Intermittent preventive treatment with sulfadoxine-pyrimethamine versus weekly chloroquine prophylaxis for malaria in pregnancy in Honiara, Solomon Islands: a randomised trial

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Background. Solomon Islands is a malarious nation in the Pacific with all four human Plasmodium species present. Although chloroquine prophylaxis is recommended for pregnant women, its effectiveness is uncertain because of chloroquine resistance.

Methods. We conducted a parallel-group, open label, individually randomised superiority trial comparing weekly chloroquine prophylaxis (CQ) with intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) between August 2009-June 2010 among pregnant women aged 15 to 49 years. Participants were randomised at the first antenatal visit using a computer-generated sequence and followed until delivery. Data on mosquito avoidance measures, and pregnancy outcomes were collected.

Results. Because of the low prevalence of malaria, enrolment was prematurely terminated. Among 660 participants (336 in CQ arm, and 324 in IPTp), 68% used a bednet, 53% used window-screens, and 26% lived in a house sprayed in the last 6 months; 91% used at least one of these methods. Peripheral parasitemia at enrolment was 1.5%. At delivery there were no differences between weekly CQ and IPTp in placental parasitemia (0/259 vs. 1/254) or peripheral parasitemia (2/281 vs. 1/267). There were no differences in maternal anaemia, birth outcomes or serious adverse events. A self-reported sulfa-allergy required non-inclusion for 199 of 771 ineligible women (26%).

Conclusions. The use of SP for IPTp is not suitable for prevention of malaria in pregnancy in Solomon Islands, given the low malaria prevalence and the possible high prevalence of sulfa-allergy. Scaling up of transmission-reducing interventions has probably contributed to the malaria reduction in Honiara.
chloroquine prophylaxis was effective in the face of increasing chloroquine resistance and incomplete compliance, whereas SP resistance still seemed low [5,6]. Intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) is used extensively in Africa and consists of two or three presumptive treatment doses of SP after the first trimester, given at least four weeks apart [7]. However, this regimen has not been evaluated in areas with co-existing transmission of P. vivax, a species known to be less responsive to this drug combination [8]. We conducted a randomised controlled trial to examine efficacy and safety of IPTp with SP compared to weekly chloroquine prophylaxis.

2 Materials and Methods

2.1 Study site and population

This parallel-group, open label, individually randomised superiority trial was conducted in Honiara, the capital of Solomon Islands, situated at sea level on Guadalcanal Island. According to the 2009 census, the population of Honiara city was 64,602 persons [9]. Malaria transmission is meso-endemic with perennial transmission. The Honiara City Council operates eight clinics, which offer antenatal clinics (ANC) one morning per week. At the end of each clinic, all ANC cards are transported to the National Referral Hospital in Honiara where most women deliver. Since 2008, long lasting insecticide-treated bednets (LLINs) are distributed free of charge in the antenatal clinics in Honiara City Council. A survey in one of the clinics in 2005-2006 revealed a malaria prevalence of 9.9% among 222 first ANC attendees (15.4% among 78 primigravidae, van Eijk, pers. comm.).

2.2 Participants

Primigravida and multigravida pregnant women attending ANC were eligible if they were 15-49 years of age, attended the ANC for the first time, were assigned routine antenatal care, had experienced quickening (feeling the movements of the baby), had a gestational age of 16-32 weeks as by the last menstrual period, or by palpation if the date of the last menstrual period was not available, and were planning to deliver in the National Referral Hospital. Exclusion criteria included use of chloroquine prophylaxis in the current pregnancy, a history of allergy to any of the study drugs, haemoglobin <7 g/dl, or being severely ill. Excluded women received the routine antenatal care with chloroquine prophylaxis as per current practice.

