Malaria During Pregnancy: A Priority Area for Malaria Research and Control in South-East Asia

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Abstract

Pregnant women and their unborn children are highly susceptible to malaria infection. Yet, authoritative documents barely mention malaria as a threat for pregnancy and normal fetal development in countries of the South-East Asia (SEA) Region. Almost all the published literature on the subject refers to Africa by presenting data principally related to *Plasmodium falciparum* which is supposed to cause a variety of adverse consequences, such as anaemia, cerebral malaria and deaths, etc. of both the mother and the baby. However, in some countries of the SEA Region, such as India and Sri Lanka, the dominant species is *P.vivax*, while in Myanmar and Thailand *P.falciparum* is the prevalent infection. *P.malariae* is also recorded in dense forests of countries of the Region. This article reviews 16 studies from India, 13 from Thailand, three from Sri Lanka, three from Myanmar and one from Indonesia, to estimate the burden of malaria-related adverse outcomes in the vulnerable group of pregnant women and their unborn children, in areas of stable and unstable (epidemic prone) transmission.

The aim of the review is to strengthen the capacity of the Region to address the burden of malaria in pregnancy through science-based policies for decision-makers in ministries of health, and in the public and private sectors.

Introduction

Pregnant women are especially prone to severe attacks of malaria which may cause abortion, premature labour and still birth.[1,2] Despite the widespread concern for high risk due to malaria in pregnancy for nearly a century, the recognition that malaria in pregnancy is a significant health problem in the SEA Region requires systematic studies. Almost all the published literature on the topic refers to Africa and presents data referring principally to *P. falciparum* which may cause a variety of adverse consequences including maternal death, anaemia, accumulation of parasites in placenta, low birth weight, fetal parasites exposure, congenital infection, infant anaemia, infant morbidity and mortality [3]. The paucity of precise information on the burden of malaria among pregnant women in countries of the SEA Region has hampered effective lobbying for the inclusion of malaria prevention among the top government priorities in these countries. Renewed interest and availability of new and effective interventions and strategies,[4,5] as well as global commitment[6,7,8] have re-generated interest in malaria in pregnancy since the turn of this century. This article reviews the evidence on the risks of malaria during pregnancy and attempts to estimate the probable burden of malaria-related

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adverse outcome in this vulnerable group. The aim of the review is to strengthen the capacity of the SEA Region to address the burden of malaria in pregnancy through research and science-based policies and action. This documentation will serve as an information and resource tool for decision-makers in ministries of health and in the public and private sectors.

Methodology

A literature search was undertaken for obtaining data on malaria in pregnant women in the SEA Region via Pub Med and MEDLINE search engines using the following key words – malaria in pregnancy, placental malaria, falciparum malaria and anaemia. Manual searches of pre-digital dates relevant to major tropical journals were also made for possible data sources. The bibliographies of all articles collected were checked for additional references. This paper reviews the surveys carried out over a period of 93 years between 1911 to 2004 to examine cases of malaria during pregnancy in the SEA Region.

A total of 36 studies were considered for this review: 16 from India; 13 from Thailand; three from Sri Lanka; three from Myanmar, and one from Indonesia. The study group sizes ranged from 21 to 4 600 persons. Most studies were largely hospital-based, and only a few were community studies. Further, in some countries of the Region, such as India and Sri Lanka, the dominant species is *P. vivax* [9,10], while in others particularly in Myanmar and Thailand, *P. falciparum* is the dominant type of infection.[11,12] Moreover, the clinical epidemiology of the two species is very different. Further, *P. malariae* and *P. ovale* are also recorded[13]. Since the species, incidence and severity of infection depend on the relative frequency of the different species of *Plasmodium*, an attempt was made to cover all available information on prevalent species of malaria.

Observations

The problem of malaria infection in pregnant women was initially described nearly 95 years ago in India during the Punjab epidemics in 1908. In Amritsar, out of 4 600 pregnant women, malaria caused 300 premature births, and 1 100 still births, miscarriages and abortions, which amounted to 30% interrupted pregnancies[14].

