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REVIEW

Impact of high human genetic diversity in Africa on immunogenicity and efficacy of RTS,S/AS01 vaccine

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Abstract

In modern medicine, vaccination is one of the most effective public health strategies to prevent infectious diseases. Indisputably, vaccines have saved millions of lives by reducing the burden of many serious infections such as polio, tuberculosis, measles, pneumonia, and tetanus. Despite the recent recommendation by the World Health Organization (WHO) to roll out RTS,S/AS01, this malaria vaccine still faces major challenges of variability in its efficacy partly due to high genetic variation in humans and malaria parasites. Immune responses to malaria vary between individuals and populations. Human genetic variation in immune system genes is the probable cause for this heterogeneity. In this review, we will focus on human genetic factors that determine variable responses to vaccination and how variation in immune system genes affect the immunogenicity and efficacy of the RTS,S/AS01 vaccine.

Keywords Africa · Genetic variation · Malaria · RTS,S/AS01 vaccine

Introduction

Despite recent reports indicating improvement in the control of malaria in some populations, and the potential for elimination of malaria from many regions of the world, *Plasmodium falciparum* malaria still causes extensive morbidity and mortality, particularly in sub-Saharan Africa (Monroe et al. 2022). In response to the persistent malaria burden, there have been increased efforts in both vector control using insecticides (Paaijmans and Huijben 2020), malaria treatment with artemisinin-based combination therapy (Kenangalem et al. 2019), and chemoprevention using antimalarial drugs (Ashley and Yeka 2020; Kirakoya-Samadoulougou et al. 2022). However, these approaches have faced challenges including insecticide and drug resistance (Asua et al. 2021; Phyo et al. 2016; Tokponnon et al. 2019). Furthermore, drug discovery for new antimalarials is challenging and costly partly due to the rapid development of malarial parasite resistance (Mukherjee et al. 2017). Given the limitations of insecticides and antimalarial drugs, a highly effective malaria vaccine would significantly contribute to malaria control.

There have been efforts to develop malaria vaccines since the 1940s. Despite several promising candidates, an effective vaccine that provides long-lived protection from malaria has not been developed. The current malaria vaccine, RTS,S/AS01, has been rolled out in Kenya, Malawi, and Ghana (Akech et al. 2020; Bell et al. 2020a, b; Bell et al. 2020a, b). However, this vaccine offers only modest and short-lived protection (Arora et al. 2021; von Seidlein and Bejon 2013), and its efficacy varies between individuals and different populations (Bejon et al. 2008; Neafsey et al. 2015; Olotu et al. 2016). Thus, continuous efforts are needed to identify human genetic factors that may be essential in improving immunization approaches and optimal

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components of the RTS,S/AS01 vaccine to prevent *P. falciparum* malaria. Other important aspects may include developing a vaccine adjuvant. A better understanding of the effect of human genetic variation on the immunogenicity and efficacy of RTS,S/AS01 vaccine may help in this regard. Novel human genetic variants that influence the presentation of *P. falciparum* antigens to the immune system and in enhancing the effectiveness of RTS,S/AS01 malaria vaccine need to be urgently identified.

Recent advances in immunogenetics and genomics are key in understanding of the influence of human genetic factors on inter-individual and inter-population variations in immune responses to RTS,S/AS01 vaccine and could prove to be instrumental in developing new strategies to improve the efficacy of RTS,S/AS01. The intersection of immunology and genetics has broadened our understanding of how the immune system responds to infection and vaccination. While the immunogenetic basis of RTS,S/AS01 vaccine in response to malaria infection is currently being extensively studied, human genetic determinants of malaria vaccine efficacy remain largely unknown. Deep immunogenetic profiling of participants during vaccine trials can provide critical mechanistic insights on the effectiveness of malaria vaccines. This will also help to explore correlates of immunity beyond the canonical mechanisms that have been identified in highly controlled malaria exposure studies. Thus, the application of omics tools, that probe more than just the specificity and magnitude of the adaptive immune response, coupled to controlled malaria exposure studies, offers a unique opportunity to guide further vaccine design.

