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Malaria vaccine-related adverse events among children under 5 in sub-Saharan Africa: systematic review and meta-analysis protocol

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ABSTRACT

Introduction The RTS,S vaccine has been approved for use in children under 5 living in moderate to high malaria transmission areas. However, clinically important adverse events have been reported in countries in sub-Saharan Africa. This systematic review aims to assess the frequency, severity and clinical importance of vaccine-related adverse events.

Methods and analysis This systematic review protocol has been prepared following robust methods and reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses for protocols guidelines. We will search PubMed, CINAHL, LILACS, Google Scholar, SCOPUS, WEB OF SCIENCE, Cochrane library, HINARI, *African Journals Online*, Trip Pro and TOXNET from 2000 to 30 September 2023, without language restrictions. We will also search conference proceedings, dissertations, World Bank Open Knowledge Repository, and WHO, PATH, UNICEF, Food and Drugs Authorities and European Medicines Agency databases, preprint repositories and reference lists of relevant studies for additional studies. Experts in the field will be contacted for unpublished or published studies missed by our searches. At least two reviewers will independently select studies and extract data using pretested tools and assess risk of bias in the included studies using the Cochrane risk of bias tool. Any disagreements will be resolved through discussion between the reviewers. Heterogeneity will be explored graphically, and statistically using the I^2 statistic. We will conduct random-effects meta-analysis when heterogeneity is appreciable, and express dichotomous outcomes (serious adverse events, cerebral malaria and febrile convulsion) as risk ratio (RR) with their 95% CI. We will perform subgroup analysis to assess the impact of heterogeneity and sensitivity analyses to test the robustness of the effect estimates. The overall level of evidence will be assessed using Grading of Recommendations Assessment, Development and Evaluation.

Ethics and dissemination Ethical approval is not required for a systematic review. The findings of this study will be disseminated through stakeholder forums, conferences and peer-review publications.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will not rely on clinical trial data only but also observational studies including case series, case reports, country-specific Food and Drugs Authorities reports and the European Medicines Agency records accruing data during the early and postmarketing phases of clinical trials (phases II, III and IV).
⇒ Pooled analysis of a number of individual clinical trials may enable the identification of missed serious or rare but clinically important adverse events following vaccination.
⇒ The study uses a comprehensive search strategy that combines a number of relevant electronic databases and non-database sources to attempt to retrieve all potentially relevant studies.
⇒ A possible limitation of this systematic review could be the lack of quality reporting of the primary studies data to be included in this review.

INTRODUCTION

An estimated 241 million cases and 627 000 deaths from malaria occurred globally in 2020.[1] Sub-Saharan Africa (SSA) accounted for 228 million (95%) of global malaria cases[1] and children under 5 years represented about 77% of malaria deaths in SSA.[2] Although the incidence of malaria reduced from 81/1000 cases in 2015 to 59/1000 cases in 2020 (a reduction of 27%), there was an increase in the number of deaths during the same period from 562 000 in 2015 to 627 000 in 2020 (an increase by 65 000; 10%).[1] The disease continues to pose a major public health threat worldwide.[3 4] Despite recent evidence showing reductions in the burden of malaria in some countries in SSA,[5] national and international health authorities continue to place a high emphasis on the deployment of malaria vaccines,[2 6] as the number of clinical cases and deaths still remain high. It has

been projected that three doses of RTS,S vaccine can avert about 93 940 clinical disease and 394 deaths per 100 000 children under 5 and up to 116 480 cases and 484 deaths per 100 000 in the same population of children receiving four doses.[7]

