ARTICLE

Congenital Malaria in the United States

A Review of Cases From 1966 to 2005

Catherine R. Lesko, BA, MPH; Paul M. Arguin, MD; Robert D. Newman, MD, MPH

Objectives: To provide an updated review and examine any trends among congenital malaria cases that might help guide diagnosis, treatment, and public health recommendations.

Design: Retrospective case series.

Setting: United States.

Participants: We reviewed all cases of congenital malaria reported to the US National Malaria Surveillance System between January 1, 1966, and December 31, 2004, including 1 unpublished case from 2005, encompassing all years for which data were collected and available.

Main Exposures: Maternal characteristics, including travel history, and malaria treatment.

Main Outcome Measure: Characteristics of congenitally acquired cases of malaria.

Results: For the 81 cases of congenital malaria reported in the United States in the past 40 years, the predominant infecting species was *Plasmodium vivax* (81%). Most mothers (96%) were foreign born, and 55 of 65 women (85%), for whom time of most recent exposure was known, were exposed 1 year or less before delivery. A common error in the treatment of infants with congenital malaria was the unnecessary administration of primaquine phosphate for *P vivax* infection.

Conclusions: Health care professionals should have heightened vigilance for malaria in pregnant women who have emigrated from or traveled to malaria-endemic areas within the past year, as well as in their offspring. Such women with episodes of fever during pregnancy should have a blood film to test for malaria performed promptly and should be treated appropriately. Treatment of a mother does not negate the need for heightened vigilance in her newborn. Health care professionals should be aware that congenital *P vivax* malaria does not need to be treated with primaquine.

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Author Affiliations: Malaria Branch, Centers for Disease Control and Prevention, Atlanta, Georgia.

INFECTION WITH *PLASMODIUM* SPECIES during pregnancy has been associated with low birth weight and a consequently increased risk of perinatal and infant mortality.[1] Another adverse outcome that has received less attention is the placental passage of *Plasmodium* parasites and the subsequent risk of malaria in the newborn. In some newborns who are parasitemic at birth, the parasites spontaneously clear without the newborn ever becoming ill. This clearance has been attributed to the protective effect of maternal antibodies that are passed to the newborn[2-5] and to the protective role of fetal hemoglobin in slowing the rate of parasite development.[6] Clearance rates in endemic areas have been reported to be high, ranging from 87% to 100%.[7,8] Conversely, some newborns without detectable *Plasmodium* organisms at birth later develop clinical malaria.[7]

Estimating the prevalence of congenital malaria is complicated by several factors. Distinguishing cases of congenital malaria from autochthonous malaria in endemic regions is difficult. For example, different case definitions, such as the presence of parasites in the placenta at delivery or clinical diagnosis of malaria in a newborn, yield different estimates, ranging from 0.03% to 46.7% in endemic areas.[2,7-9] Estimates are affected by the risk population designated as the denominator. Prevalence estimates are higher for nonimmune mothers exposed to malaria than for mothers with partial immunity,[2,10] likely because of the impact that the passage of maternal antibodies has on parasite multiplication in the infants of immune mothers.[2,5,11]

The most recent comprehensive review of the epidemiologic features of congenital malaria in the United States was 14 years ago.[12] In this article, we provide an

updated review and examine whether any trends exist among cases that might help guide diagnosis, treatment, and public health recommendations.

METHODS

The National Malaria Surveillance System (NMSS), administered by the Centers for Disease Control and Prevention (CDC) Malaria Branch, is a passive surveillance system that relies on voluntary reporting of laboratory-confirmed (blood film or polymerase chain reaction) malaria cases (a nationally notifiable condition) by state and local health departments and individual health care professionals. We reviewed all cases of congenital malaria that were reported between January 1, 1966, and December 31, 2004, to the NMSS and 1 unpublished case from 2005, encompassing all years for which data were collected and available.

We reviewed all cases of congenital malaria and abstracted data into a spreadsheet (Microsoft Excel, Windows 2000 Professional; Microsoft Inc, Redmond, Washington); SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina), was used for all statistical analyses. In examining maternal history, time of exposure was defined as the most recent reported date that the mother had been living or traveling in a malarious area. This variable was used to determine time from maternal exposure to delivery of the newborn diagnosed as having congenital malaria. Weeks from malaria diagnosis until delivery and weeks from febrile illness until delivery were determined based on the first reported incidence of diagnosis or febrile illness.