Previous reports suggested that malaria vaccines may not protect all populations or individuals equally due to multiple vaccine-specific parasite factors (Neafsey et al. 2015) and human genetic variants such as the HLA type (Nielsen et al. 2018). Specifically, human genetic variants in genes encoding antigen presentation, cytokine production, or related to immune cells activation and differentiation could influence how individuals respond to RTS,S/AS01 vaccination. Although such knowledge could be utilized to generate personalized malaria vaccine strategies to optimize vaccine response, studies in this field are still limited, yet these would be exploited as targets to enhance the immunogenicity and efficacy of RTS,S/AS01 vaccine.

Challenges faced in the control of malaria in endemic regions of Africa

P. falciparum malaria remains a major global health problem with approximately 627,000 deaths annually, mainly in young children (Steketee et al. 2021). This makes a case for Africa to pursue investment in rolling out RTS,S/AS01 malaria vaccine in endemic countries (Balakrishnan 2021). Due to the diverse nature of malaria parasites and high human genetic variability in Africa, producing a potent vaccine with high efficacy against malaria has been a challenge over the past decades. Despite the reports that RTS,S/AS01 vaccine can reduce malaria by 30% compared to the recommended 75% threshold, the WHO recommended its widespread use for children in malaria-endemic countries (Balakrishnan 2021; D'Souza and Nderitu 2021).

The Africa Union through the Africa Centers for Disease Control and Prevention (Africa CDC) is spearheading a campaign that will see African countries establish local vaccine manufacturing infrastructure and capacity (Mgone 2010). This initiative will require partnerships with already existing vaccine manufacturing companies outside Africa. Evaluating vaccines in large populations such as in Africa where there is limited healthcare infrastructure will certainly require coordinated strategic investment from different stakeholders. Vaccine manufacturers such as GlaxoSmithKline (GSK) have started developing some of the necessary capacity for the current malaria vaccine rollout in Africa (Hogan et al. 2020a). The GSK's RTS,S/AS01 post-approval plan has been designed to address important gaps in RTS,S/AS01 safety and efficacy (Praet et al. 2022b).

Countries participating in the malaria vaccine implementation program (Ghana, Kenya, and Malawi) have little or no baseline incidence data on rare genetic diseases that may be associated with immunization, a shortfall that could compromise the interpretation of adverse events or study endpoints reported following the introduction of RTS,S/AS01 vaccine in children (Praet et al. 2022a). Vaccine research, development, manufacturing, testing, and evaluation require investment in biotechnology and omics capacity in Africa (Makenga et al. 2019). The healthcare and research infrastructure capacity in Africa is not adequate to comprehensively assess the impact of human genetic variation on the efficacy of RTS,S/AS01 vaccine (Bell et al. 2021; Omotoso et al. 2022; Sirugo et al. 2008).

The high human genetic diversity in Africa has a lot to offer towards understanding the efficacy and safety of vaccines in different populations (Sirugo et al. 2008). The fact that the RTS,S/AS01 vaccine will be introduced into national immunization programs in the near future necessitates building capacity for local scientists and institutions to evaluate its safety and efficacy. This capacity will greatly impact the development and testing of other future vaccines for endemic diseases in Africa. High-throughput sequencing technologies (HTS) are essential to omics studies (Reuter et al. 2015). The last 2 years have already seen investment in installing HTS technologies at several public health institutions in Africa with a goal of incorporating genomics in routine surveillance of endemic pathogens (Inzaule et al. 2021). Omics data is very critical in assessing vaccine efficacy and effectiveness (Cotugno et al. 2019). This requires unique

techniques that utilize the technology that has remained largely unavailable in most of the low- and middle-income countries. As Africa aims for 60% of their vaccine supply to be produced within the continent by 2040, it is important to build omics capacity in Africa that will inform vaccine development and testing.

The RTS,S/AS01 malaria vaccine rollout in Africa

Recently, WHO welcomed the launch by Global Alliance for Vaccines and Immunization (GAVI), the Vaccine Alliance for malaria-endemic countries to apply for funding to introduce, or further rollout, the RTS,S/AS01 malaria vaccine (Hogan et al. 2020b). This international support of nearly US$ 160 million from 2022 to 2025 will facilitate increased access to the RTS,S/AS01 vaccine by children at high risk of morbidity and mortality from malaria. This fund has been made available starting with Ghana, Kenya, and Malawi, the three African countries that began pilot introduction of the vaccine in 2019 (Adepoju 2019), and then expanding to other eligible malaria-endemic countries. Since the RTS,S/AS01 malaria vaccine was introduced in 2019, it has been well accepted in African countries after a relatively short period of time.