This is further supported by studies conducted in Sri Lanka, during an epidemic in 1934-1935, in which the case fatality rate in pregnant women was 13% (47/358) and foetal loss or neonatal death rate was 67% (178/266) at the Colombo General Hospital[15]. In India, the hazards of this disease have been estimated and recorded recently in some hospital-based studies in different states of the country.[16,17,18,19,20,21,22,23,24] The summary of information from these studies suggests that in pregnant women, *P. falciparum* malaria, anaemia and adverse outcomes are very common (Table 1).

The prevalence and adverse outcome were significantly higher in primigravidae as compared to multigravidae [17,23,24]. The *P.falciparum* prevalence was also found to be the highest in the second trimester [24,25]. However, the studies that were reviewed here were mostly hospital-based and focused on sample groups of hospitalized subjects. Thus, their findings are liable to distort the estimates of incidence rates and the seriousness of clinical cases observed among pregnant women.

Table 1. *Adverse effects of malaria on the mother and foetus in India (Summary of hospital-based studies)*

	Gujarat (Surat) L [17]	Orissa		Madhya Pradesh (Jabalpur) M [20,21]	Rajasthan (Bikaner) L [23]	Assam (Digboi) H [19]	Uttar Pradesh (Jhansi) L [18]	Chandigarh L [16]
		Rourkela H [24]	Koraput H [33]					
Number	**322**	**55**	**209**	**365**	**45**	**206**	**256**	**78**
SPR(%)								
PG	58.0 (Pf: 62; Pv:38)	-	11.6	17.0 (Pf: 67; Pv:33)	-	1.1 (Pf: 62; Pv: 32; Pm: 0.4; Pf+Pv: 5.6)	- (Pf: 82; Pv: 18)	- (Pf: 58; Pv: 40: Pf+Pv: 2)
Control	19.0	-		8.0	-	-	-	-
High Parasitaemia(%)								
PG	-	1- 70	-	6- 69	-	-	-	-
Control	-	0.5- 11		2- 9	-	-	-	-
Cerebral malaria(%)								
PG	-	60.0	-	7.0	76.0	-	-	7.0
Control	-	30.0		0	33.0	-	-	-
Anaemia(%)								
PG	90.0	-	8.6	60.0	20.0	-	-	60.0
Control	81.0	-		10.0	4.0	-	-	-
Maternal Mortality(%)								
PG	33.0	31.0	-	7.0	38.0	66.6	-	4.0
Control	0	14.0		0	15.0	-	-	-
Placental Malaria(%)								
PG	-	-	-	29.0	-	-	18.0	-
Other Complications (%)								
PG	-	25.0	-	-	20.0	-	-	4.0
Control	-	10.5		-	6.0	-	-	-
Abortion(%)								
PG	10.0	7.2	4.2	2.0	11.0	5.3	-	1.2
Control	2.0	-	5.4	0.7	-	-	-	-
IUFD(%)								
PG	2.0	7.2	20.8	-	31.0	-	-	5.0
Control	0	-	1.6	-	-	-	-	-

	Gujarat (Surat) L [17]	Orissa		Madhya Pradesh (Jabalpur) M [20,21]	Rajasthan (Bikaner) L [23]	Assam (Digboi) H [19]	Uttar Pradesh (Jhansi) L [18]	Chandigarh L [16]
		Rourkela H [24]	Koraput H [33]					
Stillbirth (%)								
PG	6.0	-	12.5	2.0	13.0	7.2	-	-
Control	0	-	1.6	0.7	-	-	-	-
Pre- term (%)								
PG	60.0	9.0	4.2	-	20.0	11.0	-	9.0
Control	15.0	-	2.7	-	-	-	-	-
Cord Blood	4.0	-		10.0	-	-	13.0	-
Low Birth Weight (%)								
PG	82.0	5.4	25.0	89.0	-	-	83.0	-
Control	40.0	-		38.0	-	-	26.0	-

- Information not available, PG: Pregnant women, Control: Non-infected pregnant women/Infected non-Pregnant women, IUFD – Intrauterine fetus death. H – High transmission (Hyper -endemic); M – Low-to-high transmission (meso-endemic); L – Low transmission (non-endemic)

