” values, and EV kinetics and biodistribution [31,44,63]. Interestingly, in a study of monozygotic twins with sickle-trait hemoglobin HbAS RBCs, flow cytometry found elevated levels of RBC-derived microparticles [64]. Conceivably, high secretion of EVs by HbAS RBCs promotes human survival by reducing and reversing cytoadhesion via competitive binding [31]. Post-exchange parasitemia studies could determine if type-O HbAS RBC exchange triggers rapid coma-resolution that is linked to high HbAS-RBC EV levels and post-exchange “rebound parasitemia” triggered by reversal of sequestration of *Pf*-infected RBCs [63].

3. Methods

We reviewed *Pf*-genome data and transfusion-related findings potentially relevant to the rationale, safety, and feasibility of evaluating the type-O HbAS T-REX option for the rescue of children dying with severe *Pf* infections. Special attention was directed to findings about the one-and-only *Pf* genome (*Pf*sa+++) that completely eliminates HbAS RBC survival-promotion since clinician concerns about the worrisome *Pf*sa+++ strain might discourage evaluation of type-O HbAS exchange transfusion.

We searched for *Pf* genotype data and type-O and HbAS RBC research findings that might help explain why, currently, the ancient *Pf*-disease-combating type-O and HbAS RBC genetic variants (1) are prevalent and (2) are markedly promote human survival thousands of years after they first

emerged. We reviewed the prevalences of *Pfsa*-alleles in The Gambia, including the prevalence of the worrisome *Pfsa*+++ parasite strain in those normal-hemoglobin (HbAA) Gambian children who had developed severe *Pf*-malaria infections. In an article by Band et al., *Pfsa2*-allele and *Pfsa*+++ data in their text and in “Fig. 2” provided information about the prevalence of the worrisome HbAS-protection-nullifying *Pfsa*+++ strain (1) in the *Pf*-parasite population in The Gambia and (2) in HbAA Gambian children who had developed severe *Pf*-malaria infections [35].

4. Results

4.1. HbAS RBC Data

The human-survival-promoting HbAS sickle hemoglobin allele emerged about 7,000 years ago [54,65]. Regarding HbAS RBC prevalence in SSA, in studies of pregnant women, 16% carried HbAS RBCs in Benin [3] while 22% carried HbAS RBCs in Nigeria [17]. HbAS RBC protection against onset of severe *Pf*-malaria infections has been estimated to be about 90% (odds ratio of about 0.1) [18,20]. Ackerman, et al. reported “Our stratified case-control analysis confirms a strong protective effect of the sickle cell trait against both cerebral malaria and severe malarial anaemia, with a ten-fold reduction in risk” [18]. Of critical importance, we could find no data suggesting the profound human-survival-protection provided by HbAS RBCs has been decreasing. Unfortunately, no study designed to specifically assess the clinical impact of exchange transfusions of sickle-trait HbAS RBCs (HbAS T-REX) has ever been conducted.

Regarding clinician concerns about the risk of thrombosis related to sickle-cell-trait (SCT) HbAS RBCs, Sagir Ahmed and colleagues noted – for individuals who do not have a *Pf*-malaria infection – “SCT by itself is a weak risk factor for deep vein thrombosis (DVT) but it has the potential of escalating the DVT risk among patients with non-O blood groups” [62]. For *Pf*-infected patients (and consistent with HbAS RBC protection against cerebral malaria), Albiti and Nsiah found that hematologic parameters were substantially better for *Pf*-infected HbAS children than for *Pf*-infected normal-hemoglobin HbAA children, including lower erythrocyte sedimentation rates in the sickle-trait HbAS children [15].

Regarding the safety of transfusing HbAS RBCs in children and adults (in contrast to premature neonates), no reports of adverse effects attributable to HbAS hemoglobin were found [9,11,16]. Also encouraging, case-reports describing unexpected, retrospective discovery of unintended transfusion-acquired HbAS hemoglobinopathy reported, fortunately, that there were no adverse effects [16].