To date, approximately 1.3 million children have benefitted from the RTS,S/AS01 vaccine in the three African countries where it is being piloted (Adepoju 2019). GAVI's new funding opportunity brings us one step closer to reaching millions of children across Africa with the life-saving RTS,S/AS01 malaria vaccine. Following WHO's recommendation in October 2021 for widespread use of the RTS,S/AS01 malaria vaccine among children in regions with moderate to high *P. falciparum* malaria transmission, a number of malaria-endemic countries have expressed interest in adopting the vaccine and are expected to apply for funding from GAVI to introduce the RTS,S/AS01 malaria vaccine.

The RTS,S vaccine works specifically against *P. falciparum*, which is the deadliest malaria parasite and the most prevalent on the African continent. Where the vaccine has been introduced, there has been a substantial decline in children being hospitalized with severe malaria and a drop in mortality in the age group that is eligible for this vaccine (Adepoju 2019; Ndungu et al. 2019). As malaria-endemic countries in Africa embrace the RTS,S/AS01 vaccine, it is important to have a clear understanding of the impact of human genetic diversity on the efficacy and immunogenicity of this life-saving vaccine.

Human genetic variation and immunogenicity and efficacy of RTS,S/AS01 vaccine

Mass vaccination campaigns of the RTS,S/AS01 malaria vaccine have the potential to offer protection to all age groups against malaria which is however very short-lived because of the very low reported efficacies by multiple studies. A 7-year clinical trial performed among African children revealed that the RTS,S/AS01 vaccine efficacy and protection diminished over time especially in the fifth year due to repeated exposure to malaria parasites (Ndungu et al. 2019). Studies focusing on the immunogenicity of RTS,S/AS01 vaccine reported an extensive increase of CD4 + T cells after exposure to RTS,S/AS01 vaccine which is associated with increased protection (White et al. 2015).

Vaccine responses have been shown to be highly affected by human genetic differences, and association studies have identified variants in immune system genes, especially human leukocyte antigen (HLA) genes on chromosome 6 (Garamszegi 2014; Nielsen et al. 2018). This is not surprising given that HLA genes are central to the immune response (Fairfax et al. 2012). The proteins in the HLA complex are highly polymorphic, and the polymorphism lies in the grove of the HLA proteins where short peptide fragments are presented to T cells allowing for the recognition of self and non-self (malaria parasites). Key HLA genes central to adaptive responses are class I proteins that are present on every cell and aid in intracellular antigen presentation for the destruction of infected cells by CD8 T cells predominantly, and class II proteins that present extracellular antigens to promote CD4 T cell activation and B cell proliferation. The polymorphism in HLA genes is the result of balancing selection called over dominance whereby selection acts towards having two different alleles at every gene to better allow recognition and response to a broad array of pathogens or strain variation responses (Sanchez-Mazas et al. 2017). Some studies have indicated that variations in certain HLA molecules impact on immune responses to vaccines. For example, HLA-A*02-positive individuals were found to have a greater RV144 HIV-1 vaccine efficacy compared to HLA-A*02-negative individuals (Gartland et al. 2014). Therefore, it is important to conduct studies evaluating the association of HLA genetic variants and efficacy to malaria vaccine candidates.

Variation in HLA class II genes has been shown to affect antibody responses to *P. falciparum*, including liver stage antigens in monkeys (Reyes et al. 2017). There is evidence that variant epitopes of circumsporozoite protein (CSP) may be selected by HLA-restricted CTL responses and that responses to such variants may be mutually antagonistic as has been reported in some studies (Bucci et al. 2000; Gilbert et al. 1998). These data imply that parasite antigenic polymorphisms combined with HLA restriction of immunity to T cell epitopes may reduce the immunogenicity and efficacy of the RTS,S/AS01 vaccine. To date, the only HLA association study with RTS,S/AS01 vaccine efficacy has been a combined analysis of 222 subjects from 10 phase II controlled human infection trials to the vaccine strain (Nielsen et al.