Overview of malaria intervention strategies

Global efforts to combat malaria go way back to the 1900s,[8] with quinine in 1880s,[9] Indoor Residual Spraying with dichlorodiphenyltrichloroethane (DDT) between 1950s and 1960s[6] and DDT mass spraying from 1966,[10] which was abandoned in 1969 largely due to the emergence of DDT resistance.[8 11] The Roll Back Malaria Initiative started in the new millennium with insecticide-treated nets.[4 12 13] Several interventions used or tried that focused largely on reducing or interrupting malaria transmission have been abandoned over the years owing to lack of sustainability, high programme cost and the emergence of resistance.[14 15] The strategy of prompt, accurate diagnosis and treatment of malaria cases was introduced at the beginning of the new millennium,[5] to be followed by switch from monotherapies (chloroquine, amodiaquine and quinine) to Artemisinin-based Combined Therapies (ACTs),[16 17] Seasonal Malaria Chemoprophylaxis[16] and Intermittent Preventive Treatment in pregnancy.[6] Then in 2012, the WHO initiated Test, Treat and Track (3T) policy[17] that recommends universal testing of all suspected malaria cases, treatment with quality assured antimalaria drugs, mainly ACTs, and tracking all confirmed and treated patients.[18 19] Given that it has been difficult for these interventions to achieve reduction in the burden of disease, incidence of severe disease, deaths, mosquito proliferation and parasite reduction, the emphasis is shifting towards vaccine development and deployment.[20]

Malaria vaccine development

Malaria vaccine development and trials can be traced back to the 1980s and early 1990s when different vaccine candidates including the chimpanzee adenovirus 63 and Modified Vaccinia Virus Ankara (ChAd63/MVA ME-TRAP), Merozoite Surface Protein 3 (MSP3), GMZ2 and the radiation-attenuated *Plasmodium falciparum* sporozoites (PfSPZ) vaccine were tested.[21–23] The diversity in immunogenicity and the intricacy of infection restricted the development of potentially effective candidate vaccines.[21] Recent advances in antigen and adjuvant creation, however, have overcome many of these early hurdles, resulting in the development of novel vaccine candidates.[2] The RTS,S malaria vaccine is the first vaccine candidate approved for use.[21 24] The malaria vaccine RTS,S is a recombinant antigen produced in *Saccharomyces cerevisiae* that consists of a fragment of the circumsporozoite antigen, a sporozoite surface antigen of the *P. falciparum* malaria parasite, linked to the S protein of the hepatitis B virus.[25] The S protein is the surface antigen of the hepatitis B virus (HBsAg).[26] The RTS,S candidate vaccine was tested with two patented Adjuvant Systems, AS02 and AS01.[27] The immunostimulants Monophosphorylate lipid A (MPL), a detoxified derivative of the lipopolysaccharide obtained from the Gram-negative bacteria Salmonella Minnesota R595 strain, and QS21, a saponin component of tree bark, are included in both Adjuvant Systems.[28] The adjuvant AS02 has a unique oil-in-water emulsion, whereas AS01 contains liposomes.[28]

The RTSS vaccine candidates clinical trials started in the early 2001; it's development dates back to the late 1980s as a collaborative effort between Smith, Kline & Co. and the Walter Reed Army Institute of Research.[29] Two different adjuvants (AS01 and AS02) systems were tested in phase II trials[28] and their ability to elicit an immune response against malaria has been documented in several studies involving North American and African adults.[2 24 30 31] The GlaxoSmithKline's RTS,S vaccine (Mosquirix) was the first malaria vaccine to enter phase III trials[5] under the strict monitoring of the WHO and delivered through the Expanded Programme on Immunisation in malaria-endemic areas.[32] The review of unsolicited adverse event data sets from individual studies yielded the conclusion that the overall pattern of events reported was consistent with the known background disease burden.[21] There was no evidence of a worrisome imbalance in individual occurrences in the studies.[3]

