Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis

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Summary

Background **Screening for critical congenital heart defects in newborn babies can aid in early recognition, with the prospect of improved outcome. We assessed the performance of pulse oximetry as a screening method for the detection of critical congenital heart defects in asymptomatic newborn babies.**

Methods **In this systematic review, we searched Medline (1951–2011), Embase (1974–2011), Cochrane Library (2011), and Scisearch (1974–2011) for relevant citations with no language restriction. We selected studies that assessed the accuracy of pulse oximetry for the detection of critical congenital heart defects in asymptomatic newborn babies. Two reviewers selected studies that met the predefined criteria for population, tests, and outcomes. We calculated sensitivity, specificity, and corresponding 95% CIs for individual studies. A hierarchical receiver operating characteristic curve was fitted to generate summary estimates of sensitivity and specificity with a random effects model.**

Findings **We screened 552 studies and identified 13 eligible studies with data for 229 421 newborn babies. The overall sensitivity of pulse oximetry for detection of critical congenital heart defects was 76·5% (95% CI 67·7–83·5). The specificity was 99·9% (99·7–99·9), with a false-positive rate of 0·14% (0·06–0·33). The false-positive rate for detection of critical congenital heart defects was particularly low when newborn pulse oximetry was done after 24 h from birth than when it was done before 24 h (0·05% [0·02–0·12] *vs* 0·50 [0·29–0·86]; p=0·0017).**

Interpretation **Pulse oximetry is highly specific for detection of critical congenital heart defects with moderate sensitivity, that meets criteria for universal screening.**

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Introduction

Congenital heart defects are a leading cause of infant death, accounting for more deaths than any other type of malformation.[1] Up to 40% of all deaths from congenital defects[2] and 3–7·5% of infant deaths[1] are due to such abnormalities. Surgery greatly improves survival, particularly for infants with potentially life-threatening critical disorders. Most newborn babies with critical congenital heart defects can be diagnosed with echocardiography and, if necessary, stabilised with prostaglandin infusion and treated with surgery or transcatheter intervention.[3] If defects are not detected early, there is a risk of circulatory collapse, which can result in shock and acidosis with a substantial adverse effect on prognosis. Poor clinical status at the time of operation increases surgical mortality;[4] thus, timely diagnosis improves outcome.[5–7]

Screening strategies to detect congenital heart defects include antenatal ultrasound and physical examination of the newborn baby. Both techniques have a fairly low detection rate for isolated defects and many babies are discharged from hospital before diagnosis.[8–12] Pulse oximetry has been developed as a screening method to detect the defects in newborn babies.[1] The rationale for use of this method is that most critical congenital heart defects have a degree of hypoxaemia that would not necessarily produce visible cyanosis and therefore might not be clinically detectable. Although health-care systems and governments worldwide are considering pulse oximetry as a screening strategy for newborn babies,[13] uncertainty exists about false-positive rates and test accuracy.[13] The American Heart Association and the American Academy of Pediatrics have called for analysis of pooled collaborative data before generating recommendations.[3] An expert panel in the USA cited emerging evidence to propose a national plan to screen newborn babies with pulse oximtery for early detection of critical congenital heart defects. The recommendation did not provide updated data about the performance of pulse oximetry in this setting.[14]

Results of individual studies and previous systematic reviews might be imprecise because of low prevalence of congenital heart defects.[1,15] With the addition of more than 100 000 babies in studies published since the last review,[16–18] the accuracy estimates of pulse oximetry should be updated to guide screening policy. We aimed to assess the performance of pulse oximtery as a screening method for the detection of critical congenital heart defects in asymptomatic newborn babies.

Methods

Search strategy and selection criteria

This systematic review was undertaken with a prospective protocol using recommended methods.[19,20] We searched

Medline (1951–2011), Embase (1974–2011), Cochrane Library (2011), and Scisearch (1974–2011) for relevant citations, and hand searched the reference lists of relevant articles for eligble studies. We examined the reference lists of all known primary and review articles to identify cited articles not captured by the electronic searches. We applied no language restrictions. We considered both published and unpublished reports for inclusion, including those published in abstract form only. We used a combination of medical subject headings and text terms to generate two subsets of citations, one indexing pulse oximetry (pulse NEAR oximetry) and the other indexing outcomes ("infant-newborn", "neonate", "newborn", "infant", "congenital heart disease"). We combined these subsets to generate a subset of citations relevant to our research question.