2018). The analysis was limited to 37 different serotypes relating to two MHC class I genes (HLA-A, HLA-B) and one MHC class II gene (HLA-DRB1) (Nielsen et al. 2018). Three (HLA-A*01, HLA-B*08, and HLA DRB1*15/16) of the 37 broader sero-groups assessed had statistically significant protective effects, while three others (HLA A*03, HLA-B*53, and HLA DRB1*07) were associated with decreased efficacy (Nielsen et al. 2018). However, this study was relatively underpowered, implying that some of the associations were weak. While class II associations could be expected, it is interesting that associations of class I variation were found as well and potentially suggestive of variation in CD8 T cell responses. There have not been any genome-wide association studies of efficacy nor studies in the African context where the RTS,S/AS01 vaccine is planned to be most broadly delivered. Such large-scale studies in Africa are certainly warranted to fully understand the impact of human genetic variation on the immune responses to the RTS,S/AS01 vaccine.

Results from studies conducted using immunoinformatics tools to compare T helper epitopes contained in the RTS,S vaccine antigens with *P. falciparum* circumsporozoite protein (CSP) variants isolated from infected individuals in Malawi show that the prevalence of epitopes restricted by specific HLA-DRB1 alleles was inversely associated with the prevalence of the HLA-DRB1 allele in the Malawi study population (Khan et al. 2020), suggesting immune escape. Furthermore, T-cell epitopes in the CSP of strains circulating in Malawi were found to be more often restricted by low-frequency HLA-DRB1 alleles in the population (Khan et al. 2020). These together with other factors may contribute to variable and suboptimal efficacy of the RTS,S/AS01 vaccine.

The HLA complex and immunity to malaria

The unique variability of the genes that encode HLA molecules and their haplotypic composition, especially in native Africans, is proposed to have resulted from the need to fight multiple and frequent deadly infectious pathogens (Tukwasibwe et al. 2021). HLA class I molecules are major ligands for killer-cell immunoglobulin-like receptors (KIR), and as such, they play a role in regulation of NK cell activity during malaria infection (Prakash et al. 2018; Tukwasibwe et al. 2021). HLA class I molecules also present malaria antigens to T cells and are therefore important in adaptive immunity to malaria, which is critical during liver stage *P. falciparum* malaria infection. HLA class II molecules mediate the clearance of red blood cells infected with *P. falciparum* parasites through stimulation of T helper cells. Some studies have clearly shown that HLA molecules influence antibody titres to malaria antigens, including glutamate-rich protein and merozoite surface antigens (Tukwasibwe et al. 2020).

Several studies have shown some *HLA* genetic variants to be associated with susceptibility or protection from severe malaria (Diakite et al. 2009; Osafo-Addo et al. 2008). However, results have been inconsistent. The first study on the role of *HLA* in malaria described protection from cerebral malaria and severe malaria anemia conferred by the *HLA* class I allele, *HLA-Bw53*, and the *HLA* class II haplotype, *HLA-DRBl*1302-DQAl*0102-DQBl*0501* (Lyke et al. 2011). Molecular analysis revealed that liver stage antigen-I (LSA-1), a liver-stage specific antigen of *P. falciparum*, was recognized by *HLA-Bw53*-positive individuals (Lyke et al. 2011). However, these findings have not been confirmed in other malaria-endemic populations, and significant associations of malaria antigens other than LSA-1 with HLA molecules have not been discovered.

In studies of interactions between variable HLA molecules and polymorphic parasite factors, it has been demonstrated that the *P. falciparum* circumsporozoite protein binds to HLA-DR and HLA-DQ molecules in vitro as well as in animal models. Two HLA class II alleles, DRB1*04 and DPB1*1701, have been observed to be more frequent in severe, compared to uncomplicated malaria. HLA-B49, -A1, -B27, and HLA-DRB1*0809 were shown to be strongly associated with severe malaria in a study conducted in Mumbai in India (Ghosh 2008). HLA-A19 and HLA-DQB1 *0203 were associated with protection from severe malaria in the same population (Ghosh 2008). In a study conducted in Thailand in patients with severe cerebral malaria, HLA-B46 was significantly associated with the risk of cerebral malaria, while HLA-B56 and HLADR1*1001 were associated with protection from cerebral malaria (Hirayasu et al. 2012). In Senegal, HLA-DR3 and HLA-DR10 were strongly associated with cerebral malaria (Modiano et al. 2001). In the Gambia, HLA-B53 and HLA-DRB1*1302 alleles were found to be strongly associated with protection from severe malaria (Diakite et al. 2009).