In Myanmar, a scrutiny of records revealed that in Taunggyi Shan State,[11] in 52 patients with *P. falciparum* infection, the prevalence of malaria was highest among primigravidae (40%). The maternal death rate was found to be 2.4%, with the overall foetal wastage rate of 64%. In Tavoy Civil Hospital in 50 inpatient pregnant women with malaria, the case fatality rate was high (20%) and prematurity was as high as 86% [26]. Premature birth results commonly from symptomatic malaria and is usual in severe malaria. It is, therefore, common in low transmission areas, as well as in epidemics [27]. Another hospital in Thaton Mon State, Mya Thida [28] recently recorded that out of 958 asymptomatic pregnant women attending the antenatal clinic, the overall parasite prevalence was 12.3% (*P. falciparum* 63%, *P. vivax* 34% and remaining were mixed infections). Besides, maternal death (36%); miscarriages (4%); intrauterine fetus death and still birth (3.4%); neonatal malaria (1%); low birth weight (25%); neonatal para-sitaemia (3.2%); cord blood parasitaemia (4.2%), and placental malaria (7.3%) were common complications. A direct relationship between maternal malaria, anaemia and mortality was also observed, e.g. 98 deaths/ thousand live births with moderate anaemia (7-10g%) and 467 deaths/ thousand live births with severe anaemia (<7g%). The major adverse effect of malaria in pregnancy on the mother is anaemia. However, the causes of anaemia during pregnancy are multifactoral. They include an iron-and-folate-deficient diet; haemoglobinophathies, and infections such as malaria and hookworm. Thus, the interpretation must be treated with some caution, because anaemia is clearly affected by a number of factors which may also be interdependent.

Similarly, at the Thai-Kampuchean border, in Kap Choeng hospital, the case fatality rate due to malaria is 10% for pregnant women (Table 2). Besides, spontaneous abortions and still births are common including pre-term babies who die[29]. In Thailand, severe malaria was reported to be three times more common in pregnant women than in non-pregnant women [30]. In a prospective study in Thailand [31], the proportion of women having malaria during pregnancy was quite high (*P. falciparum* 80%, *P. vivax* 17% and remain-

ing were mixed infections). Asymptomatic parasitaemia was very common. Primigravidae were infected more commonly (47.5%) than multigravidae (33.3%), while anaemia was observed in more than 30% pregnant women which was proportional to the number of parasitaemic episodes. Low birth weight was commonly recorded in all gravid women. Nosten *et al,* [31,32] were of the opinion that in areas where pregnant women were often symptomatic, low birth weight resulted mainly from intrauterine growth retardation rather than from pre-term delivery.

Table 2. *Adverse effects of malaria on the mother and fetus in Thailand*

Complications	Kap Choeng Hospital Thai-Kampuchean Border [29]	Shoklo Camp, Hospital Thailand [30]	Thai-Myanmar Border [31]
Number	193	30	1358
SPR			37
Pv and Pf	100% Pf	100% Pf	80% Pf 17% Pv and 2.7 mixed
Severe malaria		20/29 (60)	
Convulsions		5/20 (17)	
Anaemia		13/20 (43)	31
High parasitaemia		9/20 (30)	
Hypoglycaemia		1/11 (9)	
Mortality	10	8/30 (27)	
Abortion	56.3	1/30 (3.3)	3.5
Stillbirth	5	4/30 (13.3)	3.2
Pre-term	4	1/30 (3.3)	
Low birth weight			0
Infant mortality		2*/30 (6.6) (Twins)	

A community-based study conducted in Mandla (Central India), in an inaccessible terrain during a malaria epidemic revealed that 55% pregnant women were infected with malaria, of which 88% were due to *P. falciparum;* 7% due to *P. vivax,* and the remaining were mixed infections [25]. All primigravidae (42%), secundigravidae (68%) or multigravidae (54%) were at great risk of developing severe malaria especially in the second trimester. Moderate anaemia was recorded in 100% pregnant women (7.5-11g%). Of the women found infected with *P. falciparum*, 3% had abortions, 4% still births and 2% neonatal deaths.