4.2. *Pfsa*+++ Parasite Data

Band et al. noted that, in The Gambia, repeated prevalence measurements of *Pf*-parasite genomes having the *Pfsa2* allele were “below 3% in all years studied” which means the prevalence of the worrisome HbAS-protection-nullifying *Pfsa*+++ parasite must also be less than 3% [35]. Unfortunately, the prevalence in The Gambia specifically of *Pfsa*+++ was not reported (possibly because it is very rare). So, in SSA, it is not known how far below 3% the *Pfsa*+++ prevalence is 7,000 years after the HbS allele first emerged. Importantly, we found no evidence that the prevalence of the worrisome *Pfsa*+++ genotype is increasing – which is consistent with finding no evidence the 90% survival-promotion of HbAS RBCs is decreasing.

Consistent with the low (<3%) frequency of the *Pfsa2* allele in The Gambia reported in the text of the Band et al. article, the prevalence of *Pfsa2*-containing *Pf* strains among normal-hemoglobin HbAA Gambian children with severe (single-strain) *Pf*-malaria infections = 1.1% (21/1850) while the prevalence of the worrisome HbAS-protection-nullifying *Pfsa*+++ strain = 0.5% (9/1850) – which is about half the *Pfsa2* prevalence for these HbAA children [35]. Interestingly, the vast majority (>86%) of the severe *Pf*-malaria infections in Gambian children were single-strain *Pf* infections [35].

4.3. Type-O RBC Data

Not surprisingly, in studies of pregnant women in *Pf*-endemic Benin and Nigeria, the prevalences of *Pf*-combating type-O blood were substantial (>39%) [3,17]. Regarding protection against death, in their article, “Cytoadherence in paediatric malaria: ABO blood group, CD36, and ICAM1 expression and severe *Plasmodium falciparum* infection,” Cserti-Gazdewich and her colleagues noted “the relative risk of fatal malaria to uncomplicated malaria was 2.3-fold higher for group A or AB versus group O” [22]. That is, in children, the type-O ABO blood group was found to provide marked protection against death from *Pf*-malaria infections compared to the non-O blood groups. Regarding onset of severe *Pf* disease, Rowe et al. noted “Group O was associated with a 66% reduction in the odds of developing severe malaria compared with the non-O blood groups (odds ratio 0.34)” [21]. Given this substantial protection against onset of severe disease and death, researchers have recommended transfusing type-O RBCs as an adjunctive treatment for severe *Pf*-malaria infections [22,41,66]. Unfortunately, no study has ever been conducted to specifically assess the clinical impact of exchange transfusions of “universal donor” type-O RBCs (type-O T-REX).

4.4. “Dual-Gene” Type-O HbAS RBC Data

In studies of pregnant women, among the 533 inpatients in Benin for whom ABO blood group data were available, 45 (8.4%) were carriers of type-O HbAS RBCs [3], and among the 300 pregnant women studied in Nigeria, 18 (6%) carried type-O HbAS RBCs [17]. These prevalences are substantial, indicating there are many potential donors of special “dual-gene-protection” type-O HbAS RBCs in SSA.

Regarding the survival-promoting interaction between type-O and HbAS, we found no data indicating “negative epistasis” (canceling of their individual benefits) that would suggest the combined survival benefit would be less than additive [65,67]. Unfortunately, no study has ever been conducted to assess the clinical impact of exchange transfusions of “dual-gene protection” type-O HbAS RBCs (type-O HbAS T-REX).

4.5. Transfusion-Related Findings

Despite use of IV artesunate, the AQUAMAT study found that the majority of children needed blood transfusions [44]. Notably, the majority of all transfusions delivered in a regional hospital in Malawi were used to treat *Pf*-infected children [45].

In SSA, modern apheresis machines are being used to safely and precisely perform RBC exchange transfusions [12,13]. Automated continuous-flow apheresis machines can now enable clinicians (and researchers) in SSA to (1) convert – to the degree desired – a child with a severe *Pf*-malaria infection (who most likely has *Pf*-disease-promoting RBCs) into a carrier of *Pf*-combating RBCs, (2) monitor and control critical parameters such as blood volumes and post-exchange hematocrit [12,13], and (3) evaluate the relationships between post-exchange rebound parasitemia, coma-recovery, and RBC EVs, and, thereby, clarify the role of cytoadherence in cerebral malaria [63].

Regarding interest in research, clinicians in SSA have advanced our understanding of type-O and non-O sickle-trait HbAS RBCs [62], and Kwabena Nsiah at the Kwame Nkrumah University in Ghana found that hematologic parameters in *Pf*-infected HbAS children are more favorable (less abnormal) than those in *Pf*-infected normal-hemoglobin HbAA children [15].