Two independent reviewers (ST and AKE) examined the electronic searches and obtained full reports of all citations that were likely to meet the predefined selection criteria. Disagreements were resolved by consensus and after discussion with a third reviewer (KSK). For duplicate publication, we selected the most recent and complete versions of reports. We selected studies if they included asymptomatic newborn babies screened by pulse oximetry for critical congenital heart defects—ie, any potentially life-threatening duct-dependent disorder from which infants die or undergo invasive procedures (surgery or cardiac catheterisation) in the first 28 days of life.[21] This definition included all infants with hypoplastic left heart syndrome, pulmonary atresia with intact ventricular septum, simple transposition of the great arteries, or interruption of the aortic arch. Furthermore, we classified as having critical congenital heart defects, all infants dying or needing surgery in the first 28 days of life with coarctation of the aorta, aortic valve stenosis, pulmonary valve stenosis, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, or total anomalous pulmonary venous connection. We contacted the investigators of the primary studies if classification of the defect as critical lesion was uncertain. When information about lesion characteristics was insufficient, they were not classified as critical.

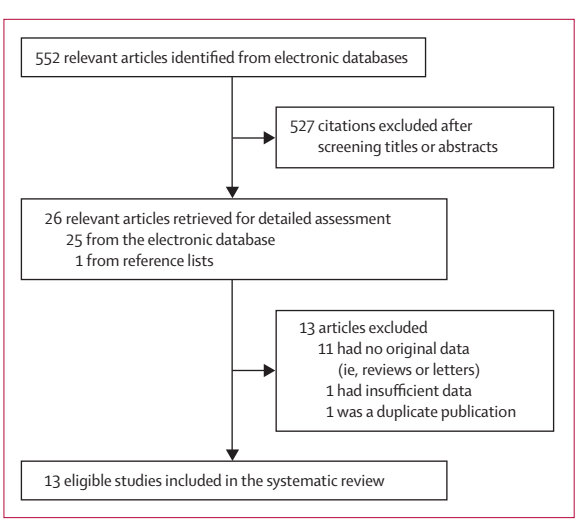

Figure 1: **Study selection**

Quality assessment and data extraction

Two reviewers (ST and AKE) extracted information about study characteristics, quality, and test results from each selected article. Data were used to construct 2×2 tables of pulse oximetry results (test was positive if levels were above the threshold defined in the primary study and negative if they were below the threshold) and infant outcomes (critical congenital heart defects). We also extracted data for the method of testing, threshold saturation levels and type of oxygen saturation measured, timing of the test, and inclusion or exclusion of infants with suspected congenital heart defects after antenatal ultrasound screening in pregnancy.

We assessed the quality of the included studies against the quality assessment of diagnostic studies criteria,[22] which included assessment of study components including population, test, reference standard, patient outcome, and study design. We considered a study to be of good quality if it had prospective consecutive recruitment, adequate description of population, test and reference standard, masking of test and reference standard, full verification of the test with reference standard, and more than 90% follow-up.

Statistical analysis

We calculated sensitivity, specificity, and corresponding 95% CIs for individual studies and displayed them in forest plots to investigate heterogeneity. True-positive and false-positive rates for various test thresholds were plotted in the receiver operating characteristics (ROC) space. A hierarchical summary ROC model was fitted with METADAS SAS macro (version 9.1), which estimates parameters for the model with SAS Proc NLMIXED (version 9.1). Hierarchical summary ROC model represents the implicit relation between logit-transformed sensitivity and specificity in each study (threshold), and the accuracy of the test (as the logarithm of the diagnostic odds ratio) with two random effects. The model includes a scale parameter that identifies the shape or asymmetry of the summary ROC. Covariates can also be included as fixed effects to explore sources of heterogeneity. The model accounts for intrastudy variability in estimates of sensitivity and specificity, and interstudy variations in test performance with the inclusion of random effects. We obtained summary estimates of sensitivity and specificity and corresponding 95% CIs from the fitted summary ROC curve. We added predetermined explanatory variables (covariates) to the model to assess whether variability between studies in accuracy of the test was associated with timing of the test (<24 h *vs* ≥24 h after birth), method of testing (right hand and foot for preductal