2.3 Randomisation

Randomisation codes were generated using web-based software prior to the start of the trial (http://www.randomization.com/, accessed 16 August 2007). The allocation ratio was 1:1 and the randomisation sequence was stratified by clinic using block sizes of 4 to 10, depending on the size of the clinic. The allocation sequence was concealed from the nurses involved in assessment and enrolment of the participants by using sequentially-numbered, opaque, and sealed envelopes containing a folded paper with the study number and assigned treatment arm. Corresponding envelopes were opened only after a participant had fulfilled the enrolment assessments and the woman had been issued with her study number. This was an open label trial; however, assessor masking was maintained throughout the study, and the technicians reading the blood smears, and the delivery staff weighing the newborn were not aware of the treatment arms.

2.4 Interventions and follow up

In the SP-arm, women received two treatment courses of IPTp with SP consisting of three tablets of SP at once (500 mg sulfadoxine and 25 mg pyrimethamine per tablet, Fansidar, Multichem, New Zealand) at enrolment and again later in pregnancy (at least four weeks apart). All SP was provided by the study staff as directly-observed therapy in the study clinic. Women in the chloroquine-arm received 300 mg base chloroquine weekly (two tablets of 200 mg equivalent to 150 mg base chloroquine in each tablet, Chloroquine, Multichem, New Zealand) from enrolment until delivery. Only the enrolment dose was supervised. A verbal history of adherence was obtained during follow-up. At enrolment, a questionnaire was administered to obtain demographic and socio-economic characteristics and obstetric information, and blood was obtained for a peripheral blood smear, a rapid diagnostic test (RDT), and assessment of haemoglobin. Women in each arm received routine antenatal care, including haematinic supplementation (fetal tablets containing 200 mg iron and 0.25 mg folic acid) and tetanus vaccinations. Women were advised to report to the clinic when ill, so they could be examined and prescribed according to the study protocol. Women with a positive RDT at enrolment or follow up were treated with Coartem (Novartis Pharma AG, Switzerland), the first line treatment in Solomon Islands. If applicable, they would start or continue with their intervention at the same time (chloroquine or SP). A haemoglobin assessment was repeated at a gestational age of approximately 36 weeks. Women with severe anaemia (haemoglobin <7 g/dl) were referred to the antenatal clinic for further evaluation and management.

2.5 Delivery

Participants were identified by study staff in the labour ward of the National Referral Hospital and delivery outcome was recorded. The birth weight was measured using an electronic balance (+/- 10 grams) immediately after delivery. Blood was obtained from the mother for a peripheral thick and thin blood smear, an RDT and a haemoglobin level, and a placental thick and thin smear was made using blood that welled up after incision of the cleaned maternal side of the placenta. Study completion was at discharge or seven days postpartum, whichever came first.
2.6 Outcomes and sample size

The primary outcome was placental malaria among primigravidae. Placental malaria is associated with infant low birth weight and maternal anaemia, and was used as a proxy indicator for malaria related morbidity [2]. Secondary outcomes among primigravidae included maternal anaemia in the third trimester, and low birth weight (a birth weight <2500 grams) at delivery. For all women, outcomes included maternal anaemia and maternal parasitemia at the time of delivery. Although the study enrolled women of all gravidae, the study was designed to detect a 50% reduction in the prevalence of placental malaria from an estimated 15% in the chloroquine group to 7.5% in the IPTp-SP group among primigravidae (80% power and two-sided alpha 0.05). Allowing for a 10% loss to follow-up, 676 primigravidae were required (338 per study arm). It was estimated that a total of 2504 women of all gravidae would be needed to enrol 676 primigravidae. An interim analysis was planned when half of the women had delivered to verify the parameters assumptions made in the design of the trial.

2.7 Laboratory assessments

Haemoglobin was measured using Hemocue (Hemocue® AB, Angelholm, Sweden). Thick and thin smears were stained with Giemsa. Asexual parasites were counted against 200 white blood cells, and expressed per microlitre assuming 8,000 white blood cells/μl. All positive smears and a random sample of 10% of the negative smears were read in duplicate for quality control. There was 92% agreement between the first and second reading. The RDTs used in the study were Carestart™ Malaria HRP2/pLDH (Pf/PAN) COMBO (Catalogue # G0131, Access BioInc, USA) and ICT Malaria Combo Cassette Test (Catalogue #ML02, ICT Diagnostics, South Africa), which also targets HRP2 to identify \textit{P. falciparum} and uses aldolase antigen to detect any malaria species. The ICT malaria Combo test was used at the beginning of the study, but replaced by Carestart when information became available about its better performance [10].