Regarding interest in using RBC exchange to improve medical care, in 2022 in Ghana, scientists and clinicians advanced their apheresis procedures to include automated therapeutic RBC exchange [12]. In Nigeria, Bazuaye and Iheanacho consider automated RBC exchange transfusion to be “an effective but relatively underutilized therapy” [13].

In 2025, clinicians in Africa warned that “most of the population needing blood transfusions do not receive them. Severe anemia due to insufficient blood supply contributes to high maternal and infant mortality rates” and “donation rates across Africa only meet 20–50% of transfusion requirements” [14].

5. Discussion

5.1. Therapeutic Implications of the HbAS RBC Data

Because clinicians in SSA have shown exchange transfusions of HbAS RBCs are safe and therapeutic [8], it is encouraging that among pregnant women, 16% were found to carry HbAS RBCs in Benin [3] and 22% in Nigeria [17]. These substantial prevalences (1) explain why cases of transfusion-acquired HbAS hemoglobinopathy are being detected despite under-reporting [16] and (2) support the position of physicians who feel collecting units of HbAS blood could help blood banks mitigate blood-shortage problems [8].

Taylor, et al. reported, “Case-control studies showed a decreased risk of severe malaria for HbAS” with an odds ratio of 0.09, indicating about 90% protection against onset of severe *Pf*-malaria disease [20]. Regarding asymptomatic *Pf* infections, the findings they reviewed revealed “HbAS does not consistently protect from *P. falciparum* parasitaemia.” Regarding human-to-mosquito *Pf* transmission, Ngou, et al. reported “transmission stages were more prevalent” in *Pf*-infected HbAS patients and there was “a twice higher risk of infection in mosquitoes fed on gametocyte-containing blood of HbAS genotype” [68].

Regarding safety, we found no evidence of adverse effects in children or adults linked to transfusions of HbAS RBCs, including in reviews of “transfusion-acquired HbAS hemoglobinopathy” [16]. Data suggest HbAS RBCs might promote clotting in women who are taking birth control pills, but this analysis did not consider ABO blood-group status and did not involve *Pf*-infected women [6,62].

Case-reports were published that described the deaths of 2 premature neonates who died after HbAS RBC transfusions. The 1963 case-report involved “a premature white infant with physiological jaundice who received an exchange transfusion of blood containing hemoglobin A and S and expired five days later” [4]. They noted, “Since apparently more than one factor is necessary for intravascular sickling to occur after exchange transfusion with sickle cell trait blood, it is very likely that this condition is rare. The present case should stimulate interest in this subject” [4]. The 1982 case-report published by Novak and Brown involved a premature neonate with “hydrops fetalis of undetermined etiology” [5].

5.2. Therapeutic Implications of the *Pf*sa+++ Parasite Data

Given that *Pf* genomes are highly adaptable and can evolve to very effectively resist the toxicity of antimalarial drugs within just decades [28–30], clinicians may worry that the therapeutic benefit of adjunctive T-REX options, such as type-O HbAS exchange, may quickly be eliminated by the emergence of a very high prevalence of *Pf* strains like the HbAS-protection-nullifying *Pf*sa+++ genotype. If that were to happen, and if a non-O HbAS individual developed a severe *Pf*sa+++ infection, then the mortality-reducing benefit of type-O HbAS RBC exchange would only come from (1) the type-O RBCs and (2) the exchange-related mechanical removal of the parasitized RBCs while for a type-O HbAS infected with *Pf*sa+++, the therapeutic benefit would only be due to the reduction in parasitemia. Fortunately, currently (after thousands of years of *Pf*-human coevolution), onset of severe *Pf* infections is rare among HbAS-hemoglobin individuals in that non-O HbAA humans are about 10-times more likely to develop severe *Pf* disease with the present (low) prevalence of the *Pf*sa+++ genotype [18–20]. Also encouraging, we found no evidence the prevalence of the worrisome *Pf*sa+++ strain is increasing. And so, clinicians should not be discouraged from evaluating type-O HbAS exchange because they fear *Pf* parasites will rapidly evolve to nullify HbAS survival-promotion.

