DOES THE AVAILABILITY OF BLOOD SLIDE MICROSCOPY FOR MALARIA AT HEALTH CENTERS IMPROVE THE MANAGEMENT OF PERSONS WITH FEVER IN ZAMBIA?

LAWRENCE BARAT, JAMES CHIPIPA, MARGARETTE KOLCZAK, AND THOMAS SUKWA

Abstract. Some Ministries of Health in Africa plan to make blood slide microscopy available in peripheral health centers to improve malaria diagnosis over the current practice, which relies solely on clinical findings. To assess whether microscopy improves the management of febrile persons in health centers, we prospectively reviewed medical records of all outpatients visiting six health centers with laboratories in Zambia during a 2–3-day period. Staff interviews and a blinded review of a series of blood slides from each facility by two expert microscopists were also conducted. Of 1,442 outpatients, 655 (45%) reported fevers or had a temperature ≥37.5°C. Blood slide microscopy was ordered in 28–93% of patients with fever (mean = 46%). Eighty-eight (35%) patients without parasitemia were prescribed an antimalarial drug. Antimalarial drugs were prescribed with equal frequency to those who were referred for a blood slide (56%) and those not referred (58%). The sensitivity of microscopy was 88% and the specificity was 91%. Use of malaria microscopy varied widely, indicating that clinicians are not using standard criteria for ordering this test. Although diagnosis by microscopy was generally accurate, it appeared to have had little impact on the treatment of persons with fever. Guidelines for using blood slide microscopy are needed and prescription of antimalarial drugs should be discouraged when slide results are negative.

Since few health facilities in sub-Saharan Africa have clinical laboratories, the diagnosis of malaria is usually based on the patient’s history and findings on physical examination. In this region, a documented fever or recent history of fever has traditionally been considered sufficient evidence for prescribing antimalarial therapy. The World Health Organization (WHO) and the United Nations Children’s Education Fund (UNICEF) have incorporated this approach for the presumptive diagnosis of malaria in children less than 5 years of age in their algorithms for the Integrated Management of Childhood Illness (IMCI).1

The primary drawback to the presumptive diagnosis and treatment of malaria is its lack of specificity.2–4 Many persons with fever caused by other conditions receive antimalarial treatment. While this may be appropriate in areas where the first-line treatment for malaria is safe and inexpensive, the spread and intensification of chloroquine (CQ)–resistant Plasmodium falciparum in Africa makes this approach to management of febrile illness problematic.5–7 For example, a patient presenting to a health facility with a febrile illness that has not responded to CQ treatment could either have CQ-resistant malaria or a febrile illness other than malaria. As countries move to replace CQ with an alternative antimalarial drug, empiric treatment of malaria may become impractical because of the higher cost and more frequent occurrence of adverse reactions to the replacement regimen.

Recognizing the limitations of presumptive malaria diagnosis, Ministries of Health in several countries in sub-Saharan Africa have begun to expand the use of malaria microscopy in peripheral health facilities. In Zambia, more than 70 urban and rural health centers already have laboratories and expansion of these services into 200 additional health centers is planned by the Zambian Ministry of Health.

However, it remains unclear whether the introduction of malaria microscopy into peripheral health facilities will have sufficient impact on the management of persons with fever to justify the costs of establishing and maintaining these laboratories. If blood slides are requested for inappropriate indications or are incorrectly read, or if clinicians ignore the results when prescribing treatment, these services will not achieve their maximal effectiveness. This study was conducted to determine the impact malaria microscopy has had on the management of fever and malaria in Zambia and the accuracy of malaria blood slide diagnosis in health centers.

MATERIALS AND METHODS

During September and October 1997, six health centers (HCS) with clinical laboratories in Lusaka, Copperbelt, and Eastern Provinces in Zambia were visited for the assessment. Sites were selected to include three urban and three rural sites, four government and two mission-supported facilities, and HCs in different locations. This study was approved by the Institutional Review Board (IRB) of the Centers for Disease Control and Prevention and the Ethical Committee of the Tropical Disease Research Center (Ndola, Zambia) and was conducted in accordance with regulations of the U.S. Office of Protection of Research Risks and the Zambian Ministry of Health governing human subjects research. Verbal informed consent was obtained from all clinical and laboratory staff who underwent evaluation.