Of the babies born, 85% were of low birth weight. On the contrary, no significant difference in the outcome of pregnancies in women with or without malaria parasites in their peripheral blood was recorded in Koraput district, India [33]. Further, we were unable to estimate the association between *P. vivax* infection and adverse pregnancy outcomes in Mandla [25], even though *P. vivax* malaria during pregnancy had been associated with maternal anaemia and low birth weight according to an earlier study carried out in a tertiary hospital facility in Central India [21] and in Thailand [12,27]. On the contrary, a study conducted in a predominantly *P. vivax*-endemic region of Sri Lanka failed to detect a significant impact of malaria on pregnancy or the newborn [34]. Clearly, there is a need to understand whether there is any association between increasing levels of malaria transmission and disease outcome during pregnancy. Surprisingly, very little is known about placental infection with *P. falciparum* or *P. vivax* from countries of the SEA Region. Recently, in the District Hospital, Mandla, 29% placental infection (93% *P. falciparum;* 2% *P. vivax,* and 5% mixed infection of *P. vivax* and *P. falciparum*) cases were found during the transmission season (Meso-endemic area) in patients who came for

delivery with or without fever [22], while peripheral smears were positive in only 12% of mothers. Parasitaemia of *P. vivax*, *P. falciparum* and their mixed infections were also recorded in 10% umbilical cord blood smears, even with very scanty infection (Singh, unpublished data). From Jhansi Medical College Hospital (low endemic area), Uttar Pradesh, placental infection was reported to be 18% histopathologically and cord blood smears were positive in 13% of *P. falciparum* infected placentas (Table 1). The presence of cord blood parasitaemia probably reflected a recent active transmission. Interestingly, in Thailand, researchers did not come across a positive placenta with negative blood smears, which suggested that most malaria infections in pregnancy were associated with placental parasitaemia [31,35]. Interestingly, in Mandla, India, we recorded that most placentas had scanty parasitaemia and were peripheral smear-negative, even in women with clinical symptoms. Babies born from infected placentas were of significantly low birth weight as compared to babies from uninfected placentas. Though mortality was rare, these babies remained underweight till six months after their birth (Singh, unpublished data). On the contrary, Das [33] recorded 17.7% neonatal and perinatal mortality in Koraput, India though he did not record birthweights of newborns. Further, it is stated that malaria during pregnancy is not associated directly with increase in infant mortality. However, as low birth weight is a major determinant of infant mortality [36], it is assumed that malaria and anaemia during pregnancy would increase infant mortality indirectly by lowering the birth weight. In Thailand, severe maternal anaemia was found to be associated with an increased risk of infant death in the postnatal period [37,32]. It is thus concluded that, malaria and anaemia are likely to act together to reduce the birth weight [27]. However, their independent effects are difficult to distinguish. Further, in a highly endemic area of Bengal, India, Strickland and Sengupta [38] calculated that the average age of infants undergoing their first attack of malaria was about two months. In Mandla, India, we recorded that during an outbreak, 30% infants were infected with malaria at the age of two months with *P. vivax* representing >50% of infections [25]. Similarly in Koraput, India, Das [33] recorded about 18% malaria prevalence in neonates (*P.vivax* 30%; *P.falciparum* 60%, and 10% mixed infection of *P.vivax* and *P.falciparum*). In Thailand, maternal infection within the week before delivery was a risk factor for infant deaths from one to three months of age [27]. It is noted that no single study has been conducted to observe the full sequence of events from maternal malaria infection to infant mortality.

Further, the complications of malaria during pregnancy are due to the direct effect of parasitaemia, to high fever as an accompanying symptom and to anaemia. Up to 70% parasitaemia (Table 1) was recorded in India [20,24]. Control programmes need to tackle these factors singly or in combination. Ideally, all preventive and control programmes should start early during the first half of pregnancy, which is the time of peak prevalence of malaria and anaemia [39]. The relationship between anaemia and its treatment with iron and folate, and malaria was studied in Thailand recently [40]. The results showed that while there was no association with *P. falciparum*, infection with *P. vivax* had a predilection for young erythrocytes. Thus in *P. vivax*-endemic areas, systematic iron and folate supplementation confers both benefit and risk in pregnancy.

The Global Malaria Control Strategy of the World Health Organization [42] advocates that all pregnant women living in high-risk

areas should receive malaria chemoprophylaxis. Only one hospital-based study carried out in Surat, India described the potential benefit of weekly Chloroquine (CQ) chemoprophylaxis during pregnancy in terms of an increase in birth weight of newborns [17]. However, the study had limited value because of the low numbers involved (n=53). On the contrary, Singh and Shukla [41] in central India had problems in conducting the field study involving delivering of weekly CQ chemoprophylaxis due to strong socio-cultural practices prevailing in the peri-urban community. The characteristics of urban/ peri-urban malaria may differ because of access to medication and health services.

