TRANSFUSION-TRANSMITTED MALARIA IN THE UNITED STATES FROM 1963 THROUGH 1999

MARY MUNGAI, M.D., GARY TEGTMEIER, PH.D., MARY CHAMBERLAND, M.D., M.P.H., AND MONICA PARISE, M.D.

ABSTRACT

Background Transfusion-transmitted malaria is uncommon in the United States. After the report of three cases of complicated Plasmodium falciparum infection acquired by transfusion, we reviewed all cases of transfusion-transmitted malaria reported to the Centers for Disease Control and Prevention (CDC) from 1963 through 1999.

Methods Information on the patients was from surveillance reports sent to the CDC. Information about the implicated blood donors came from the National Malaria Surveillance System. To determine whether donors should have been excluded from donating blood, we compared their characteristics with the exclusion guidelines of the Food and Drug Administration and the American Association of Blood Banks.

Results Of 93 cases of transfusion-transmitted malaria reported in 28 states, 33 (35 percent) were due to P. falciparum, 25 (27 percent) were due to P. vivax, 25 (27 percent) were due to P. malariae, 5 (5 percent) were due to P. ovale, 3 (3 percent) were mixed infections, and 2 (2 percent) were due to unidentified species. Ten of the 93 patients (11 percent) died. There were potentially 91 donors (in two cases, two patients received blood from the same donor), 67 of whom (74 percent) could be identified as infective. Of 64 implicated donors whose country of origin was reported, 38 (59 percent) were foreign born. Among those for whom complete information was available, 37 of 60 donors (62 percent) would have been excluded from donating according to current guidelines (in place since 1994), and 36 of 48 donors (62 percent) should have been excluded under the guidelines in place at the time of donation.

Conclusions Careful screening of donors according to the recommended exclusion guidelines remains the best way to prevent transfusion-transmitted malaria. (N Engl J Med. 2001;344:1973-8.)

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From the Divisions of Parasitic Diseases (M.M., M.P.) and Viral and Rickettsial Diseases (M.C.), National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta; the Public Health Service, Department of Health and Human Services, Washington, D.C. (M.M., M.C., M.P.); and the Community Blood Center of Greater Kansas City, Kansas City, Mo. (G.T.). Address reprint requests to Dr. Parise at the Division of Parasitic Diseases, Mailstop F-22, Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30333, or at mep0@cdc.gov.

In the United States, the estimated incidence of transmission of malaria by blood transfusion (less than 1 case per million units collected) is less than that of hepatitis B virus (7 to 32 cases per million units) and bacterial infections (e.g., 1 case of platelet-related sepsis per 12,000 units) and is similar to that of hepatitis C or human immunodeficiency virus after the introduction of nucleic acid–testing techniques. There are few data on the risk of transfusion-transmitted babesiosis (approximately 6 cases per million units). Since there is no approved laboratory test in the United States to screen donated blood for malaria, prevention depends on the exclusion of potentially infected donors who are identified during the donor interview. The Food and Drug Administration and the American Association of Blood Banks have recommendations for the exclusion of potentially infected donors (Table 1). However, it can be difficult to obtain accurate travel and immigration histories and to ascertain the areas of a country in which malaria is transmitted.

From 1996 through 1998, three cases of transfusion-transmitted malaria occurred, two of which were fatal. To gain a better understanding of how to prevent such cases, we reviewed the epidemiologic features of cases of transfusion-transmitted malaria in the United States, as reported to the Centers for Disease Control and Prevention (CDC) from 1963 (the first year complete records were available) through 1999.

METHODS

Information about the patients was obtained from reports of cases of malaria sent to the National Malaria Surveillance System at the CDC, which include information on demographic characteristics, date of the onset of illness, species responsible for the infection, history of travel or blood transfusion, type of antimalarial therapy, and outcome of the illness. Because malaria infections acquired in the United States are further investigated by the CDC (in conjunction with state or local health departments), further details on transfusion-transmitted cases were obtained by reviewing the annual malaria-surveillance summaries of the CDC. During the epidemiologic investigations that ensue after a case is detected, an attempt is made to collect serum from the donors involved so that it can be tested at the CDC for antimalarial antibodies by the indirect fluorescence antibody assay. Antibody titers of 1:64 or more are considered positive and to indicate previous or current infection. When possible, donors are reinterviewed regarding their travel history, any prior diagnosis of malaria, country of birth, and date of entry into the United States, and a blood smear is obtained and reviewed at the CDC. We considered a donor to be the source of the malaria infection if at least one of three criteria was met: the donor had a positive blood smear; the donor had a positive serologic test result; or the patient had received blood from no other donor.