How the intervention might work

The malaria vaccine RTS,S/AS01 targets the circumsporozoite protein on the sporozoite surface of the disease stages. It is made up of the central tandem repeat and carboxyl-terminal part of the *P. falciparum* Circumsporozoite Protein fused to the HBsAg, which is coexpressed in yeast with the non-fused HBsAg. The RTS malaria–hepatitis B fusion protein is coexpressed with the S antigen alone in *Saccharomyces cerevisiae* yeast cells, and then fuse into virus-like particles to display the CSP and S sequece at their surface.[33 34] It is formulated as 25 g with AS01 made up of liposomes and immunomodulatory components as an adjuvant[22] is reconstituted as a 0.5 mL vaccine. The RTS,S/AS01 vaccine is administered intramuscularly into the anterolateral thigh. Children receive the first dose at either 5 months or 6 months after birth; the second and third doses are repeated at 7 months and 9 months after birth; while the fourth dose is administered when the child is 18 months.[21] The RTS,S/AS01 has shown higher efficacy in children aged 5–17 months than those aged 6–12 weeks who received three or four doses of the vaccine and were followed up for 12 months: 51% (range 47%–55%) for age 5–17 months,[3] whereas this was 32.9% (range 26.3%–38.9%) for the 6–12 weeks age group,[21] for uncomplicated malaria and 45% (22%–60%) for 5–17 months age group[3] as compared with 38.5% (7.8%–59.0%) for the 6–12 weeks age group, for severe malaria.[21] For children up to 40 months of age who received their fourth dose at 18 months after the third dose of RTS,S/AS01, vaccine efficacy rate was 39% (range 34%–43%) and 29% (range 6%–46%) against uncomplicated and severe malaria, respectively.[3]

Why it is important to do this review

The RTS,S/AS01 vaccine has been assessed in phase II and III trials and shown good pharmacokinetic and pharmacodynamic properties.[3 35–37] The phase III trials conducted in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania) involved a large number of children and reduced clinical malaria in children aged 6–12 months by 28% and up to 44% in children 5–17 months.[2 21 24 38] However, some potential safety concerns were raised in the phase III trials.[36] For example, febrile seizures (which were self-limiting) have been reported to be higher among vaccinated children.[21] There have also been reports of febrile convulsion at 104 cases/100 000 doses within 7 days of RTSS/AS01 administration; 25 cases/10 000 doses among those receiving the fourth dose and 12 cases/10 000 doses among those receiving their third dose.[21 31] Additionally, meningitis and cerebral malaria were eight times more likely to develop among those receiving the RTS,S/AS01 vaccine than non-vaccinated.[31 38] This resulted in the European Medicine Agency recommending a post-marketing phase IV trial on a larger scale to further investigate RTSS/AS01 safety profile.[34]

The occurrence of meningitis was suspected to be associated with those receiving the vaccine for the first time (mostly infants between 6 and 12 weeks) and those receiving their fourth dose,[39] suggesting a possible relationship between age and dose. A recent phase IV trial and pilot phase of the Malaria Vaccine Implementation Programme (MVIP) have shown that those excesses in meningitis and cerebral malaria were not found to be associated with the RTS,S vaccination.[3] However, there may be variations in the vaccine safety across SSA settings. Therefore, extensive and adequate data are needed. Pooled data of individual clinical trials and spontaneous reporting may enable the identification of serious but rare adverse events missed during the trial phase.

This systematic review and meta-analysis aims to conduct a comprehensive assessment of adverse events associated with the RTS,S vaccines among infants and young children in SSA. Through a pooled analysis of clinical trial data and other studies, we aim to provide valuable information about the magnitude (frequency and severity) of adverse events associated with the vaccine, as well as variations across implementing sites. In particular, we will investigate whether there is any evidence of vaccine-related meningitis and cerebral malaria. By conducting a thorough and rigorous analysis, we aim to provide programme managers in endemic countries with reliable information that can help guide decisions around the malaria vaccine. We believe that expert peer review of this manuscript will provide a rich source of additional information that will enable us address potential loopholes, particularly in the methods, and ensure robust and trusted systematic review conclusions on this important topic.

REVIEW METHODS

This systematic review protocol has been prepared in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses protocol (PRISMA-P) (online supplemental file 1).[40] Electronic databases and other sources searched will be reported using the PRISMA flow diagram (online supplemental file 2)[41] and a pretested flow chart will be used for study selection. The full review will be reported in accordance with the PRISMA guidelines[41] and it is expected to start on 1 September 2023, data analysis on 1 November and the review completed by 31 December 2023.

Patient and public involvement

The review questions and outcomes to be assessed have been developed collaboratively with patients and public involvement, and informed by their priorities, experiences and preferences in line with GRIPP2 reporting checklists. The review findings will be shared with relevant patient communities who will also be involved in the dissemination of the results.