2.8 Definitions and data analysis

Maternal malaria and placental infection was defined as the presence of asexual parasites of any species or density detected in the blood smear or by RDT, and clinical malaria as ‘documented fever or a history of fever in the past 24 hrs in the presence of parasitaemia’. A haemoglobin <11 g/dl was defined as anaemia, and <8 g/dl as moderate-to-severe anaemia. A stillbirth was defined as a newborn that showed no signs of life at delivery (no gasping, no breathing, and no heart beat). Unanticipated severe adverse events included any maternal death, any serious drug reaction, any foetal death not explained by prematurity, delivery complications or low birth weight or any additional unexpected outcome. Data were analysed according to intention to treat and availability of outcomes, and women were included regardless of whether they had received the intervention and the intended number of doses. Twins were excluded from all analyses of foetal outcomes and of maternal haemoglobin at the time of delivery. Summary statistics were used to describe the study sample. Relative risks and mean differences and their confidence intervals were used to compare data from the study arms. The means of birth weight and haemoglobin were compared by Student’s t-test and one-way analysis of variance. Proportions were compared using the Chi square test or Fisher’s exact test if appropriate, and a \( P < 0.05 \) was regarded as significant. Data were analysed using SAS version 9.2.

2.9 Ethical approval

The study protocol received ethical approval from the National Health Research Ethics Committee in Solomon Islands and was reviewed by the Technical Working Group of the World Health Organization Western Pacific Region. The study was registered in a clinical trial database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT00964691). An independent data safety monitoring board oversaw implementation and the interim analysis of the trial. Written consent was obtained from all participants before enrolment.

2.10 Role of the funding source

The sponsor of the study had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3 Results

3.1 Enrolment

Of the 1526 women screened, 660 fulfilled the enrolment criteria and were randomised between August 2009-February 2010 (Fig. 1). Because of the unexpected low prevalence of malaria noted at enrolment and delivery (1-2%), a futility interim analysis was conducted after approximately 25% of women had been enrolled in February 2010. Enrolment was halted in March 2010 for futility, and because it became clear that an unexpected high proportion of the pregnant women reported SP allergy during the screening phase (Fig. 2A), severely limiting the potential application of SP as IPTp in this population. A reported sulfa allergy was the reason for eligibility for 25.8% of women who did not meet the inclusion criteria; a further 21.1% of women who declined participation reported as reason they were not willing to use SP (Fig. 2B). Twelve women were excluded for a haemoglobin < 7 g/dl (1.6%) and nine women because they were severely ill (1.2%). Enrolled participants were followed until the last delivery in August 2010.
3.2 Characteristics of the study population

Of the 660 pregnant women enrolled, 336 were randomised to the chloroquine regimen, and 323 to the SP regimen (Fig. 1). Baseline demographics and clinical characteristics were comparable (Table 1). Use of malaria prevention methods reported at baseline was good, with 68.0% of the women using bednets during pregnancy (98.9% LLINs), 52.5% of women living in houses with screened windows to prevent mosquitoes from entering, and 26.1% of the women living in houses that had been sprayed in the last six months. When combining these methods, 91.1% of women used at least one of these three malaria prevention methods. Antimalarial treatment during pregnancy before enrolment was reported by 13 women (2.0%). Antimalarials used included: arteether monotherapy (1 woman), quinine (2), chloroquine (4), and arteether-lumefantrine (6). The malaria prevalence was low by RDT (0.6%) and blood smear (1.5%). Two-thirds of the participants were anaemic at baseline (66.8%).