In general, when a case of transfusion-transmitted malaria occurs, any remaining blood components from potentially infective donors are withheld from transfusion pending evaluation of the donors. Once an infective donor is identified, any recipient of his or her blood components (from the same or a prior donation) is evaluated for malaria.

The cases of transfusion-transmitted malaria we reviewed occurred over a period of years, during which donor-exclusion guidelines changed several times (Table 1). During this time, the guidelines evolved to provide specific durations of deferral; a diagnosis...

<table>
<thead>
<tr>
<th>YEAR</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958</td>
<td>A donor shall be free from any disease transmissible by blood transfusion insofar as can be determined by history.</td>
</tr>
<tr>
<td>1963</td>
<td>A donor shall be free from any infectious disease, including syphilis and malaria, transmissible by blood transfusion insofar as can be determined by history.</td>
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</tbody>
</table>
| 1970 | i) Travelers to malarious areas may be accepted as regular donors 6 months after return to the United States providing that they have been free of symptoms and have not taken antimalarial prophylaxis.  
   ii) Travelers who have taken antimalarial prophylaxis shall be deferred for 2 years after cessation of suppressive therapy. |
   ii) Travelers to malarious areas who have taken antimalarial prophylaxis shall be deferred for 3 years after cessation of therapy. Military personnel who have been in a malarious area should be considered to have received suppressive therapy whether or not they report it. |
| 1974 | Same rule as for 1970.  
   ii) Prospective donors who have taken antimalarial prophylaxis or who have been military personnel in areas where malaria is endemic shall be deferred for 3 years after cessation of therapy or after departure from the area if they have been asymptomatic. |
| 1978 | Same rule as for 1974 (except there is no separate mention of military personnel). |
| 1994* | Travelers who are residents of nonmalarious areas who have been in a malarious area may be accepted as donors 1 year after their return to the nonmalarious area (irrespective of the use of chemoprophylaxis) if they have been free of malaria symptoms. |
| 2000† | Same rule as for 1974. |

<table>
<thead>
<tr>
<th>TRAVELERS TO MALARIOUS AREAS</th>
<th>IMMIGRANTS OR REFUGEES FROM OR RESIDENTS OF MALARIOUS AREAS</th>
<th>PERSONS TREATED FOR MALARIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same rule as for 1974.</td>
<td>Immigrants or visitors from endemic areas may be accepted as regular donors 3 years after departure from the area if they have been asymptomatic.</td>
<td></td>
</tr>
<tr>
<td>Same rule as for 1974.</td>
<td>Prospective donors who have had malaria shall be deferred for 3 years either after becoming asymptomatic or after cessation of therapy.</td>
<td></td>
</tr>
<tr>
<td>Same rule as for 1974.</td>
<td>Same rule as for 1974.</td>
<td></td>
</tr>
<tr>
<td>Same rule as for 1974.</td>
<td>Same rule as for 1974.</td>
<td></td>
</tr>
<tr>
<td>Same rule as for 1974.</td>
<td>Same rule as for 1994.</td>
<td></td>
</tr>
</tbody>
</table>

*In 1994, the FDA continued to recommend a three-year deferral for persons who had had malaria, whereas the American Association of Blood Banks during 1994 through 1996 recommended deferring such persons indefinitely. In 1996, the American Association of Blood Banks returned to recommending a three-year deferral for such persons. The 1994 guidelines of the FDA were used for donor-suitability analyses in this article.

†The guidelines proposed by the FDA in 2000 are currently in draft form.

RESULTS

Patients

Ninety-three cases of transfusion-transmitted malaria were reported from 1963 through 1999 by 28 states. Sixty (65 percent) were reported by six jurisdictions: New York City (14); Texas (13); California (13); New York State, excluding New York City (7); Pennsylvania (7); and Florida (6). Of 91 patients whose sex was reported, 53 (58 percent) were male. The patients ranged in age from 2 days to 85 years; 24 (26 percent) were older than 65 years of age; in comparison, approximately 54 percent of persons who receive red-cell transfusions in the United States are older than 65 years old.17 Table 2 shows the species of malaria parasite identified. There was an increase in the proportion of cases caused by Plasmodium falciparum in the 1990s. The number of donors per patient ranged from 1 to 192 (median, 7). Among the 70 patients for whom information was available, the infective component was whole blood in 63 percent, packed red cells in 31 percent, and platelets (which can transmit malaria because of contamination with residual red cells) in 6 percent. The proportion of cases attributed to whole blood decreased from 88 per-
cent from 1963 through 1979 to 27 percent from 1980 through 1999 (P<0.001).