In examining the infant's history, time to seeking care was defined as the number of days between symptom onset and first presentation to the health care system. If no history of symptoms was noted in the case narrative, time to seeking care was assumed to be less than 1 day. The frequency of symptoms, signs, and laboratory findings was calculated based on the assumption that an instance of nonreporting signified the absence of the symptom, sign, or laboratory finding.

Time to diagnosis was defined as the number of days between the initial presentation of the infant to the health care system and the diagnosis of malaria. If insufficient information was given regarding the period between presentation and malaria diagnosis, it was assumed that no delay occurred. If the child was diagnosed as having another condition before or in addition to malaria, it was assumed that malaria was present at the time of presentation in addition to the accompanying condition, and time of initial presentation was used in determining delay. Appropriateness of treatment was determined for the treatment regimens of both mothers and newborns based on the most recent recommendation from *The Medical Letter*[13] for that year or from CDC treatment guidelines (for 2004 and 2005).

RESULTS

From 1966 to 2005, 81 cases of congenital malaria were reported to the CDC. The states that reported the highest number of cases of congenital malaria were California (30), New York (8), and Texas (6); all other states reported 4 or fewer cases during the 40-year period.

MATERNAL HISTORY

Seventy-eight women were foreign born. In 3 cases, the mother's most recent exposure was the result of travel in a malaria-endemic area, and her country of birth was not specified. Forty-four women (54%) reported emigrating from Asia, 27 (33%) emigrated from South or Central America, and 7 (9%) emigrated from Africa (**Table 1**). Countries with a high number of case mothers were India (16), Laos (8), Mexico (7), Guatemala (7), Cambodia (6), El Salvador (5), and Vietnam (5). The number of cases reported each year ranged from 0 to 10. A clear peak occurred in cases centered around 1981 and a less distinct peak between 1991 and 1995 (**Figure 1**). The number of reported cases of congenital malaria in any given year was significantly correlated (Spearman $P<.001$) with the number of reported cases of malaria among foreign-born civilians in the United States but not with the number of cases of malaria in US civilians or with the total number of cases reported to the NMSS.

In almost all cases the country of exposure of the mother was the same as her country of origin. In 7 cases, a woman had an exposure in a country that was not her country of origin; such cases occurred most commonly because the woman spent time in a refugee camp before entering the United States. Of the 78 women for whom

Table 1. Region of Origin of Mothers of Newborns Diagnosed as Having Congenital Malaria, United States, 1966-2005

Region	Frequency, No. (%)
Central Africa	2 (3)
East Africa	1 (1)
West Africa	4 (5)
Caribbean	1 (1)
Mexico or Central America	24 (30)
Tropical South America	2 (3)
East Asia	2 (3)
South Asia	18 (22)
Southeast Asia	24 (30)
Unknown	3 (4)
Total	**81** (102)[a]

[a] Percentages sum to more than 100% because of rounding.

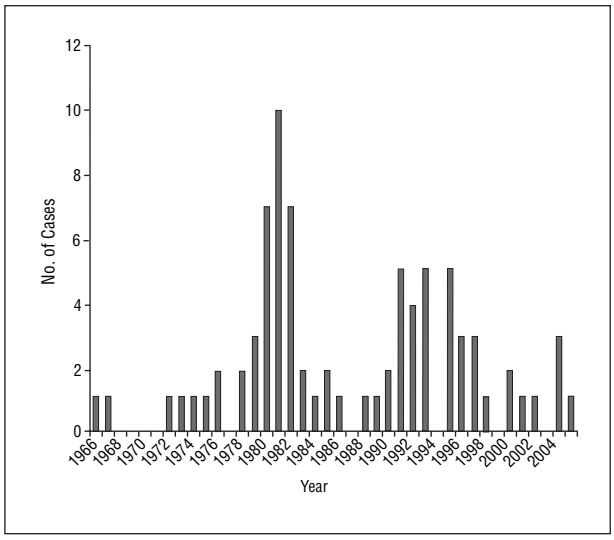

Figure 1. Number of cases of congenital malaria reported to the National Malaria Surveillance System per year, 1966-2005.