5.3. Therapeutic Implications of the Type-O RBC Data

Type-O RBCs are especially valuable because, as “universal donor” RBCs, they can safely be used for simple or exchange transfusions in emergency situations. High demand and usage of type-

O RBCs help explain why blood banks often face shortages type-O units. Notably, because type-O RBCs are *Pf*-disease-combating RBCs, researchers have previously suggested transfusing type-O donor RBCs adjunctively to rescue patients with severe *Pf*-malaria infections [22,41,66].

5.4. Therapeutic Implications of the Type-O HbAS RBC Data

Fortunately, prevalences of type-O HbAS RBCs in some *Pf*-endemic regions of SSA are substantial (8% in Benin and 6% in Nigeria, for example) [3,17]. Thus, there are many thousands of potential volunteer “contactable” type-O HbAS donors in Africa. Perhaps carriers of type-O HbAS RBCs could be motivated to join a special-blood-donor registry by explaining they have a unique opportunity to rescue young children dying from severe *Pf* infections. Conceivably, a substantial number of type-O HbAS carriers would be eager to help young *Pf*-infected children suffering with life-threatening anemia, seizures, or coma.

Since (1) the protection provided against onset of severe *Pf* disease is about 66% for type-O RBCs [21] and about 90% for HbAS RBCs [20] and (2) there is no evidence of negative epistasis (interaction that reduces the simple addition of survival benefits) between type-O blood group and HbAS hemoglobin [65,67], “dual” type-O HbAS RBC protection against severe *Pf* infections and death might, conceivably, be near 100%. That is, converting type-A normal-hemoglobin HbAA children dying with CM into type-O HbAS patients might markedly reduce mortality. Oddly, this evolutionary-biology-based possibility has not (yet) prompted clinical evaluation of type-O HbAS RBC exchange despite the thousands of gruesome *Pf*-malaria deaths occurring each year.

Given that (1) about half of HbAS RBCs in SSA are type-O RBCs and (2) only about 10% of patients with severe *Pf*-malaria infections have sickle-trait HbAS hemoglobin (HbAS provides 90% protection against severe *Pf* disease), this means about 5% of the time the only benefit of treating a child with a severe *Pf*-malaria infection with type-O HbAS exchange will be due to removal of parasitized RBCs via the exchange procedure which, alone, could be life-saving [56]. That is, for about 95% of the children treated with type-O HbAS exchange, protection against death will involve some form of RBC-related survival-protection combined with mechanical removal of parasitized RBCs.

Until proven otherwise, it seems prudent to assume type-O HbAS exchange transfusion can safely and substantially reduce the mortality of dying *Pf*-infected children given that (1) exchange of HbAS RBCs in SSA has already been found to be safe [8], (2) there are no reports of adverse reactions attributable to HbAS RBC transfusions in children or adults [9,16] and (3) the hematologic parameters of *Pf*-infected HbAS children are more favorable than in *Pf*-infected normal-hemoglobin HbAA children [15]. Because the prevalence of type-O HbAS individuals in SSA is substantial (6% to 8%) [3,17], type-O HbAS exchange seems feasible if these unique citizens can be motivated to register as special contactable blood donors.

5.5. Possible “Fitness Costs” That May Help Explain the Low *Pfsa+++* Prevalence

This section is for clinicians interested in how a favorable, relatively stable *Pf*-human coevolutionary balance could have emerged at the same time they are frequently warned about the rapid development of *Pf* drug-resistance alleles and the survival-threatening “arms race” between humans and pathogens – fears that can induce a sense of futility [28–30]. Fortunately, the Band et al. data show that, in The Gambia, the prevalence of HbAS RBCs (among Gambian “controls” who did not have severe *Pf*-malaria infections) is substantial (15%) while the prevalence of the worrisome HbAS-protection-nullifying *Pfsa+++* genotype, although unknown, must be very low (<3%) [35]. Of note, consistent with the 15% HbAS prevalence in The Gambia, the prevalence of HbAS among pregnant women in Benin was found to be 16% [3]. After thousands of years of *Pf*-human genome coevolution, there seems to be an equilibrium between the very low *Pfsa+++* prevalence and the substantial HbAS prevalence in *Pf*-endemic SSA. Reviewing possible explanations for this apparent equilibrium among key *Pf* and human genotype prevalences might be reassuring for clinicians who fear *Pf* parasites are rapidly evolving to eliminate the survival-promotion of *Pf*-combating RBCs.