At each clinic, a consecutive series of patients of all ages who sought outpatient treatment during the hours the laboratory was operating were monitored throughout their outpatient visit. After initial assessment by the clinical staff, medical records were reviewed and each patient’s age, sex, temperature (if available), and time of consultation were recorded. If the patient was referred to the laboratory for a blood slide examination for malaria, the initial (working) diagnosis, time the blood sample was taken, result of blood slide, and the time result was available from the laboratory were also recorded. For all patients, notation was made of the final diagnosis, the time the final diagnosis was made, and the prescribed treatments. All patients were tracked until approximately 50 patients had been referred to the labora-
for blood slide examination. Patients admitted or referred to another health facility immediately after their initial consultation were excluded because follow-up to obtain data on diagnosis and treatment was not possible.

For all patients referred by the clinical staff for microscopic diagnosis of malaria, blood slides were obtained, stained, and examined by the HC technician per his or her usual procedures (first reading). Two laboratory technicians experienced in malaria microscopy (expert microscopists) re-examined each of these slides without knowledge of the first reading. The results of expert microscopists were compared with the first reading to assess for discordant results (positive to negative). If the first reading matched one or both of the results of the expert microscopists, these results were classified as true positives or true negatives. First readings that differed from the results of both expert microscopists were classified as false positives (if the first reading was positive) or false negatives (if the first reading was negative).

Once the observational component of this assessment was completed at each HC, the HC technicians were asked to continue to collect blood slides on the next 50–100 patients referred by the clinical staff. Each slide was to be stained and examined by the HC technician per his usual routine, and the result recorded. These specimens were later re-examined by both expert microscopists without knowledge of the original result to assess the accuracy of the first reading.

Data were collected from health center records and laboratory log books in each HC on the numbers of outpatient visits, patients diagnosed with malaria, blood slide examinations performed, and positive blood slides for the months of January, May, and August 1997. These 3 months were chosen to include the peaks of rainy season (January) and dry season (August), and a transitional month (May).

Interviews were conducted with one clinical officer working in the outpatient department of each HC to identify criteria being used for ordering a blood slide, to determine whether the clinical staff had confidence in the results they received from the laboratory, and to assess whether and under what circumstances they prescribed antimalarial treatment to patients with a negative result. Interviews were also conducted with HC laboratory technicians to assess how frequently they received supervisory visits, to identify supply and equipment problems, and to clarify laboratory and record-keeping procedures.

Data were entered into an Epi Info 6.02 database. Univariate analyses to assess for differences in patient characteristics and outcome variables between health facilities were conducted using the chi-square test, or Fisher’s exact test when cell counts were < 5. A backward step-wise logistic regression was conducted using SAS to determine factors that predicted referral for a blood slide examination and predictors of antimalarial treatment and to assess for potential confounders. The Hosmer-Lemeshow test was used to determine the goodness-of-fit of the final models. Sensitivities, specificities, and predictive values positive and negative of blood slide diagnosis were calculated using standard formulas.

**RESULTS**

**Patient follow-up.** Of the 1,442 persons observed during their outpatient visit, 44% were < 5 years of age and 52% were female (Table 1). Age and sex distributions were similar at the six clinics. Only 23% had a temperature measured during their visit (range 2–48%). Overall, 45% of all outpatients and 65% of 631 children < 5 years of age reported having had fever and/or had a measured temperature ≥ 37.5°C. The percentage of outpatients with fever at HC #6 (30%) was significantly lower than at all other sites (P < 0.05).

Twenty-five percent of all outpatients and 30% of children < 5 years of age were referred by the clinical staff for a blood slide examination (Table 2). Significantly higher percentages of patients and children < 5 years of age at HCs #3 and #6 (the two mission-supported clinics) were referred for blood slide examination than at the other sites (P < 0.01). Significantly fewer children < 5 years of age (10%) at HC #2 were referred for blood slide (P < 0.01).