Table 2. Number of Weeks Between Most Recent Maternal Exposure to Malaria and Delivery Among Mothers of Newborns Diagnosed as Having Congenital Malaria, United States, 1966-2005

Infecting Species	No. of Cases[a]	Time From Malaria Exposure to Delivery, wk		
		Range	Mean	Median
Plasmodium falciparum	4[b]	9-13	10	9
Plasmodium vivax	54	1-104	34	34
Plasmodium malariae	6	156-624	404	405
Plasmodium ovale	1	<1	<1	<1

[a] Cases for which the infected species was not known or reported are excluded.
[b] One case was excluded because of a probability of misdiagnosis or inaccurate travel history; mother immigrated to the United States from Haiti 7 years before delivery and reported no exposure since that time.

travel history was available, the most recent exposure for 65 (83%) was immediately before immigrating to the United States; 13 women (17%) had been residing in the United States and were exposed most recently during travel to a country with endemic malaria transmission. Among 53 immigrant women for whom time of immigration was known, the median time from immigration to delivery was 9.5 months; 40 (75%) had immigrated 1 year or less before delivery.

The range of time from mother's last exposure to delivery was 36 hours to 12 years (median, 9.5 months). Of 65 women for whom time of exposure was known, 55 (85%) had been exposed 1 year or less before delivery. Of the 5 women whose newborns were diagnosed as having falciparum malaria, 4 had been exposed less than 6 months before delivery. One woman reported emigrating from Haiti 7 years before delivery and having no history of travel to a malaria-endemic area since that time. The range of time from last exposure to delivery among 66 mothers of infants diagnosed as having *Plasmodium vivax* was less than 1 week to 2 years. Among 6 mothers of infants diagnosed as having *Plasmodium malariae*, time from last exposure to delivery ranged from 2 to 12 years. The 1 mother who gave birth to a newborn subsequently diagnosed as having *Plasmodium ovale* infection had immigrated to the United States from a malaria-endemic area less than 1 week before delivery (**Table 2**).

Of 48 women for whom history of fever was available, 32 (67%) reported having fever during pregnancy. Fourteen of the 27 women for whom fever timing was known (52%) reported fever during the third trimester, and 9 (33%) reported fever during the week before delivery. Forty-six of the 75 mothers for whom information was available (61%) reported a history of malarial illness during pregnancy; 6 of the 46 (13%) reported multiple episodes. Twenty-one mothers (26%) reported being diagnosed as having malaria during pregnancy; malaria infection was laboratory confirmed in 12 of these 21 women (57%). Ten women (53%) had their infections diagnosed during the third trimester.

Maternal blood films for malaria were conducted after either symptomatic illness or malaria diagnosis in the infant; some diagnoses were made as incidental findings on other laboratory evaluations. Overall, 34 women (42%) had peripheral blood films positive for malaria, 32 (40%) had blood films negative for malaria, and 15 women (19%) did not have blood films performed. Of 42 maternal blood films performed after the diagnosis of malaria in the infant, 9 (21%) were positive for malaria (*P vivax* = 7, *P ovale* = 1, and unknown = 1). Of 13 women for whom infection status at the time of delivery was known, 11 (85%) had blood films positive for malaria and were symptomatic. Two asymptomatic women had blood films negative for malaria. An additional 5 women had stored blood samples that were available for retrospective review after diagnosis of malaria in the infant; 4 were found to be parasitemic. Of the 11 infants born to women known to be parasitemic at delivery, only 3 had blood films performed at birth. All 3 tested negative for malaria at that time. An additional 2 newborns born to mothers who were diagnosed as having malaria shortly after delivery (+1 day and +3 days) were also examined for parasitemia and were found to have blood films negative for malaria.

INFANT HISTORY

The predominant infecting *Plasmodium* species was overwhelmingly *P vivax* (66 cases, 81%). Eight infants were infected with *Plasmodium falciparum* (10%), 6 with *P malariae* (7%), and 1 with *P ovale* (1%).