Criteria for considering studies for inclusion in this systematic review

Types of study

Randomised controlled trials (RCTs) and quasi-randomised controlled trials (qRCTs) of phases II, III and IV that assessed safety of RTS,S in SSA will be eligible for inclusion in this systematic review. Other study types (cohort, case–control and cross-sectional studies, as well as case series and case studies) that investigated adverse events associated with the RTS,S/AS01 malaria vaccine will be included. Programmatic databases from the Malaria Vaccine Pilot Evaluation (MVPE) across Ghana, Kenya and Malawi will be included in this review. Reviews, opinions and commentaries will not be included, but we will go through the full reference lists to identify any potentially eligible primary study missed by our searches. If the review involves the global community but has SSA subset, we will retrieve the studies conducted in SSA for inclusion. In the case where the results of a multicentre or multicountry study have been pooled, we will attempt to disaggregate the data for each study site or country.

Participants

Children 6 weeks to 5 years living in malaria-endemic areas in SSA, who have received 1–4 doses of RTS,S/AS01 malaria vaccine will be eligible for inclusion.

Intervention

The RTS,S malaria vaccine, a hybrid recombinant protein vaccine with a target function at the pre-erythrocytic stage of malaria. It is made up of the central tandem repeat and carboxyl-terminal part of the *P. falciparum* Circumsporozoite Protein fused to the HBsAg, which is coexpressed in yeast with the non-fused HBsAg. The RTS malaria–hepatitis B fusion protein is coexpressed with the S antigen alone in *Saccharomyces. cerevisiae* yeast cells, and then fuse into virus-like particles to display the CSP and S sequence

at their surface[33 34] and administered in 25 ug with AS01 as an adjuvant. The RTS,S/AS01 is reconstituted as a 0.5 mL vaccine and it is administered intramuscularly into the anterolateral thigh. Children received the first dose at either 5 months or 6 months after birth; the second and third doses are repeated at 7 months and 9 months after birth; while the fourth RTS,S/AS01 dose is administered when the child is 18 months of age.[21]

Comparison

Infants and children under 5 years who received an intervention other than RTS,S/AS01 or a placebo will be used for comparison. Other control subjects will include children up to 24 months who received two doses of pneumococcal conjugate vaccine (Prevnar, Wyeth Lederle Vaccines) and one dose of Haemophilus influenzae type b (Hib) vaccine (GSK Biologicals) or the rabies vaccine.[21] Children who received three doses of RTS,S/AS01 (as 25 g of RTS,S antigen in a 0.5 mL dose) or fractional doses (as 25 ug of RTS,S antigen in 0.1–0.5 mL) will be considered as the intervention.[2]

Outcomes

Primary outcomes

- Serious adverse event defined as any untoward reaction or event that requires additional intervention or results in disability, hospitalisation or death among vaccinated children.
- Meningitis among vaccinated compared with unvaccinated children.
- Cerebral malaria among vaccinated and unvaccinated children.
- Febrile convulsion among vaccinated and unvaccinated children

Secondary outcomes

- All non-serious adverse events categorised as mild to moderate events which do not meet the definition of a serious Adverse Events Following Immunisation (AEFI).

Search strategy

We will search PubMed, CINAHL, LILACS, Cochrane library, HINARI, *African Journals Online*, Google Scholar, Scopus, Web of Science, Trip Pro and TOXNET from 2000 to 30 September 2023 without language restriction. The key search terms will include RTS,S vaccine, RTS,S/AS01, Mosquirix; malaria vaccine, clinical trials, phase II and III trials, AEFI, adverse events, drug adverse reactions and side effects (table 1). Other sources to be searched for additional studies include grey sources such as conference proceedings, dissertations, preprint repositories, World Bank Open Knowledge Repository, and WHO, PATH, UNICEF, Food and Drugs Authorities and European Medicines Agency databases. We will review the reference lists of relevant studies and contact experts for published and unpublished studies.

Managing the search results and study selection

We will upload all references identified through our searches (electronic database and additional searches) into Mendeley where duplicates will be removed. The remaining references will be exported into Rayyan[42] where screening/selection of studies will be carried out by at least two of the reviewers independently using pretested study selection flow chart developed from the inclusion/exclusion criteria. First, titles and abstracts will be screened and those articles that meet the inclusion criteria will be listed and full text will be obtained for further assessment for inclusion/exclusion. The PRISMA flow diagram (online supplemental file 2) will be used to document the flow of studies and reasons for exclusion. Any disagreements between screening authors will be resolved through discussion.