In practice, effective antenatal coverage is very limited as most pregnant women seek care in the middle of the second trimester or in the third trimester of pregnancy. The effect of antimalarial drug use for malaria control is difficult to evaluate as there is widespread use of incomplete treatment course from outside sources [43], probably leading to frequent recrudescent infections of *falciparum* malaria with repeated production of gametocytes after a single infective mosquito bite. The common problems are that provision in government health facilities are limited, antenatal care attendance is inadequate, and compliance with therapy is poor. This indicates that all preventive and control programmes should first address the means of facilitating early reporting for antenatal care. Regular attendance of all pregnant women with or without clinical signs and symptoms in antenatal clinics is required, in order to implement the intervention strategy. It is possible that if wide coverage of ANC services is not attainable, community-based health workers such as *anganwadi* workers (mother and child care unit) or village-based malaria link workers (MLVs), could collect blood smears and deliver intervention. MLVs were found to be an effective and appropriate channel for providing antimalarials in central India (unpublished report, NVBDCP Bhopal, India). Furthermore, antimalarial medications for prophylaxis must also be acceptable to pregnant women as chloroquine is also considered a potent abortifacient as compared to any other drug. Thus, good quality socio-cultural research is needed to find ways of improving and maintaining compliance. Further, while delivery and compliance are extremely important, an effective and safe drug is equally critical. While poor compliance will reduce the effectiveness of the regimen, good compliance cannot improve the benefits of an ineffective regimen. A very high level of drug resistance has already been recorded in pregnant women of Mandla district, India,[44] though the study itself suffers from a limitation because of the small sample size (n=21).

The problem of drug resistance in *P. falciparum* is particularly acute on the Thai-Myanmar border where even mefloquine and quinine give unsatisfactory treatment response when used as single agents in pregnancy [45]. Consequently, the options for treatment of a pregnant woman and her baby are restricted because of the unknown effects of antimalarials on the fetus. Mefloquine antimalarial prophylaxis in pregnancy was given on the Thai-Myanmar border [32]. This drug gave >85% protection against *P. falciparum* and complete protection against *P. vivax*. Mefloquine is safe and effective for antimalarial prophylaxis in the second half of pregnancy. Furthermore, the most rapidly acting and effective of all antimalarial drugs are artemisinin derivatives (artesunate and artemether). These were also used for treatment of multidrug-resistant malaria in pregnant women in Thailand. Both artesunate and artemether were well tolerated, and there were no drug-related side-effects [46,47,48].

Limitations, Scope and Strategies

This review has several limitations. First and foremost, while some studies were prospective, others were retrospective and some were case studies. They were carried out in different geographic terrains covering a wide range of intensity of malaria transmission in different racial groups. Different studies presented different outcomes and different classification of outcomes. In most cases these studies had small sample sizes. Some studies did not observe a statistically significant association between outcomes.

The second limitation is that there was vast heterogencity in the measurement techniques for haemoglobin estimation and there was no indication of the true exposure of each woman from each study site. Third, the accuracy of the values shown in Table 1 relied heavily on the correct diagnosis of malaria infection status. Because these studies defined infection status as the presence of parasitaemia in a peripheral blood smear, it is probable that many women who harboured sequestered placental infections were misclassified. It is therefore likely that the values shown in Table 1 represented an underestimation of the proportion of adverse outcomes due to malaria. Lastly, these adverse outcomes were attributed to malaria, thereby but not exclusively due to malaria suggesting that they contributed to only a proportion of an event and that they were not the only cause of that event. Nevertheless, the relative consistency of findings and estimates across the studies suggests that malaria infection in pregnancy does present a real and quantifiable risk for both the mother and her baby, which needs to be estimated. Therefore, the recognition that malaria in pregnancy is a significant health problem in countries of the SEA Region requires systematic studies. In this context, almost nothing is known from Bangladesh and Indonesia. The only information available from Indonesia is that 56% pregnant women receive prenatal care, and that there has been a reduction in the prevalence of anaemia during pregnancy [49]. The ratio of *P. falciparum* and *P. vivax* in pregnant women is 41.4% and 58.6% respectively, while in non-pregnant women the corresponding figures were 51.4% and 48.5% respectively, (Gita Maya, unpublished data). Therefore, an extensive field research project needs to be undertaken in the SEA Region in order to: address some important issues; understand the epidemiology of malaria in pregnancy; determine the effect of maternal malaria on birth weight and infant mortality; determine the association of malaria and anaemia, and assess the different impacts of *P. vivax* and *P. falciparum* on pregnancy and their frequently different susceptibility to commonly-used antimalarials. This requires regular follow-up of pregnant women during pregnancy, delivery and post-delivery. All aspects of epidemiology of *P. vivax* and *P. falciparum* malaria in pregnancy should be well defined in order to develop malaria prevention strategies.