Among those with reported or documented fever, 46% of
655 outpatients and 41% of 413 children < 5 years of age were referred for blood slide examination (Table 2). Significantly higher percentages of outpatients and children < 5 years of age with fever at HCs #3 and #6 ($P < 0.01$) and significantly fewer children with fever at HC #2 ($P < 0.05$) were referred for blood slide examination compared with other HCs.

Antimalarial treatment with either CQ or sulfadoxine-pyrimethamine (SP) was prescribed for 32% of 1,442 outpatients and 42% of 631 children < 5 years of age (Table 2). Patients at HCs #1 and #2 were prescribed antimalarial treatment more frequently than patients at the other sites ($P < 0.05$). A smaller percentage of all patients and children < 5 years of age at HC #4 were prescribed an antimalarial drug ($P < 0.05$).

Fifty-seven percent of 655 outpatients with fever and 58% of 413 children < 5 years of age with fever were prescribed an antimalarial drug (Table 2). Outpatients and children < 5 years of age with fever at HC #4 were less likely ($P < 0.01$) and outpatients and children < 5 years of age with fever at HC #6 were more likely ($P < 0.05$) to be prescribed antimalarial treatment than patients at other sites. Eighty-seven (11%) of 787 patients without a history of fever or an elevated temperature were prescribed antimalarial treatment (range = 2–21%).

Of persons referred for blood slide examination, 2–70% (29% overall) had a positive first reading for malaria parasites by the HC technician (Table 3). The frequency of positive blood slides for malaria was significantly lower at the three periurban HCs (HCs #1, 2, and #4) than at the three HCs located in rural settings ($P < 0.05$). For patients referred for blood slide examination, the average length of time from the initial consultation with the clinical staff until treatment was prescribed was 57 minutes (SD = 30.6 min).

Information on final diagnosis was available on 92% of the 366 patients referred for blood slide. Clinical staff modified the patient's diagnosis in the medical record after the result was available from the laboratory in only 21% of these patients (range = 0–76%). Of the 233 patients with negative results and available information, 72% still had fever or malaria listed as their final diagnosis (range = 11–78%). In contrast, 19% of 463 persons prescribed an antimalarial drug

### Table 2

<p>| Clinical management of outpatients and outpatients with fever at six health centers (HCs) in Zambia, 1997 |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>HC #1</th>
<th>HC #2</th>
<th>HC #3</th>
<th>HC #4</th>
<th>HC #5</th>
<th>HC #6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total febrile outpatients</td>
<td>135</td>
<td>174</td>
<td>86</td>
<td>110</td>
<td>105</td>
<td>45</td>
<td>655</td>
</tr>
<tr>
<td>Referral for blood slide</td>
<td>50</td>
<td>48</td>
<td>67</td>
<td>42</td>
<td>49</td>
<td>42</td>
<td>298</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>48</td>
<td>67</td>
<td>42</td>
<td>49</td>
<td>42</td>
<td>298</td>
</tr>
<tr>
<td>$&lt;5$ years of age</td>
<td>50/83</td>
<td>48/28</td>
<td>67/78</td>
<td>42/38</td>
<td>49/47</td>
<td>42/93</td>
<td>298/466</td>
</tr>
<tr>
<td>Prescribed CQ or SP†</td>
<td>Total</td>
<td>$&lt;5$ years of age</td>
<td>Total</td>
<td>$&lt;5$ years of age</td>
<td>Total</td>
<td>$&lt;5$ years of age</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>105</td>
<td>42</td>
<td>35</td>
<td>70</td>
<td>37</td>
<td>376</td>
</tr>
<tr>
<td></td>
<td>87/63</td>
<td>105/103</td>
<td>42/49</td>
<td>35/32</td>
<td>70/67</td>
<td>37/82</td>
<td>376/576</td>
</tr>
</tbody>
</table>