Table 1 Search strategy for retrieving studies in PubMed (this will be adapted to the other databases)

Search	Query
#1	Search: ((((((((((((safety) OR (“side effects”)) OR (“adverse effects”)) OR (“adverse drug effects”)) OR (“adverse drug reactions”)) OR (“adverse events”)) OR (toxicity)) OR (tolerance)) OR (“immune tolerance”)) OR (tolerability)) OR (“Adverse events following immunization”)) OR (AEFI)) OR (“Adverse events of special interest”)) OR (AESI)
#2	Search: (((((((RTSS) OR (RTS,S)) OR (RTS,S/AS01)) OR (RTSS/AS01)) OR (“Malaria vaccine”)) OR (Mosquirix)) OR (MVIP)) OR (MVPE)) OR (Immunization)
#3	Search: ((((((((((((children) OR (infant)) OR (infants)) OR (toddler)) OR (toddlers)) OR (kid)) OR (kids)) OR (juvenile)) OR (“children below 5 years”)) OR (minor)) OR (minors)) OR (“young children”)) OR (“under 5 years”)) OR (“under 5”)) OR (“children 0–59 months”)
#4	Search: (#1) AND (#2) AND (#3)
#5	Search: ((“sub-Saharan Africa”) OR (Africa)) OR (SSA)) OR (Angola)) OR (Benin)) OR (Botswana)) OR (“Burkina Faso”)) OR (Burundi)) OR (Cameroon)) OR (“Cape Verde”)) OR (“Central African Republic”)) OR (Chad)) OR (Comoros)) OR (Congo)) OR (“Cote d'Ivoire”)) OR (Djibouti)) OR (“Equatorial Guinea”)) OR (Ethiopia)) OR (Eswatini)) OR (Gabon)) OR (“The Gambia”)) OR (Ghana)) OR (Guinea)) OR (“Guinea-Bissau”)) OR (Kenya)) OR (Lesotho)) OR (Liberia)) OR (Madagascar)) OR (Malawi)) OR (Mali)) OR (Mauritania)) OR (Mauritius)) OR (Mozambique)) OR (Namibia)) OR (Niger)) OR (Nigeria)) OR (Rwanda)) OR (“Sao Tome and Principe”)) OR (Senegal)) OR (Seychelles)) OR (“Sierra Leone”)) OR (Somalia)) OR (“South Africa”)) OR (Sudan)) OR (Swaziland)) OR (Tanzania)) OR (Togo)) OR (Uganda)) OR (Zaire)) OR (Zambia)) OR (Zimbabwe)
#6	Search: (#4) AND (#5)

Data extraction and management

A pretested data extraction sheet will be used by two reviewers to collect data on study characteristics, participants, interventions and outcomes. Information on study characteristics (country and year study was conducted, study design type, sample size, etc), details about the participants (target population, prior treatment status, sex, age, etc), context (malaria endemicity, prevalence), intervention (RTSS vaccination, dose, dosage, efficacy, safety and AEFI), process data on the implementation of RTS,S vaccines and comparison. For pooled primary study data involving different communities or countries, data will be disaggregated and where this is not possible, the study will be presented as one and the individual countries listed. For continuous data presented as geometric means, means and their SD will be extracted on the log scale. If the data were summarised as arithmetic mean, the means and their SDs will be extracted. We will extract medians or ranges when they are reported. Where data are unavailable or lacking the first or corresponding author will be contacted for information. When possible, we will contact the primary study investigators for the raw data. Any disagreements will be resolved through discussion between the review authors.

Dealing with missing data

Efforts will be made to identify reasons for missing data, the pattern of missing data and the potential impact of the missing data on the study. We will not impute as a means of addressing missing data but instead, we will contact primary study authors and where necessary ask for the raw data to enable us extract the missing data, where possible.