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and postductal *vs* foot only for postductal), oxygen saturation (functional *vs* fractional), or antenatal screening (cases screened positive for congenital heart defects excluded *vs* included). Estimates of sensitivity and false-positive rates were computed and plotted in forest plots according to the predefined subgroups. For sensitivity analysis, we checked the effect of exclusion of studies according to their design characteristics. We used SAS version 9.1 for the analyses.

We assessed publication bias by representing diagnostic odds ratio—a single measure of diagnostic accuracy—against the effective sample size. With no bias the plot should show an inverted symmetrical funnel shape. The degree of asymmetry was statistically assessed by regression of the logarithm of diagnostic odds ratio on the inverse of the square root of the effective sample size, weighted by this sample size.[23]

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 552 studies, we identified 13 primary studies that were eligible for inclusion, with data for 229 421 newborn babies (figure 1). The table shows accuracy estimates of the primary studies.[16,17,24–34] 12 cohort[16,17,24–26,28–34] and one case-control study[27] assessed the accuracy of pulse oximetry in the detection of critical congenital heart defects in asymptomatic newborn babies. Nine studies excluded babies who were suspected antenatally to have congenital heart disease (table). Pulse oximetry was done at less than 24 h after birth in six studies (table). About 60% of studies used the foot alone (postductal) to measure oxygen saturation and the remainder used both right hand and foot (preductal and postductal). Eleven studies described the test adequately and all described the reference standard adequately (figure 2). All the studies used different methods to verify test results: positive test results were verified by echocardiography and negative results by interrogation of congenital anomaly registers, mortality data, or clinical follow-up (appendix pp 1–4). Although all studies had follow-up, it was more rigorous in some than in others (figure 2). We analysed the cohort studies separately from the

See Online for appendix