### Table 3

<p>| Result and prescribed treatment among patients referred for a blood slide examination at six health centers (HCs) in Zambia, 1997 |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>HC #1</th>
<th>HC #2</th>
<th>HC #3</th>
<th>HC #4</th>
<th>HC #5</th>
<th>HC #6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral for blood slide</td>
<td>61</td>
<td>53</td>
<td>75</td>
<td>54</td>
<td>57</td>
<td>66</td>
<td>366</td>
</tr>
<tr>
<td>Result reported by laboratory technician</td>
<td>Positive</td>
<td>Negative</td>
<td>Not done/Missing</td>
<td>Time (mean ± SD) from initial consultation to treatment (min)</td>
<td>Slide-negative patients prescribed CQ or SP†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1 (2)*</td>
<td>2 (4)</td>
<td>33 (44)</td>
<td>6 (11)</td>
<td>18 (32)</td>
<td>46 (70)</td>
<td>106 (29)</td>
</tr>
<tr>
<td>Negative</td>
<td>56 (92)</td>
<td>50 (94)</td>
<td>42 (56)</td>
<td>46 (85)</td>
<td>39 (68)</td>
<td>20 (30)</td>
<td>253 (69)</td>
</tr>
<tr>
<td>Not done/Missing</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>7 (2)</td>
<td>64 ± 32.2</td>
<td>54 ± 24.1</td>
<td>61 ± 26.1</td>
</tr>
<tr>
<td>CQ or SP†</td>
<td>30 (54)‡</td>
<td>21 (42)</td>
<td>9 (21)</td>
<td>12 (26)</td>
<td>12 (31)</td>
<td>4 (20)</td>
<td>88 (35)</td>
</tr>
</tbody>
</table>

* Number (%).
† CQ = chloroquine; SP = sulfadoxine-pyrimethamine.
‡ Number (%) of patients with negative blood slides.
had a final diagnosis that did not include fever or malaria (range = 5–28%).

Of the 253 patients without parasitemia, 35% were still prescribed an antimalarial drug (Table 3). Patients with negative blood slides at HC #1 were more likely to be prescribed an antimalarial drug than similar patients at HCs #3, 4, 5, and 6 (P < 0.01).

Figure 1 summarizes the outcomes of the 1,442 outpatients observed for this assessment. Only 102 (51%) patients with fever and negative blood slides did not receive antimarial treatment. The combined percentage of outpatients referred for a blood slide who were then prescribed an antimalarial drug (56% of 298) did not differ from the percentage prescribed antimalarial treatment in persons without respiratory complaints (OR = 18.0, 95% CI = 12.2–26.5) than in those with respiratory complaints (OR = 7.6, 95% CI = 5.0–11.5). Among persons with fever, those with respiratory symptoms were less likely to be treated for malaria than those without such complaints (OR = 0.39, 95% CI = 0.28–0.55).

**Blood slide review.** A total of 680 blood slides at the six HCs were reviewed by the two expert microscopists (Table 4). The HC technician and at least one of the expert microscopists agreed on the result of 144 positive slides (true positives) and 470 negative slides (true negatives). Both expert microscopists disagreed with the reading of the HC technician for 46 slides with a positive first reading (false positives) and 20 slides with a negative first reading (false negatives). Overall sensitivity was 88% and specificity was 91%. Predictive values positive and negative were 76% and 96%, respectively.

**Clinic and laboratory records.** When the recorded number of blood slide examinations performed was compared with the number of outpatient visits collected from HC records for the same month (Table 5), average use of blood slide microscopy was ≤ 3%. More importantly, the mean percentage of persons diagnosed with malaria who had a positive blood slide was ≤ 3%. There was no seasonal variation in any of these percentages.

**Table 4**

Sensitivity, specificity, and predictive values of blood slide microscopy at six health centers (HCs) in Zambia, 1997