Ten of the 93 patients (11 percent) died. Patients who died were significantly older than those who survived (mean, 71 vs. 47 years; P<0.001; range, 53 to 85 years and 2 days to 78 years, respectively). Six of the patients who died had \textit{P. falciparum}, two had \textit{P. vivax}, and two had \textit{P. malariae}. The reported cause of death of the two patients infected with \textit{P. vivax} was the underlying disease. The reported cause of death of the two patients with \textit{P. malariae} infection involved unusually high densities of parasites, although the specific densities were unknown. The incubation period was available in 57 cases (Table 2).

In 43 cases for which data were available, the number of days from the onset of symptoms to the diagnosis of malaria ranged from 1 to 180 (median, 10).

**Implicated Donors**

There were a presumed 91 infective donors for the 93 patients (in two different episodes, 2 patients had the same donor). In 67 of the 91 episodes (74 percent), an infective donor could be identified. Fifty-three of 59 donors (90 percent) whose sex was reported were male. In 37 cases in which information was available, the implicated donors’ ages ranged from 19 to 59 years (median, 27); 78 percent were 21 to 40 years old. In 64 cases, the country of origin of the implicated donor was known. Twenty-six (41 percent) were born in the United States, and 38 (59 percent) were born in other countries (24 in Africa, 4 in Asia, 6 in the Americas, and 4 in Europe). The proportion of implicated donors in the past 20 years who were former residents of countries where malaria was endemic (86 percent) was significantly greater than the proportion from 1963 through 1979 (26 percent, P<0.001) (Table 3).

Forty-eight of the 67 implicated donors were identified by serologic tests (72 percent), 7 by blood smear (10 percent), 10 by both serologic tests and blood smear (15 percent), and 2 by the sole-donor criterion (3 percent). Serologic tests were positive in 58 of 59 implicated donors in which testing was performed (98 percent); a blood smear showed malaria parasites in 17 of 49 donors in which it was performed (35 percent).

There was enough information in the records to permit a judgment to be made as to whether the donor should have been excluded according to current exclusion criteria in 60 cases and according to prior exclusion criteria in 48 cases. Thirty-seven of 60 donors (62 percent) should have been excluded according to current FDA guidelines, and 30 of 48 (62 percent) according to the guidelines in place at the time of donation. The species distributions for cases in which current guidelines were followed and those in which they were not are shown in Table 4. Of the 15 \textit{P. malariae} infections that occurred when current guidelines were followed, 12 were due to foreign-born donors and 3 to U.S.-born donors. The time

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**Table 2.** The causative species of \textit{Plasmodium} and incubation periods in 93 cases of transfusion-transmitted malaria in the United States, 1963 through 1999.

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</thead>
<tbody>
<tr>
<td>\textit{P. falciparum}</td>
<td>8 (47)</td>
<td>10 (29)</td>
<td>5 (18)</td>
<td>10 (71)</td>
<td>8–36 (n=20)</td>
<td>17±8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>\textit{P. vivax}</td>
<td>2 (12)</td>
<td>14 (41)</td>
<td>8 (29)</td>
<td>1 (7)</td>
<td>11–42 (n=16)</td>
<td>20±9</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>\textit{P. malariae}</td>
<td>5 (29)</td>
<td>8 (24)</td>
<td>10 (36)</td>
<td>2 (14)</td>
<td>8–90 (n=15)</td>
<td>50±23</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>\textit{P. ovale}</td>
<td>1 (6)</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>1 (7)</td>
<td>19–30 (n=2)</td>
<td>24±8</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (6)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0</td>
<td>10–21 (n=3)</td>
<td>14±6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>2 (7)</td>
<td>0</td>
<td>11 (n=1)</td>
<td>11±0</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

* A listing of all cases, with details on the year, the number of donors involved, demographic characteristics and travel or immigration history of the implicated donor, laboratory results, and compliance with donor-deferral guidelines is available from the authors.

† Values in parentheses are the numbers of cases with data on the incubation period.
between the donor’s immigration to the United States or last foreign travel to a malarious area and blood donation ranged from 3 to 44 years (median, 8).

Of the four P. falciparum infections that occurred even though current guidelines had been followed, one was due to a foreign-born donor who had immigrated to the United States 3½ years before donation (more than the 3-year deferral period). The remaining three were due to U.S.-born donors; the time between their last travel to a malarious area and blood donation ranged from 1 to 5 years (median, 13 months).

The implicated donors in two cases of P. vivax malaria that occurred despite adherence to guidelines had been born in the United States but had subsequently lived in malarious areas; one had been in the United States for one year before donation, and the other for two years. One case caused by P. ovale was associated with a U.S.-born donor who had lived in Liberia for several years but who had reportedly last been in a malarious area four years before donating blood. The implicated donor in a case of mixed infection (P. malariae and P. ovale) was foreign born and had reportedly last been in a malarious area seven years before donating.