Effective measures to reduce the burden of malaria in unstable transmission settings would differ from those recommended for high-transmission areas. For instance, insecticide treated bednets (ITN) were found to be not effective for preventing anaemia in pregnancy in a high-transmission area in Kenya[50], while they reduced anaemia in an area of low transmission on the Thai-Myanmar border [37]. The current strategies to prevent and control malaria in pregnancy promote a package of interventions which include the use of ITN, and intermittent preventive treatment (IPT) with full curative doses of an effective antimalarial, which currently is Sulfadoxine-pyrimethamine (SP), delivered through a routinely scheduled antenatal clinic visit and appropriate case management [6,51]. An important aspect of the renewed strategy is partnership with reproductive health services and the

recognition of antenatal care services as the focal point to prevent malaria during pregnancy[51]. In most countries of the SEA Region, the intensity of transmission varies considerably over short geographical distances. However, although microfoci of intense transmission are present, in general they are both low (<1 infection/year) and seasonal. Thus, premonition does not develop fully with the result that symptomatic and sometime life-threatening disease is seen at all ages. The challenges for the Region are to determine what interventions are appropriate, both for areas where transmission is more or less perennial but of relatively low intensity, and for areas with unstable transmission (epidemic prone). In some countries indoor residual spraying (IRS) of dichlorodiphenyl-trichloroethane (DDT) is still being used for reducing and controlling malaria. This intervention is continually under scrutiny for its harmful effects on the environment, and on mothers and newborn babies [52]. Chen and Rogan [53] claimed that DDT causes reduced duration of lactation and increased incidence of pre-term births. However, the validity of their arguments requires evidence-based confirmation. Therefore, the Sri Lanka data on deaths attributed to malaria and to premature births in the years before DDT was used, and in the years when DDT IRS was used, in [21] districts of varying malaria endemicity was examined [54]. After DDT was introduced in 1946, malaria deaths declined greatly. However, deaths attributable to premature births increased slightly. Investigators attributed this to improvement in reporting and diagnosis rather than to any decline in the health of expectant mothers, which, according to all other criteria, showed improvement. Thus, this evidence did not support the idea that the reported increase in premature births was a side-effect of DDT use [55]. Further, maternal infection with anaemia at delivery was an additional contributor to neonatal death, as well as to inducing premature birth [32]. Thus, focusing on the prevention of malaria near delivery would have the greatest overall benefit in resource-poor areas [27].

Conclusion

To work in an area of unstable and seasonal malaria tansmission requires patience on the part of both the sponsors and the scientist. However, this approach is expensive and not very scientifically productive at times. In such areas, the routine use of chemoprophylaxis may be inappropriate because of the very low prevalence of parasitaemia in a non-epidemic year. However, its association with adverse outcomes for pregnant women who become ill with malaria in such regions is unexpectedly strong [24,23]. There is, therefore, an urgent need to evaluate the magnitude of the burden of malaria during pregnancy during an epidemic, in order to examine the prevention and intervention opportunities. If the finding of such a study shows a significant burden of malaria during pregnancy during an epidemic, then the challenge will be to design an effective and acceptable intervention. Clearly, there is need for a strategy that is based on prevention. At the same time, however, the strategy should limit the use of unnecessary antimalarials so as to check the spread of drug resistance.

It is thus concluded that malaria in pregnancy is a problem which warrants increased research and investment. A workable policy needs to be put in place, based on a multicentric study covering areas of different endemicity. In addition, collaboration between the scientist and the control programmes should be strengthened, and community-level research needs to be carried out to guide programmes and to monitor and evaluate the markers of success.

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