	Limb	Antenatal diagnosis of CHD	Test timing	Total	True positive	False positive	False negative	True negative	Sensitivity (%; 95% CI)	Specificity (%; 95% CI)	Likelihood ratio positive (%; 95% CI)	Likelihood ratio negative (%; 95% CI)	False-positive rate (%; 95% CI)
Meberg et al (2008)[30]	Foot only	Excluded	<24 h	50 008	27	297	8	49 676	77·1% (59·9–89·6)	99·4% (99·3–99·5)	129·8% (104·9–160·6)	0·23% (0·13–0·43)	0·6% (0·5–0·7)
Bakr et al (2005)[25]	Foot and right hand	Excluded	>24 h†	5211	3	2	0	5206	100·0% (29·2–100·0)	100% (99·9–100·0)	1823·1% (500·1–6646·1)	0·13% (0·01–1·67)	0% (0–0·1)
Arlettaz et al (2006)[24]	Foot only	Included	<24 h	3262	12	12	0	3238	100·0% (73·5–100·0)	99·6 % (99·4–99·8)	250·1% (142·3–439·5)	0·04% (0·01–0·59)	0·4% (0·2–0·6)
Sendelbach et al (2008)[26]	Foot only	Excluded	<24 h	15 233	1	24	0	15 208	100·0% (2·5–100·0)	99·8 % (99·8–99·9)	466·3% (191·0–1138·5)	0·25% (0·02–2·8)	0·2% (0·1–0·2)
Reich et al (2003)[31]*	Foot and right hand	Excluded	>24 h†	2114	0	4	0	2110	..	99·8% (99·5–99·9)	..	..	0·2% (0·1–0·5)
Koppel et al (2003)[29]	Foot only	Excluded	>24 h	11 281	3	1	2	11 275	60·0% (14·7–94·7)	100·0% (100·0–100·0)	6765·6% (839·8–54 506·3)	0·40% (0·14–1·17)	0% (0·0–0·0)
Rosati et al (2005)[34]	Foot only	Excluded	>24 h	5292	2	1	1	5288	66·7 % (9·4–99·2)	100·0% (99·9–100·0)	3526·0% (424·6–29 282·9)	0·33% (0·07–1·70)	0% (0·0–0·1)
Richmond et al (2002)[32]	Foot only	Included	<24 h	5626	8	56	1	5561	88·9% (51·8–99·7)	99·0% (98·7–99·2)	89·2% (62·9–126·3)	0·11% (0·02–0·71)	1% (0·8–1·3)
de Wahl Granelli (2009)[16]	Foot and right hand	Excluded	>24 h†	39 821	19	68	10	39 724	65·5% (45·7–82·1)	99·8% (99·8–99·9)	383·4% (268·8–546·9)	0·35% (0·21–0·57)	0·2% (0·1–0·2)
Riede (2010)[33]	Foot only	Excluded	≥24 h	41 442	14	40	4	41 384	77·8% (52·4–93·6)	99·9% (99·9–99·9)	805·5% (542·0–1197·0)	0·22% (0·09–0·53)	0·1% (0·1–0·1)
Ewer et al (2011)[17]	Foot and right hand	Included	<24 h	20 055	18	177	6	19 854	75·0% (53·3–90·2)	99·1% (99·0–99·2)	84·9% (64·6–111·6)	0·25% (0·13–0·50)	0·9% (0·8–1·0)
Kawalec et al (2006)[28]	Foot only	Excluded	≥24 h	27 200	7	13	1	27 179	87·5% (47·3–99·7)	100·0% (99·9–100·0)	1830·2% (1001·2–3345·9)	0·13% (0·02–0·78)	0% (0·0–0·1)
Hoke et al (2002)[27]*	Foot and right hand	Included	<24 h	2876	4	53	0	2819	100·0% (39·8–100·0)	98·2% (97·6–98·6)	48·3% (32·6–71·7)	0·10% (0·01–1·40)	1·8% (1·4–2·4)
Summary estimate	..	..	..	229 421	..	..	..	..	76·5% (67·7–83·5)	99·9% (99·7–99 9)	549·2% (232·8–1195·6)	0·24% (0·17–0·33)	0·14% (0·06–0·33)