Median age at symptom onset was 21.5 days for all species combined (**Figure 2**). Infants infected with *P malariae* were significantly older at symptom onset (mean, 53 days) than infants infected with *P vivax* or *P falciparum* (mean, 25 days; $P = .003$). The range of time from symptom onset to presentation was 0 to 8 weeks. In 32 of 34 cases, time to presentation was 4 weeks or less.

The most common symptom reported on presentation was fever (86% of cases); the most common signs were anemia (35%), splenomegaly (31%), hepatomegaly (20%), thrombocytopenia (15%), and jaundice (14%) (**Table 3**).

MEDICAL TREATMENT

A delay in diagnosis of more than 1 day occurred in 12 infants (15%); 8 (67%) were infected with *P vivax*, 2 (17%) with *P falciparum*, and 2 (17%) with *P malariae*. In 11 of these cases, the length of delay was between 2 days and 2 months. The median length of delay was 8.5 days. One infant infected with *P malariae* was seen by several physicians and treated with antibiotics for persistent inter-

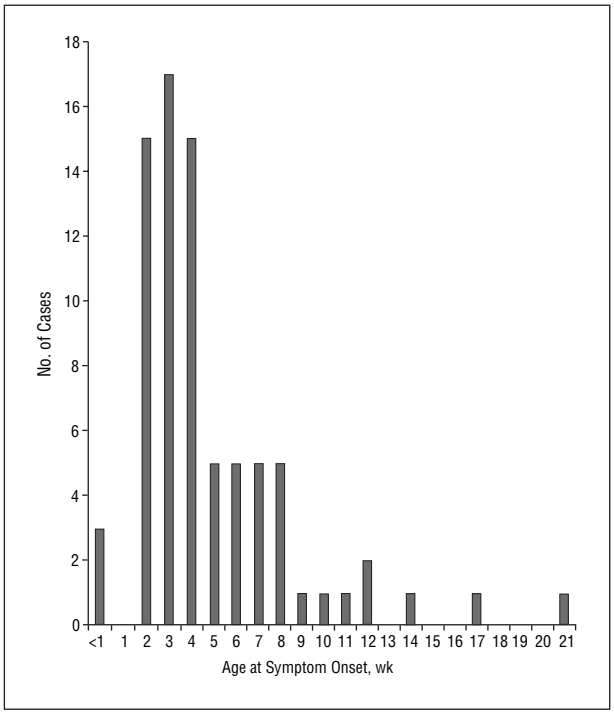

Figure 2. Age in weeks at symptom onset of infants with reported congenital malaria, United States, 1966-2005.

Table 3. Frequency of Symptoms, Signs, and Laboratory Findings Among 81 Infants Diagnosed as Having Congenital Malaria, United States, 1966-2005

Symptoms, Signs, and Laboratory Findings	Infants, No. (%)[a]
Fever	70 (86)
Anemia	28 (36)
Splenomegaly	25 (31)
Hepatomegaly	16 (20)
Thrombocytopenia	12 (15)
Jaundice	11 (14)
Irritability	8 (10)
Anorexia	8 (10)
Vomiting	8 (10)
Cough	6 (7)
Diarrhea	3 (4)
Lethargy	3 (4)
Hemolysis	3 (4)
Pallor	3 (4)
Hyperbilirubinemia	2 (3)
Failure to thrive	2 (3)
Seizures	2 (3)
Dyspnea	1 (1)
Purpura	1 (1)
Tachycardia	1 (1)
Monocytosis	1 (1)

[a] Percentages do not total 100% because each case can have more than 1 symptom, sign, or laboratory finding.

mittent fever between 2 and 5 months of age. On initial presentation, 6 infants were diagnosed as having presumptive sepsis. Six infants received other diagnoses, including "flu," viral gastroenteritis, jaundice, anemia, hyperbilirubinemia, and thrombocytopenia.