Worried clinicians should know there is no evidence the prevalence of the worrisome *Pfsa+++* strain is increasing. Also fortunate, the *Pfsa+++* prevalence among normal HbAA hemoglobin Gambian children with severe (single-strain) *Pf*-malaria infections is very low (<0.5%), and if the prevalence of the worrisome *Pfsa+++* genotype is also just 0.5% among the Gambian “controls” (those who did not have severe *Pf*-malaria infections) and just 0.5% among *Pf* parasites in SSA, then *Pfsa+++* is too rare to meaningfully reduce the survival-promotion of HbAS RBCs [35].

Of course, among the Gambian “controls” (who did not develop severe *Pf* infections) and among the population of *Pf* parasites in The Gambia, the *Pfsa+++* prevalence could be much higher than 0.5% (but must be <3%). “Old school clinicians” may enjoy visualizing the following simple 2x2 table that suggests a potential “fitness cost” for the *Pfsa+++* genotype that prevents the *Pfsa+++* prevalence from increasing. For a 2x2 table involving normal HbAA hemoglobin Gambian children with and without severe *Pf* disease and with and without a *Pfsa+++* infection, if we assume a *Pfsa+++* prevalence of 2% in the “controls” (without severe *Pf*-malaria infections), then cell “a” = 9, “b” = 46, “c” = 1841 and “d” = 2238. This 2x2 table produces a relative risk value <1, suggesting *Pfsa+++* protects HbAA Gambian children against onset of severe *Pf* disease – protection that may substantially reduce *Pfsa+++* parasitemia, human-to-mosquito *Pf* transmission, and *Pf* survival compared to the other, non-*Pfsa+++*, *Pf*-parasite strains. This means any *Pf*-survival-promoting benefit *Pfsa+++* enjoys in being able to cause severe disease in HbAS humans is opposed by protecting against severe disease in HbAA individuals (having the opposite effect). That is, the HbAS-protection-nullifying *Pfsa+++* genotype may pay a “fitness cost” in the majority of humans who have normal-hemoglobin HbAA RBCs. Of note, the critically important underlying issue is that the number of HbAA Gambian children with severe *Pfsa+++* infections is conspicuously low: only 9 cases (<0.5% of the 1,850 single-strain severe-disease cases).

Also possibly relevant to the low *Pfsa+++* prevalence, Ngou et al. recently found that when *Pf* parasites infect sickle cell trait (SCT) HbAS hemoglobin individuals, *Pf* transmission might be greater than when *Pf* parasites infect normal HbAA hemoglobin patients: “Plasmodium transmission stages were more prevalent in SCT individuals. This may reflect the parasite’s enhanced investment in the sexual stage to increase their survival rate . . . Our study indicated a higher risk of mosquito infection when fed on blood from HbAS individuals and this suggests higher infectiousness of gametocytes circulating in HbAS blood. Our observation may represent a mechanism underlying host–pathogen co-evolution, whereby *P. falciparum* would have developed means to increase its infectiousness for the mosquito to compensate the protection against malaria conferred by the SCT in the human host” [68]. And so, the coexistence of a low prevalence of *Pf* parasites that completely nullify HbAS survival-promotion with the substantial prevalence of sickle-trait humans in *Pf*-endemic regions might reflect an equilibrium among *Pf* and human genotypes that is, in part, the result of increased human-to-mosquito *Pf* transmission in *Pf*-infected HbAS individuals.

5.6. EV-Related Research Opportunities

Our findings have identified opportunities for RBC nano-particle studies that might help promote evaluation of T-REX studies in SSA by EV researchers and biotech firms. Given that a subset of exchange transfusions have triggered rapid coma-recoveries [31], it seems prudent to consider that these exchanges involved special donor RBCs that converted patients into carriers of *Pf*-combating RBCs. For example, regarding the case-report published by Anani et al., perhaps the rapid coma-resolution triggered by the type-O exchange transfusion unknowingly involved units of type-O HbAS RBCs [69]. Perhaps the nano-sized EVs secreted by special RBC genetic variants function therapeutically as rapidly acting “decoy ligands” that quickly reverse microvascular obstruction by competing with the pathogenic binding of *Pf*-infected RBCs [31]. Do the key molecular mechanisms by which *Pf*-combating RBCs promote human survival involve EVs?