CHD=congenital heart defect. *Studies by Hoke and colleagues and Reich and colleagues excluded from the analysis. †Mean age at testing >24 h after birth.

Table: **Accuracy estimates of primary studies for pulse oximetry in the detection of critical congenital heart defects in newborn babies**

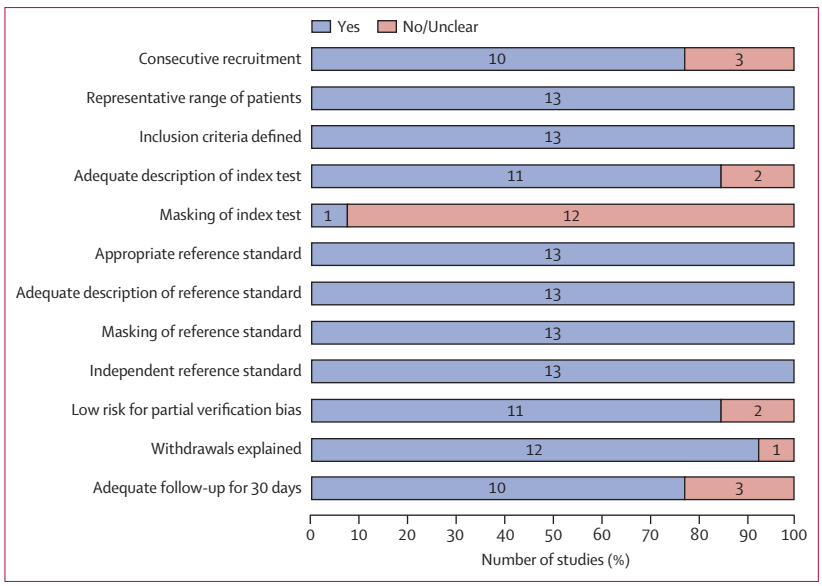

Figure 2: **Quality of included test accuracy studies**

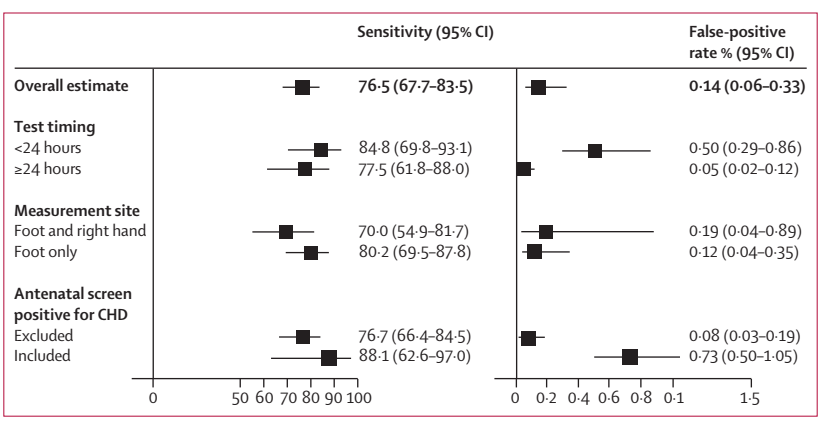

Figure 3: **Accuracy estimates based on clinical and test characteristics of pulse oximetry in detection of critical congenital heart defects in newborn babies**
CHD=congenital heart defects.

case-control study for pooled estimates of sensitivity and specificity of pulse oximetry for detection of critical congenital heart defects. We excluded one cohort study[31] from the meta-analysis because it included no newborn babies with critical congenital heart defects. This study provided a partial 2×2 diagnostic table from which estimation of sensitivity was not possible; this precluded inclusion of the study to fit the summary ROC model.

Overall, pulse oximetry had high specificity and moderately high sensitivity for detection of critical congenital heart defects (table; I^2 98·5% and 25%, respectively) and a low false-positive rate (table). The specificity of Reich's study[31] was similar to our pooled estimate (table). The table provides accuracy measures of the studies with their saturation thresholds. Because all studies reported almost identical high specificity, correlation was low between sensitivity and specificity; thus, the shape of the summary ROC curve was asymmetrical for detection of critical congenital heart defects (data not shown). The appendix shows the true-positive and false-negative measures for detection of individual lesions. The false-positive rate for detection of defects was significantly lower when pulse oximetry was done after 24 h than when it was done before 24 h (figure 3; p=0·0017). We noted no significant difference in sensitivity of pulse oximetry when the test was done before versus after 24 h (figure 3; p=0·36). We noted no significant differences in sensitivity for pulse oximetry when measures were obtained in the foot alone versus in both foot and right hand (figure 3; p=0·22). False-positive rates did not differ significantly when either method of probe positioning was used (p=0·66).

The sensitivity of the test did not increase significantly with inclusion of newborn babies with antenatal suspicion of congenital heart defects compared with when these babies were excluded (figure 3; p=0·18). Inclusion of newborn babies suspected to have congenital heart defects resulted in a significant increase in the false-positive rate (figure 3; p<0·0001). We recorded significant publication bias (appendix). The funnel plot showed an asymmetrical shape (symmetry test p value 0·03) because of the scarcity of small studies with low estimations of diagnostic accuracy (appendix p 9).

Discussion

Our findings show that pulse oximetry is a highly specific test for detection of critical congenital heart defects in asymptomatic newborn babies with low false-positive rates. The false-positive rates were affected by the timing of the test and were significantly lower when the screening was done after 24 h of birth than when it was done before 24 h. This reduction did not compromise test sensitivity; the sensitivity of the test was moderate overall.

In this Article we collated the largest set of accuracy data so far, thus doubling the numbers used in previous reviews. The included studies were done in various newborn-care settings. Most the studies were of good quality with prospective design and adequately described the population, test, and reference standard. The precision of the findings has improved since the last review. In view of the many babies that have now been tested with pulse oximetry, further research in this area is unlikely to produce substantially different findings.