Treatment regimen was reported for 78 of the 81 infants with congenital malaria. Seventy-six (97%) were treated appropriately according to the guidelines published at the time with respect to maternal region of exposure and infecting species. The 2 infants who did not receive appropriate treatment were born to mothers who had passed on falciparum malaria acquired in Africa (1995) and Asia (1980); both were initially treated with chloroquine. The infections in both infants ultimately cleared, although treatment initially failed in 1 and subsequent treatment was required. Eleven infants infected with *P vivax* were treated with chloroquine and primaquine phosphate; primaquine is not necessary in the treatment of congenitally acquired *P vivax*. There were no reports of death or other significant sequelae after any of the 81 reported cases.

Nineteen mothers were diagnosed as having malaria before delivery. The treatment regimen was not known for 11, 7 were treated appropriately, and 1 reported having had malaria during pregnancy (trimester unknown) but was not treated. After delivery, 36 (84%) of 43 women for whom information on treatment regimen was available were appropriately treated. Four women were asymptomatic and were not treated at all, despite having necessarily been parasitemic to pass *P vivax* parasites to their infants. Other treatment errors included using primaquine or chloroquine alone for treatment of *P vivax* and chloroquine to treat a case of *P falciparum* acquired in Africa in 1995.

COMMENT

Congenital malaria is rare in the United States and has not been associated with poor outcomes. To put these numbers into context, of the 4.1 million live births in the United States in 2004, only 3 infants were reported to have congenital malaria. In our review of 40 years of data, we identified only 81 cases.

Nearly all of the cases of congenital malaria were among infants whose mothers were foreign born. This finding suggests that congenital malaria is primarily a health problem among recent immigrants to the United States rather than among US-born travelers to malaria-endemic countries. Health care professionals who treat recent immigrants or refugees should be aware of the potential for relapsed malaria during pregnancy and the possibility of congenital transmission. The appropriate diagnosis and treatment of malaria in a pregnant woman with a history of recent travel to a malaria-endemic country and heightened vigilance for fever in her infant, along with early diagnosis and treatment of congenital malaria cases, could prevent unnecessary morbidity and potential mortality.

The predominance of *P vivax* infection underscores how little is known about the effects of *P vivax* during pregnancy and on infant outcomes. *Plasmodium vivax* causes far fewer cases of severe or fatal malaria than does *P falciparum*,[14] which may explain the lack of severe illness or death among our cohort of infants, even when delays in identification and treatment of cases occurred. Pregnancy has been described as a cause for relapse in women harboring *P vivax* hypnozoites.[15] Generally, re-

lapse of malaria due to *P vivax* is thought to be rare beyond 2 to 3 years after the initial infection,[16,17] and symptoms may be milder than those observed during a primary attack.

The literature describes symptom onset of congenital malaria as typically occurring 3 to 6 weeks after birth, coinciding with the half-life of maternal IgG antibody in infants, but possibly as late as 15 months.[18] Although our observed age at symptom onset is generally consistent with this cited range, more than a fourth of cases occurred before 3 weeks of age. This finding may be attributable to residence in a nonendemic area such as the United States because maternal antibody levels would be expected to decrease in the absence of repeated exposure, so the passage of passive immunity to the infant might also be decreased. *Plasmodium vivax* generally predominates in areas where overall *Plasmodium* transmission is less intense, and thus protective immunity to *P vivax* is not as commonly acquired.[14] If the transfer of protective immunity is one of the main factors that affects the age at symptom onset, the fact that most of the cases in the United States were *P vivax* infections may be the reason for our observation of an earlier age at symptom onset.

In non–malaria-endemic areas, the clinical appearance of congenital malaria has been previously described as febrile illness in a jaundiced, anemic infant with hepatosplenomegaly.[12] The symptoms observed in the cohort of infants diagnosed as having congenital malaria in the United States are consistent with this description.