Since the *Pf*-combating donor RBCs delivered to patients via T-REX secrete phosphatidylserine-expressing EVs that compete with pathogenic *Pf*-infected RBCs for binding to human-cell CD36 receptors, T-REX resembles competitive-binding (“decoy ligand”) aptamer strategies [70,71]. Nik

Kamarudin, et al. noted, “As the threat of anti-malarial drug resistance grows, there is increasing pressure to develop alternative treatments . . . The development of an anti-adhesive drug as an adjunct therapy to treat severe malaria could be considered” [70]. Thus, it seems prudent to consider that T-REX options – as non-drug adjuncts that deliver rapidly acting EVs – may slow the emergence of antimalarial drug resistance [31]. Researchers and biotech firms interested in the kinetics, biodistribution, and physiologic impacts of nano-sized RBC EVs should know that clinical evaluations of T-REX options in SSA can provide massive amounts EV-related data likely to have therapeutic implications.

6. Conclusions

Hospitals in Africa with sufficient transfusion-related resources should (1) identify carriers of type-O HbAS RBCs [3,17], (2) encourage them to register as special contactable blood donors, and (3) evaluate use of exchange transfusions of “dual-protection” *Pf*-disease-combating type-O HbAS RBCs as a rescue adjunct for children dying with cerebral malaria or severe anemia. It seems prudent to evaluate type-O HbAS RBC exchange since it is very likely these exchanges are already being used, but unknowingly, without understanding their therapeutic value [16]. Safety should not be a concern because we found no reports of adverse effects among cases of “transfusion-acquired HbAS hemoglobinopathy” [16]. Since there is no evidence of negative epistasis, the individual survival-promotion effects of HbAS hemoglobin and the type-O ABO blood group are likely to be additive and, therefore, substantially exceed 90% protection against death.

Because clinicians and scientists in SSA are currently advancing transfusion services (including use of modern automated continuous-flow apheresis machines), evaluating type-O HbAS exchange (T-REX) is feasible [12,13]. If exchanging *Pf*-combating RBCs is found to reduce mortality, this might substantially increase motivation to advance transfusion-medicine services and apheresis procedures that can benefit a wide range of patients. If exchange of *Pf*-combating RBCs reduces the suffering and mortality of children with cerebral malaria, this might motivate carriers of type-O HbAS RBCs to become contactable blood donors.

Because front-line clinicians worry about rapid *Pf*-parasite evolution and drug-resistance, geneticists should explain that, after thousands of years of *Pf*-human coevolution, the prevalence of the only *Pf* genotype (*Pf**sa*+++) that can completely nullify the molecular protection mechanisms of HbAS RBCs (1) is very low and (2) is not increasing [35]. Geneticists should also explain how the coevolution of human and *Pf* genomes can (1) result in a relatively stable equilibrium among the prevalences of therapeutically-relevant human and *Pf* genotypes and (2) provide extraordinary “evolution-engineered” cell-therapy opportunities [36,37]. Such reassurance can reduce the sense of futility among clinicians who are discouraged by frequent use of the “arms race” metaphor and little mention of stable “coevolutionary balance.”

Research-oriented clinicians in SSA should consider investigating how nano-sized extracellular vesicles (EVs) secreted by special *Pf*-combating RBCs impact the life-threatening adhesion of *Pf*-infected RBCs. Global-health specialists and biotech firms should appreciate that, in some regions of SSA, this is an ideal time to evaluate exchange of “evolution-engineered RBCs” for the rescue of *Pf*-infected children, motivate genetically-unique citizens to become special blood donors, and collect massive amounts of EV-related data.

Finally, this simple question warrants serious consideration: Has any human with type-O HbAS RBCs ever died from a *Pf*-malaria infection? Given that type-O HbAS RBC protection against death might be nearly 100%, when feasible, clinicians in SSA should be encouraged to evaluate, record, and publish the impact of exchanging type-O HbAS RBCs for the rescue of children dying with cerebral malaria [72]. Regarding the unique nano-sized EVs secreted by *Pf*-combating RBCs, EV-related type-O HbAS exchange data might explain the very rapid and stunning coma-recoveries triggered by a subset of exchange transfusions. [Jajosky pre-print]

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