<table>
<thead>
<tr>
<th>HC</th>
<th>HC #1</th>
<th>HC #2</th>
<th>HC #3</th>
<th>HC #4</th>
<th>HC #5</th>
<th>HC #6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of blood slides reviewed</td>
<td>143</td>
<td>85</td>
<td>125</td>
<td>102</td>
<td>116</td>
<td>109</td>
<td>680</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>60%</td>
<td>25%</td>
<td>98%</td>
<td>100%</td>
<td>86%</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98%</td>
<td>100%</td>
<td>96%</td>
<td>99%</td>
<td>85%</td>
<td>56%</td>
<td>91%</td>
</tr>
<tr>
<td>Predictive value positive</td>
<td>75%</td>
<td>100%</td>
<td>94%</td>
<td>93%</td>
<td>71%</td>
<td>59%</td>
<td>76%</td>
</tr>
<tr>
<td>Predictive value negative</td>
<td>97%</td>
<td>95%</td>
<td>99%</td>
<td>100%</td>
<td>95%</td>
<td>90%</td>
<td>96%</td>
</tr>
</tbody>
</table>
Clinician and laboratory technician interviews. Only one clinical officer could outline specific standard criteria that he/she used to decide when to request a blood slide examination. This clinician referred any patient for microscopy if they had either a documented temperature $\geq$ 37.5°C or a history of fever with associated symptoms (particularly cough, vomiting, and body aches). All clinicians reported that they were more likely to order a blood slide examination if they strongly suspected a patient had malaria. Although clinical staff stated that they generally had confidence in the laboratory results, all reported that they sometimes prescribed antimalarial treatment to persons with negative microscopy results, particularly if a patient’s clinical symptoms and signs were highly suggestive of malaria.

Only one laboratory assistant had ever received a supervisory visit related to malaria diagnosis. This consisted of an annual visit by staff from the provincial health office during which some blood slides were re-examined. Difficulties reported in some laboratories included shortages of reagents (three HCs), poor quality microscopes (two HCs), frequent electrical outages (three HCs), and inadequate water supply (one HC).

DISCUSSION

Blood slide microscopy for malaria is a potentially powerful tool for the diagnosis of febrile illnesses in sub-Saharan Africa, but its specific role in improving patient management has yet to be defined. Zambia has made malaria microscopy available in peripheral health centers with the aim of improving the ability of clinical staff to differentiate fever caused by malaria from fever resulting from other illnesses, thereby reducing the frequency of misdiagnosis and the overuse of antimalarial drugs. Our assessment in six HCs demonstrates that this approach is falling short of achieving its intended impact.

Although populations were similar at the six HCs, we observed significant disparities in how patients were managed. The percentage of patients who had a temperature measurement varied from 2% to 48%, with fewer than 25% of patients having their temperature measured at all but one HC.

The study findings also indicate a lack of standard clinical criteria for the use of laboratory diagnostic services for malaria. Despite similar frequencies of reported and/or documented fever at the six HCs, the percentage of outpatients and febrile outpatients referred for blood slide examination differed as much as 3-fold overall and 7-fold in children < 5 years of age. These disparities could not be explained by differing use at urban versus rural facilities. Of note, patients at the two mission-supported facilities were more often referred for a blood slide. Interviews with healthcare workers support our conclusion that standard criteria for ordering a blood slide are lacking.

In spite of these findings, multivariable analysis suggests that clinicians do share some common approaches in deciding whom to refer for blood slide microscopy. Persons with fever were much more likely to be referred for a blood slide, while persons with rash/skin lesions or respiratory symptoms were less likely to have this test performed. Interestingly, in children < 5 years of age, if GI symptoms were present in the absence of respiratory complaints, or vice versa, clinicians were less likely to refer them for malaria microscopy. These negative associations were not present when children had both GI and respiratory symptoms.

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The overall accuracy of microscopic diagnosis of malaria was high. Most notably, the predictive value negative was $\geq 90\%$, indicating that clinicians can be confident that a negative blood slide result strongly suggests that malaria is not the cause of the patient’s illness. The predictive value positive was lower (76\%), possibly indicating a tendency among technicians to report a blood slide as positive when they are in doubt. Data from other countries in sub-Saharan Africa are limited. A similar assessment in four HCs in Blantyre District, Malawi found somewhat lower overall sensitivity (82\%) and specificity (85\%, Centers for Disease Control and Prevention, unpublished data). A study in South Africa compared the readings by laboratories in four health facilities of a series of pre-prepared, unknown blood slides.