Physicians in nonendemic countries often fail to diagnose malaria on initial presentation,[19] and delay in diagnosis among US travelers has been associated with mortality.[20] Prompt diagnosis of malaria can be even more challenging when the patient has no history of travel, as is the case with these infants. Twelve infants experienced a delay in diagnosis, although none had a poor outcome as a result of the delay, perhaps partially because of the preponderance of *P vivax* as opposed to *P falciparum* in our series. Recommendations have previously been made regarding the inclusion of malaria in the differential diagnosis of fever in infants born to mothers who have been exposed to malaria.[21]

Most infants received treatment that was appropriate for their infecting species and mother's region of exposure. However, in 11 cases, infants with *P vivax* infection were treated with chloroquine and primaquine. In congenital malaria cases, there is no exoerythrocytic phase, and thus treatment with primaquine is unnecessary. Current treatment recommendations should be referenced on diagnosis of malaria to avoid unnecessary morbidity or mortality due to treatment with inappropriate or unnecessary drugs (http://www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm).

It has previously been suggested that infants should be presumptively treated if their mothers are identified as being parasitemic at delivery.[22] However, our review did not identify any severe disease or death associated with congenital malaria during a 40-year period. Most infections in our series were attributed to *P vivax*, which is generally a far less serious illness than *P falciparum*. In addition, the literature contains compelling data that describe spontaneous clearance of parasites in infants without treatment,[7,8] although the direct relevance of these observations to infants born to women living in nonendemic areas is not entirely clear. Conversely, in 5 cases the mother was determined to be parasitemic at delivery or shortly thereafter and at that time parasitemia was not detected in the infant, but the infant later developed clinical malaria despite an initial blood film negative for malaria. The number of cases of malaria in the United States among pregnant women has ranged from 22 to 35 since reporting for this group began in 1999.[23-28] Data are insufficient, however, to draw conclusions about the relative risk of an infant developing congenital malaria when born to a woman identified with parasitemia during pregnancy or delivery in a nonendemic setting. We therefore hesitate to recommend presumptive treatment of infants in cases in which mothers are found to be parasitemic either during pregnancy or at delivery. Rather, we suggest that physicians judge each case individually, considering such factors as reliability of follow-up and access to medical care. In some cases it may be appropriate to simply educate the mother about the risk of congenital malaria and instruct her to seek medical care if the infant develops symptoms of malaria. In others, presumptive treatment of the newborn may be warranted.

Of all the mothers diagnosed as having malaria before delivery, none were treated with primaquine during pregnancy because pregnancy is a contraindication for primaquine use. Primaquine can cross the placenta and result in hemolytic anemia in the fetus if it is glucose-6-phosphate dehydrogenase deficient.[29]

After delivery, 7 women were not appropriately treated. The main issue in postdelivery treatment of mothers was failure to properly treat *P vivax* infections. Mothers who give birth to infants diagnosed as having congenital *P vivax* or *P ovale* infection are necessarily infected and should be treated with both chloroquine (to eradicate blood stages of the parasite) and primaquine (to eradicate the dormant liver stage [hypnozoite]), regardless of blood film results, to prevent unnecessary morbidity as a result of later relapse. If both the mother and infant have normal glucose-6-phosphate dehydrogenase levels, primaquine may be administered to a lactating woman.[30]

In summary, we found that congenital malaria in the United States is rare and not associated with poor outcomes. *Plasmodium vivax* is responsible for the preponderance of cases. Almost all mothers of infants with congenital malaria are foreign born. All pregnant women who have emigrated from malaria-endemic areas within the past year or have traveled to a malaria-endemic area within the past year should have heightened vigilance for malaria in themselves and their offspring. Such women with episodes of fever during pregnancy should have a blood film for malaria performed promptly and should be treated appropriately. Appropriate treatment of the mother, however, does not obviate the need for heightened vigilance for symptoms of malaria in the offspring. Health care professionals should be reminded that congenital *P vivax* malaria does not need to be treated with primaquine because only blood stage parasites are present in a congenitally acquired infection.

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Correspondence: Paul M. Arguin, MD, CDR (USPHS), Malaria Branch, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, Mail Stop F-22, Atlanta, GA 30341 (pma0@cdc.gov).
Author Contributions: Ms Lesko had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Lesko and Newman. *Acquisition of data:* Lesko and Newman. *Analysis and interpretation of data:* Lesko, Arguin, and Newman. *Drafting of the manuscript:* Lesko and Newman. *Critical revision of the manuscript for important intellectual content:* Lesko, Arguin, and Newman. *Statistical analysis:* Lesko. *Study supervision:* Arguin and Newman.
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