Killer cell immunoglobulin-like receptors

Killer-cell immunoglobulin-like receptors (KIRs) are a family of highly polymorphic type 1 transmembrane glycoproteins expressed on the surface of NK cells and some T cells that bind HLA class I molecules and regulate NK cell functions. KIRs are encoded by a set of highly polymorphic genes located within the leukocyte receptor complex on human chromosome 19q13.4. *KIRs* are the second most genetically diverse family in the mammalian genome after *HLA*, and they differ between individuals mainly at three levels, gene content, allelic diversity of individual *KIR* genes, and variation in the binding specificity of individual KIRs to HLA class I ligands (Tukwasibwe et al. 2021).

The human *KIR* genes are grouped into KIR A and KIR B haplotypes. Haplotype A comprises by definition a fixed number of 7 KIR genes, including 3 "framework"

genes present in all haplotypes (*KIR3DL3*, *KIR2DL4*, and *KIR3DL2*) and KIR2DL1, KIR2DL3, *KIR3DL1*, and KIR2DS4—which is the only activating KIR in this haplotype (Tukwasibwe et al. 2020). Because *KIR2DS4* often codes for a deleted variant, this activating receptor is non-functional in most individuals; hence, haplotype A is thought to be mostly inhibitory (Tukwasibwe et al. 2020). About half of the individuals in any population studies to date will have a haplotype A (Tukwasibwe et al. 2020). Most diversity in Haplotype A is conferred by allelic polymorphism (Tukwasibwe et al. 2020). By definition, all other combinations of 4–16 *KIR* genes are classified as Haplotype B, including many activating KIR such as *KIR2DS1*, *KIR2DS2*, *KIR2DS5*, *KIR3DS1*, and *KIR2DL5* (Tukwasibwe et al. 2020). Diversity of haplotype B is conferred by gene content. Many disease association studies with *KIR* genes actually analyze the association with haplotypes because, due to the tight linkage disequilibrium, it is difficult to isolate the role of single *KIR* genes (Tukwasibwe et al. 2020).

It has been proposed that *KIR* A is specialized in fighting infectious pathogens, while KIR B is important in ensuring successful reproduction (Nakimuli et al. 2015). *KIR2DP1* and *KIR3DP1* are pseudogenes that do not encode cell surface receptors (Nakimuli et al. 2013). The strength of KIR and HLA binding varies depending on the specific receptor-ligand pair, and the affinity of several pairs, and, in turn, it impacts on the regulation of NK cell activity. Heterogeneity in *KIR* gene content combined with allelic polymorphisms may lead to extensive haplotypic diversity and highly diverse NK cell populations within an individual. *KIR* diversity may in turn contribute to heterogeneous NK cell responses to malaria infection which will in turn supplement the action of RTS,S/AS01 vaccine.

Genetic diversity in cytokine genes

Host genomic studies offer an invaluable approach to find genes and molecular pathways involved in the inflammatory response to malaria, but researchers in high malaria burden settings need to embrace the application of omics tools (Hodgson et al. 2019). Experimental models and novel genotyping by sequencing techniques are promising approaches to delineate the relevance of inflammatory response gene variants in the natural history of malaria infection (Penha-Gonçalves 2019). Diversity in genes secreting cytokines also plays a role in determining malaria infection outcomes (Natama et al. 2021). This further is likely to influence malaria vaccine responses in different populations. A reciprocal relationship exists between pro- and anti-inflammatory cytokines. In general, during acute malaria infection, the net effect of interactions between pro-inflammatory Th-1 type responses during the early stage of infection is generally mediated by IL-12, TNF, IL-6, and IFN-γ; all these are necessary for parasite control and robust timely anti-inflammatory Th-2 restricted responses mediated primarily by IL-10, IL-4, and TGF-β which are vital for the prevention of host tissue damage determine disease outcome (Ademolue et al. 2017; Popa and Popa 2021).