There was wide variability in the percentage of these slides that were read as positive in the four laboratories ($6.3\%\pm 45.8\%$, kappa = 0.11). A lack of technical supervision, poor condition of microscopes, and a high volume of blood slide requests may have contributed to lower accuracies of malaria microscopy at some HCs. If routine supervision had been in place and included a blinded review of a consecutive series of blood slides, the two laboratories with a high number of inaccuracies could have been quickly identified and remedial actions taken. This type of review should be neither costly nor time-consuming, since a trained microscopist can easily review 50 blood slides in a day. A supervisory visit would also have quickly identified equipment problems contributing to the higher number of inaccurate readings at two facilities.

Antimalarial drugs were frequently but inconsistently prescribed by clinical staff. A total of 32% of all outpatients and 42\% of children < 5 years of age were prescribed either CQ or SP. Antimalarial drugs were prescribed to 57\% of persons with fever and 11\% of those without evidence of fever. Multivariable analysis demonstrated that persons with fever were more likely, and those with rash or respiratory complaints less likely, to be prescribed antimalarial drugs. This unrestricted and unselective use of antimalarial drugs is undoubtedly contributing to the intensification of antimalarial drug resistance.

The most disturbing finding of this study was that 20–54% of persons with reported negative blood slides were still prescribed antimalarial drugs. In such cases, referring these patients to the laboratory appears to have had no effect on their treatment and added 1 hr to their clinic visit. The clinicians interviewed did report that they sometimes elected to treat persons with negative microscopy results for malaria if their clinical suspicions strongly suggested the diagnosis. Clinicians would appear to be using circular reasoning as they were also more likely to refer patients for microscopy if they strongly suspected malaria.

Overall, we found that malaria microscopy had minimal impact on antimalarial treatment at the six HCs. Antimalarial drugs were prescribed with equal frequency in febrile patients referred for a blood slide and in those whose treatment was based solely on clinical findings.

In view of our findings, the role of blood slide microscopy in peripheral health facilities in Zambia should be carefully reviewed. At a minimum, guidelines to assist clinicians in using this service appropriately would be beneficial. With the large number of patients treated at these facilities, it would be impossible to examine blood slides on all patients with symptoms suggestive of malaria. Therefore, these guidelines should focus on targeting the use of microscopy to specific clinical situations in which it would have the most influence on patient care. This might include patients with persistent symptoms of malaria in spite of antimalarial therapy, suspected severe or complicated malaria, or symptoms attributable to multiple possible causes. Once guidelines are developed, training of clinicians in these guidelines and subsequent ongoing supervision would help to ensure that the malaria microscopy will be used appropriately and treatment prescribed consistently.

Given present resource constraints in Zambia, empiric treatment of children with symptoms and signs highly suggestive of malaria is a reasonable approach in most settings, although obtaining a blood slide may be appropriate in areas where transmission is low (e.g., urban centers) or during the dry season. If microscopy is performed and no parasites are seen, clinicians should be discouraged from prescribing antimalarial treatment.

Rather than expanding malaria microscopy into additional HCs in Zambia, emphasis might best be placed on improving the efficiency of utilization and performance of malaria microscopy in those HCs in which laboratories already exist. A cost-effectiveness analysis of malaria microscopy in peripheral health facilities, taking into account the current inefficiencies identified in this assessment, and with an analysis examining the marginal costs and benefits of expansion of these services to other health facilities is warranted before laboratories are placed in additional health centers. Two studies conducted at Queen Elizabeth Hospital in Blantyre, Malawi (an area of moderate transmission), found that use of microscopy for malaria diagnosis in a hospital outpatient department resulted in a cost savings for children only during the dry season, but during all seasons for adults (Sullivan AD, Michigan State University, East Lansing, MI, unpublished data). An assessment of the performance of other laboratory services offered in HCs may also be warranted, since many laboratories offer testing for other diseases.

Finally, plans to implement IMCI in many countries need to take into account the existence of clinical laboratories in some facilities. Since some health centers will continue to have laboratories and clinicians will continue to make use of this service, it would be prudent to consider how best laboratory diagnosis of malaria can be used to complement clinical diagnosis and management of febrile illness in children < 5 years of age.

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