Definitions of severity of congenital heart defects varied in the published work. Terms such as major, critical, severe, complex, serious, and significant were frequently used, but the absence of agreed definitions made comparisons between studies difficult. Our attempt to categorise critical congenital heart defects according to our strict definition has reduced the likelihood of incorrect definition. In the included studies differential verification was unavoidable with echocardiography, which is the gold standard used in babies testing positive for heart defects. Verification of negative results varied in

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robustness and rigour between individual studies, which raises the possibility of missed false negatives. If the studies have a large sample size, small amounts of clinically negligible heterogeneity can lead to results that are highly statistically significant. This is the case with specificity in which the χ^2 test is highly significant, but heterogeneity is clinically unimportant. Although we tried to gather all evidence in the published works, funnel plot asymmetry shows that we cannot rule out the existence of unpublished studies with low accuracy estimations for pulse oximetry. Therefore, our results might be biased towards greater associations than are actually present. Several individual cardiac lesions were categorised as critical congenital heart defects in the included studies, with few babies in each category. Presence of more than one cardiac lesion in newborn babies diagnosed with defects restricts our interpretation of accuracy estimates for detection of individual lesions.

The sensitivity of pulse oximetry in our meta-analysis is higher than that from the American Academy of Pediatrics scientific statement.[3] The low false-positive rate, particularly when babies were tested after 24 h of birth, is important because of the potential assessment costs of those who test positive, including the costs of echocardiography. This finding should be balanced against the increasing tendency of many countries to discharge babies early (between 6 and 24 h), and the risk of infants with serious disorders deteriorating before screening has been done. The significant reduction in the false-positive rates associated with test timing was not associated with a compromise in the specificity of the test. Similarly, we recorded no significant difference in the sensitivity with undertaking the test after 24 h of birth. This information should be carefully considered when screening programmes are set up. Pulse oximetry testing at home by health-care workers could overcome some of the difficulties associated with short postnatal stay in hospitals or home births. The cost implications of this strategy should be assessed for deliveries outside hospitals.

We recorded no significant difference in sensitivity based on the site of testing. In the meta-analysis, only three studies tested preductal and postductal saturations, compared with eight studies testing only postductal saturations, which included more than twice the number of newborn babies. The sensitivity estimates from both subgroups were too imprecise, which makes any inference on possible difference weak. However, in studies that used both preductal and postductal saturations, individual defects were detected, which would not have been identified by postductal saturations alone.[16,17] Most studies used oximeters that provided functional saturations; and the recent large studies[16–18] used motion tolerant sensors, which function in states of low perfusion.

Pulse oximetry is a non-invasive test that is easy to do with high accuracy. Some babies with critical congenital heart defects might be missed with this technique, particularly those with obstruction of the aorta (coarctation and interruption of the aortic arch). Introduction of pulse oximetry for the detection of defects could identify other equally devastating disorders, such as group B streptococcal pneumonia or symptomatic pulmonary hypertension. We noted no reported cases of genetic abnormalities of the cilia, such as primary ciliary dyskinesia, in the newborn babies who tested positive. Patients with primary ciliary dyskinesia and heterotaxy (situs ambiguus) have an increased risk of congenital heart disease.[35] Findings from the published studies did not address the effects of altitude on oxygen saturation values. Further research is needed in this area before recommendations can be made for cutoff levels for screening at high altitude. Findings from an economic assessment with decision analytical modelling for the role of pulse oximetry as a screening test in the UK showed that the additional cost of this technique as an adjunct to practice was likely to be cost effective, particularly if the outcomes of neonatal cardiac surgery continued to improve.[36] Importantly, the mothers given false-positive results after screening were no more anxious than those given true-negative results. The predictors of satisfaction with screening were an understanding of the heart disease in newborn babies and the potential of the treatment to improve outcome, levels of baseline stress, anxiety, and depression.[36]

The findings of this meta-analysis provide compelling evidence for introduction of pulse oximetry as a screening method in clinical practice. The sensitivity of the test is higher than present strategies based on antenatal screening and clinical examination, and the false-positive rate is very low, especially when done after 24 h of birth. Strong evidence exists for health-care systems to consider introduction of pulse oximetry as a screening test for critical congenital heart defects in asymptomatic newborn babies.

Contributors

ST, KSK, and AKE conceptualised and designed the systematic review. ST did the literature search with the help of a clinical librarian. ST and AKE selected the studies and extracted the data. JZ and ST analysed the data. KB and ST designed the tables and figures. All authors contributed to the draft and final versions of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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