3.3 Follow up

Similar proportions of women were lost to follow-up before delivery in the two groups (Fig. 1). Among 273 women with documented follow-up visits in the chloroquine arm, 97% reported using chloroquine prophylaxis per protocol on a weekly basis. Among 255 participants in the SP arm with documented follow-up visits, 224 (87.8%) received a second dose of SP. Thirteen women in the chloroquine arm and 16 in the SP arm made at least one unscheduled visit to the clinic because they did not feel well (RR 0.78, 95% CI 0.38-1.60). Eight women were diagnosed as ‘clinical malaria’ (five in the chloroquine and three in the SP arm), although only five women had malaria confirmed using an RDT or a blood smear prepared (four in the chloroquine arm [P. falciparum 1, P. vivax 1 and mixed infections 2], and one in the SP arm [P. falciparum]; RR 3.86, 95% CI 0.43-34.33). Except for one woman in the chloroquine arm with P. vivax at enrolment who presented with P. vivax at delivery, none of the other women with malaria at or after enrolment had a positive malaria test during the remainder of the pregnancy or at delivery. The participant with P. vivax at enrolment and delivery had a negative malaria test result one month after enrolment; she reported not to take the chloroquine as instructed during her last month of pregnancy.
There were no clinically relevant differences in anaemia or haemoglobin level by treatment arm among the 295 women who contributed in the third trimester and the same pattern was seen at delivery among the 535 women with a haemoglobin result (Table 2). Birth outcomes were available for 88.9% of the participants. There were nine twin deliveries, all live born. Among the 578 singleton deliveries, there were 10 stillbirths, with no difference by prevention regimen (Table 2). The risk of low birth weight and the mean birth weight were not significantly different between the treatment groups (Table 2).

### 3.5 Adverse events

One participant in the chloroquine arm developed a feeling of "pins and needles" and withdrew from the study. In the SP arm, three participants reported potentially serious adverse events (one severe vomiting, two skin rash and
Table 2. Outcomes in the study comparing IPTp (SP) versus CQ prophylaxis, Honiara, September 2009-May 2010.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CQ prophylaxis</th>
<th>IPTp with SP</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental parasitemia (%)</td>
<td>0/128 (0.0)</td>
<td>2/278 (0.8)</td>
<td>2.88 (0.30-27.54)</td>
</tr>
<tr>
<td>Maternal parasitemia delivery (%)</td>
<td>2/128 (1.6)</td>
<td>4/278 (1.4)</td>
<td>1.90 (0.17-20.84)</td>
</tr>
<tr>
<td>Maternal RDT</td>
<td>3/128 (1.1)</td>
<td>1/278 (0.4)</td>
<td>1.90 (0.17-20.84)</td>
</tr>
<tr>
<td>Hb &lt;11 g/dl, 3rd trimester (%)</td>
<td>85/134 (63.4)</td>
<td>112/161 (69.6)</td>
<td>0.91 (0.77-1.07)</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>38/52 (41.3)</td>
<td>49/52 (39.6)</td>
<td>1.01 (0.88-1.15)</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>11/26 (42.3)</td>
<td>14/26 (53.8)</td>
<td>1.72 (1.04-2.80)</td>
</tr>
<tr>
<td>Hb &lt;11 g/dl, delivery (%)†</td>
<td>212/273 (77.3)</td>
<td>122/262 (46.7)</td>
<td>0.96 (0.51-0.71)</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>35/75 (46.7)</td>
<td>34/75 (45.4)</td>
<td>0.43 (0.04-1.16)</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>96/198 (48.7)</td>
<td>172/172 (64.6)</td>
<td>0.91 (0.77-1.07)</td>
</tr>
<tr>
<td>Hb &lt;8 g/dl, delivery (%)†</td>
<td>7/314 (2.2)</td>
<td>16/314 (5.1)</td>
<td>1.90 (0.39-0.79)</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>1/35 (2.9)</td>
<td>0/35 (0.0)</td>
<td>1.00 (0.00-1.00)</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>11/99 (11.1)</td>
<td>33/99 (33.3)</td>
<td>2.88 (0.30-27.54)</td>
</tr>
<tr>
<td>Mean Hb 3rd trimester (SD, n) g/dl</td>
<td>10.4 (1.5, 134)</td>
<td>10.3 (1.2, 161)</td>
<td>0.10 (-0.21 to 0.41)</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>10.3 (1.6, 35)</td>
<td>10.8 (1.2, 49)</td>
<td>0.10 (-0.35 to 0.71)</td>
</tr>
<tr>
<td>Mean Hb delivery (SD, n) g/dl †</td>
<td>11.0 (1.9, 273)</td>
<td>10.9 (1.8, 262)</td>
<td>0.17 (-0.14 to 0.48)</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>10.9 (2.0, 75)</td>
<td>10.7 (1.9, 90)</td>
<td>0.20 (-0.39 to 0.79)</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>11.1 (1.9, 198)</td>
<td>11.0 (1.7, 172)</td>
<td>0.14 (-0.23 to 0.50)</td>
</tr>
<tr>
<td>Mean birth weight (SD, n), grams †</td>
<td>3044 (516, 297)</td>
<td>3086 (559, 281)</td>
<td>42 (-46 to 130)</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>2812 (531, 83)</td>
<td>2924 (416, 93)</td>
<td>112 (-29 to 233)</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>3134 (482, 214)</td>
<td>3166 (603, 188)</td>
<td>32 (-75 to 139)</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval, Hb: haemoglobin, LBW: low birth weight, RDT: rapid diagnostic test, RR: risk ratio, SD: standard deviation. *P<0.04, †Among singleton deliveries only.