Human genetic variants controlling inflammatory responsiveness have been implicated in determining malaria clinical outcomes depending on the history of exposure to infections. Under the framework of a polygenic model of malaria susceptibility, the additive effects of genetic variants conferring strong inflammatory responsiveness to infection concur to severe disease but may favor the efficiency of anti-parasite responses in repeatedly exposed individuals. On the other hand, joint effects of host alleles conferring low inflammatory responsiveness result in increased resilience to severe malaria but are associated with asymptomatic parasitemia in exposed individuals possibly due to inefficient parasite clearance (Clark et al. 2006).

Polymorphisms in Fc gamma receptors and susceptibility to malaria

Antimalarial antibodies, IgG, bind directly to malaria parasites causing their neutralization. However, the action of antibodies alone is not always sufficient to eliminate parasites from humans (Amiah et al. 2020). One key element involved in the recognition of IgG that plays a crucial role in the destruction of malaria parasites is Fc gamma receptors (Amiah et al. 2020). These receptors are expressed on the surface of immune cells (Amiah et al. 2020). Several polymorphisms have been detected in the genes encoding these receptors, associated with susceptibility or resistance to malaria in different populations (Amiah et al. 2020). Polymorphisms within the family of Fc gamma receptors may impact on the efficacy and immunogenicity of the RTS,S/AS01 malaria vaccine.

Recent results indicate that the FcγRIIa-R/R131 is associated with severe malaria. Higher levels of IgG1, IgG2, and IgG4 have been shown to be associated with the FcγRIIa-H/H131 genotype among patients with uncomplicated malaria (Nasr et al. 2021). Although the FcγRIIa-F/V176 genotype was not associated with uncomplicated malaria, it showed a significant association with severe malaria (Nasr et al. 2021). Interestingly, the FcγRIIIa-V/V176 genotype offers protection against severe malaria. Severe malaria patients carrying the FcγRIIIa-F/F genotype have higher levels of AMA-1-specific IgG2 and IgG4 antibodies (Nasr et al. 2021). The *FcγR* (*IIa*, *IIIa*, and *IIIb*) gene variants and anti-malaria IgG subclasses play an important role in susceptibility to malaria infection (Nasr et al. 2021). The implications of specific Fc gamma receptor (*FCGR*) genes in innate and adaptive immunity are of particular interest in understanding the efficacy and immunogenicity of RTS,S/AS01 vaccines.

Concluding remarks

Understanding how human genetic variation modulates vaccine efficacy is critical for guiding the RTS,S/AS01 vaccine use. Researchers must uncover the genes involved and evaluate their relative importance in order for the vaccine implementation to fully contribute towards the goal of malaria elimination. Furthermore, any malaria vaccine will not be used in isolation, but rather as part of an integrated program leveraging other control measures due to the modest efficacy of RTS,S/AS01. It is crucial to understand how to best integrate vaccination into specific malaria control programs, as this information will be utilized in policy decisions concerning the RTS,S/AS01 vaccine use.

The lack of ownership of genomics, transcriptomics, proteomics, metabolomics, and cell phenotyping studies by African researchers and institutions has generally been attributed to a lack of local capacity and infrastructure. However, recently, there have been growing efforts to develop this capacity across Africa through several consortia such as the Human Health and Heredity in (H3Africa), Africa CDC, Africa Centre of Excellence in Bioinformatics and Data Intensive Sciences, and Universities that have started developing and integrating omics into their training programs. Indeed, the African continent has recently contributed important omics research data in fields ranging from infectious diseases, such as the discovery of the omicron and delta SARS- CoV-2 variants in Botswana and South Africa to ecological studies such as the Africa Biogenome project.

It is important that Africans through their local institutions take the lead in applying omics approaches to develop solutions to malaria. Africans need to be empowered to undertake omics studies to understand immune responses if they are to contribute in malaria vaccine development and testing. There is a need to apply for capacity-building grants in the field of malaria omics research aimed at developing capacity in African institutions to sequence HLA and KIR genes up to allele level. This will help in the optimal utilization of the infrastructure that has been put up with funding from agencies such as the NIH and Wellcome Trust. African institutions with capacity in omics should offer support to other institutions where this capacity is not available.

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Declarations

Conflict of interest The authors declare no competing interests.

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