Assessment of quality of the included studies

Two reviewers will independently assess the risk of bias in the included studies using the Cochrane Risk of Bias (RoB) Tool for RCTs[43] (online supplemental file 3). This tool is a standardised method for evaluating the risk of bias in RCTs. The tool consists of seven domains namely: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Responses to each of the seven domains of the RoB will be rated as 'low', 'high' or 'unclear' risk of bias. Each study's overall risk of bias will be assessed by combining the risk of bias of the seven domains and rated as 'low', 'high' or 'unclear'.[43] For observational studies, the risk of bias in the included studies will be assessed using the quality assessment tool developed by Hoy *et al*[44] (online supplemental file 4). The tool assesses 10 domains, namely, representation, sampling, random selection, non-response bias, data collection, case definition, reliability tool, prevalence period, numerators and denominators. The first four domains assess the external validity in the included studies, whereas domains 5–10 assess internal validity. Responses to each of the 10 criteria in the appraisal tool will be rated as either 'low', 'high' or 'unclear' risk of bias. The overall rating of risk of bias will be based mainly on the internal validity domains and will be rated as 'low' or 'high'. We will not assign an overall numeric rating. This method agrees with the Grading of Recommendations Assessment, Development and Evaluation approach. Any disagreements will be resolved through discussion.

Strategy for data synthesis

Review Manager V.5.4 will be used to conduct the meta-analysis for each relevant comparison between the intervention and control. The analysis will be done separately for RCTs and quasi-RCTs. Analysis of each adverse event identified will be compared across studies. Dichotomous outcome will be presented as risk ratio (RR) or OR, whereas continuous outcome will be presented as mean difference (MD), each will be presented with their CI. Where applicable, heterogeneity will be investigated using meta-regression (either fixed or random-effect models) to examine the impact of potential effect modifiers. Subgroup analyses (age group, sex, etc) from included studies will be retrieved and compared in meta-regression analysis.

Assessment of heterogeneity and subgroup analysis

Heterogeneity will be assessed visually by inspecting overlaying CIs of the forest plots and outlying data, and quantitatively using the I^2 statistic. Where significant heterogeneity is detected, that is, I^2>75%, we will perform subgroup analyses to explore potential sources of variability. This will include examination of study characteristics such as study design, population characteristics (child's age, sex, malaria endemicity and number of doses of vaccine administered) and vaccine dosage. AEFIs identified among the age groupings, sex and number of doses received will be analysed and compared. Other subgroup analyses from included papers will be retrieved and compared with the meta-regression analysis. In addition, we will also perform sensitivity analyses to assess the impact of individual studies on overall effect estimates.

Sensitivity analysis

Sensitivity analysis will be conducted on the risk of bias domains to test the robustness of the effect estimates generated from the meta-analysis. Sensitivity analysis will be used to assess the impact of individual outliers on the overall effect estimate, and it will also be used to assess the effect of missing data and unpublished studies.

Ethical approval and dissemination

Ethical approval will not be needed since this study will be based on published data. This systematic review and meta-analysis is expected to provide data on adverse events that could potentially influence future policies. The final report of this study will be in the form of a scientific paper published in a peer-reviewed journal. Study findings will be presented at conferences, and copies shared with relevant stakeholders, authorities and agencies.

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Contributors Protocol conceptualisation and design: KO-A and AD-A. Drafting the work or revising it critically for important intellectual content: KO-A, KPA, KOA, NT, MA, DO, AAM and AD-A. Acquisition, analysis or interpretation of data: KO-A, KPA, KOA, NT, MA, DO, AAM and AD-A. Agreement to be accountable for accuracy or integrity of all aspects of the work: KO-A, KPA, KOA, NT, MA, DO, AAM and AD-A. Final approval of the version to be published: KO-A, KPA, KOA, NT, MA, DO, AAM and AD-A. Supervision of this work: AD-A.

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Patient and public involvement The review questions and outcomes to be assessed have been developed collaboratively with patients and public involvement, and informed by their priorities, experiences, and preferences in line with GRIPP2 reporting checklists. The review findings will be shared with relevant patient communities who will also be involved in the dissemination of the results.

Patient consent for publication Not required.

Ethics approval Not required.

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