mouth blisters); however, hospital admissions were not required. Six women reported non-specific complaints after the first dose (body weakness, drowsiness, numbness, and shortness of breath). All these women did not receive a second dose of SP; five of them withdrew from the study (two with severe complaints, and three with non-specific complaints). No congenital abnormalities were detected.

4 Discussion

This was the first trial to evaluate the role of IPT for the control of malaria in pregnancy outside of Africa. The trial was stopped prematurely because of an unexpected low prevalence of malaria at enrolment and at delivery. Furthermore, an unexpected high proportion of women reported potential sulfa-allergy at screening. No differences were noted in the proportion of women with placental malaria, maternal malaria or adverse birth outcomes between the IPTp and chloroquine arms, but the study was not powered to detect differences because of the low malaria prevalence.

Malaria prevalence (1.5%) at enrolment had declined remarkably compared to early estimates from a survey among first antenatal attendees in 2006 (9.9%, van Eijk, pers. comm.). A similar decline in malaria prevalence was noted during mass screening surveys in the general population in Honiara City; 9.7% in 2007 and 1.4% in 2010 [11,12]. The decrease in annual malaria incidence per 1000 population was less steep; from 219 in 2006 to 101 in 2010. Although the use of individual (ITNs and screening of windows), and population level (IRS) malaria-prevention methods in this study population was not optimal, the use of at least one of the three methods was high (91%). ITNs and IRS are known as effective tools in decreasing malaria and its associated effects during pregnancy [13-15]. Use of ITNs during the study (67.3%) was...
higher compared to a report for 2006-7 (48.4% in Honiara and 54.2% in Guadalcanal), whereas the report of IRS (26.1% in the preceding six months, 43.6% in the preceding year) was lower than reported for 2010 (73.6%, and 84.1%, respectively) [12,16]. The benefit of window screens as malaria protection in Honiara is not clear [17]. Most parasitemias detected were low, and this may explain the discrepancies between microscopy and RDT results.

The high rate of self-reported sulfa-allergy in this population is of concern. About a quarter of women were ineligible because they reported sulfa-allergy during the screening phase. Possible causes of bias could include staff that thought SP not suitable for pregnant women. However, a high rate of sulfa-allergy was also reported in a delivery survey (15%) conducted in the National Referral Hospital during the same period by staff not involved in recruitment for the trial (B. Appleyard, pers. comm.). Reports by many women included a history consistent with sulfa-allergy of a potentially serious nature such as swelling of the mouth, oral and skin blisters, itching and dark spots on the skin following use of SP or cotrimoxazole. This finding was unexpected because SP has been used as first-line treatment for malaria in combination with chloroquine for several years in Solomon Islands, and no excess of adverse drug reactions had been reported. These rates are much higher than those reported from Africa [18-28]. Although SP is no longer recommended for use as a chemoprophylactic drug for malaria [29], hypersensitivity is rare when SP is administered for treatment or IPTp: a comprehensive study in Malawi estimated the rate of severe adverse reactions to SP in pregnancy at 1.7 adverse events per 100,000 SP exposures, which would translate to 0.6/100 person years of exposure [30]. This is significantly lower than the rate of sulfa-allergy reported in long-term use of the drug for prophylaxis of urinary tract infections in children (4.6/100 person years of exposure) [31]. The basis for our finding is not clear, but ethnic differences in metabolism of antifolate drugs have been reported in the region [32]. A pharmacokinetic study of SP in Papua New Guinea among pregnant women suggested that dose-adjustments might be needed for SP in pregnancy, whereas studies in Africa showed variable results [33-35]. In addition, cotrimoxazole is a widely used antibiotic in this region, potentially resulting in sensitisation to sulfa drugs.

In 2009, Solomon Islands switched from SP-chloroquine to artesinin-based combination therapy for the first line treatment of malaria (both for P. falciparum and P. vivax). The results of the current trial raises uncertainty regarding the malaria programme policy, i.e. whether to stop the use of chloroquine prophylaxis in Solomon Islands because the uptake is high; in a survey conducted in the same period, 89% of the women attending for delivery reported use of CQ at some point during pregnancy whereas 68% reported regular use of chloroquine prophylaxis (Appleyard et al., in prep.). The same survey also confirmed the low malaria prevalence at delivery (~2%) and the deleterious effects of malaria such as low birth weight and maternal anaemia among those infected (Appleyard et al., in prep.). There is limited information on drug efficacy of chloroquine chemoprophylaxis in this setting. Available data on in vivo efficacy have indicated a median of 17.9% 28-day treatment failure in two studies for the combination chloroquine-SP (range 11.6-23.2%) [6,36]. P. falciparum parasites with chloroquine-resistant genotypes seem fairly common [37]; 98.4% of 61 asymptomatic P. falciparum infections from Honiara and 76% of 22 infections in Marovo lagoon contained chloroquine resistant mutations, notably C72 S, and K76 T [5,6]. No data documenting the rate of chloroquine resistant P. vivax could be identified, but confirmed treatment failures have been reported [36]. Thus, it is not likely that chloroquine is very effective for either prevention or treatment of P. falciparum, but for P. vivax data are not conclusive. A trial at the Thai-Burmese border showed a 100% efficacy of weekly supervised chloroquine prophylaxis for the prevention of P. vivax episodes among pregnant women [38]. In our study, two participants in the chloroquine arm had a P. vivax infection at delivery. Although non-adherence could explain the infection in one woman, this did not seem the case for the other participant. The withdrawal of chloroquine from treatment and prevention guidelines may potentially result in a reversion back to the sensitive wild-type in this population [39]. It is possible that the combination of vector control methods is sufficient to control malaria in pregnancy in this region. A trial in an area of low malaria endemicity in Uganda reported no difference in birth outcome among women who used ITNs, IPTp or the combination; the malaria prevalence at delivery was 3-4% using these strategies [40]. Intermittent screening and treatment for malaria in pregnancy may be an option [41]; screening at antenatal booking is already commonly practiced in some parts of Solomon Islands (B. Appleyard, pers. comm.). It will be worthwhile to assess if chloroquine prophylaxis can be abandoned without adverse effects for mother and infant. However, malaria conditions differ widely between islands in the archipelago. Indeed, in the mass surveys conducted in 2010, slide positivity rates ranged from 0.2% to 14.5% in different island provinces [12], so strategies may need customisation to local conditions.

5 Conclusions

In Honiara, Solomon Islands, in a setting with high use of malaria prevention methods, malaria prevalence among pregnant women at first ANC visit decreased to a level of less than 2%, making a comparison in malaria prevention strategy between chloroquine prophylaxis and IPTp with SP futile. The high number of reports of potentially serious adverse events on SP in this study raises concerns about the suitability of this drug for use by the malaria control programme.

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