Trends in the Incidence of Transfusion-Transmitted Malaria

The incidence of transfusion-transmitted malaria in the United States has decreased in the past three decades and now remains at a stable low level (Fig. 1). From 1965 through 1970, the incidence rate ranged from 0 to 1.37 cases per million units transfused; from 1993 through 1998, the incidence rate ranged from 0 to 0.18 case per million units transfused. The peak in cases of transfusion-transmitted malaria in the late 1960s and early 1970s was associated with the return of military personnel from Vietnam and was accompanied by an increase in the overall numbers of cases of malaria reported in the United States, largely caused by increased immigration from Southeast Asia. The reason for the increase in the number of cases of transfusion-transmitted malaria in the early 1980s is unknown.

**DISCUSSION**

Transfusion-transmitted malaria remains rare in the United States. Its reported incidence has not changed substantially in the past decade; however, there have been important changes in the patterns of transmission in the past three decades. Although implicated donors were approximately evenly distributed between those born in the United States and those born in other countries, in the past decade most infective donors have been immigrants. Although P. malariae and P. vivax have been reported as the species most frequently associated with transfusion-transmitted malaria,18-20 in our series the most common infecting species was P. falciparum, particularly in more recent years. This may be due to increasing immigration from malarious areas, particularly sub-Saharan Africa, where P. falciparum is the most common species transmitted.

Prevention of transfusion-transmitted malaria relies entirely on the exclusion of potentially infected donors. However, in approximately two thirds of cases, the donor-screening process failed, illustrating the difficulties in obtaining accurate travel and immigration histories from donors. Information on previous exposure to malaria was elicited from the potentially infected donors during the epidemiologic investigations initiated after the identification of a transfusion-transmitted case.

Because not all records of the donor interviews were available to us, we do not know whether these donors had given the same history at the time of donation nor do we know exactly how the blood-bank staff may have evaluated the travel and immigration history. To assist blood banks in screening, the American Asso-

**TABLE 3. CHARACTERISTICS OF DONORS IMPLICATED IN CASES OF TRANSFUSION-TRANSMITTED MALARIA IN THE UNITED STATES, 1963 THROUGH 1999.**

<table>
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</thead>
<tbody>
<tr>
<td>Former resident of malarious area</td>
<td>4 (36)</td>
<td>5 (21)</td>
<td>15 (88)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>U.S. civilian traveler</td>
<td>0</td>
<td>2 (8)</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Visitor to country of origin†</td>
<td>1 (9)</td>
<td>4 (17)</td>
<td>2 (12)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>U.S. military personnel</td>
<td>6 (55)</td>
<td>13 (54)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data were available for 64 of the 67 implicated donors.
†A visitor was defined as a person who had lived in a malarious area before coming to live in the United States and who returned to the country of origin to visit friends or relatives.

**TABLE 4. INFECTIVE PLASMODIUM SPECIES IN 23 CASES IN WHICH CURRENT DONOR-EXCLUSION GUIDELINES WERE CORRECTLY IMPLEMENTED AND IN 37 CASES IN WHICH THE GUIDELINES WERE NOT IMPLEMENTED CORRECTLY.**

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>GUIDELINES CORRECTLY IMPLEMENTED (N=23)</th>
<th>GUIDELINES NOT IMPLEMENTED CORRECTLY (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. (%)</td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>4 (17)</td>
<td>22 (59)</td>
</tr>
<tr>
<td>P. vivax</td>
<td>2 (9)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>P. malariae</td>
<td>15 (65)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>P. ovale</td>
<td>1 (4)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>
Association of Blood Banks modified its uniform donor-screening questionnaire in 1999. Blood-bank personnel inquire generally about travel outside the United States or Canada within the previous three years (instead of relying on donors to report whether they have been in a malarious area) and then probe to determine whether travel was to a malarious area. To improve the assessment of such donors, the FDA has recently proposed that donors first be asked whether they were born in the United States. If they were not, they are asked when they moved to the United States and whether they have traveled outside the United States since their arrival.

Approximately one third of the cases of transfusion-transmitted malaria occurred despite adherence to current guidelines. The donor-exclusion criteria have their scientific basis in the biologic behavior of the different plasmodium species. Infections with species that cause relapsing illness (P. vivax and P. ovale) rarely persist longer than three years. Infections with P. falciparum rarely persist longer than one or two years, and 99 percent of patients present within one year of departure from a malarious area.

National malaria-surveillance data from 1985 through 1997 included 7407 reported cases in U.S.-born residents and 6252 in foreign-born residents. Among 5737 cases in U.S.-born residents for which information was available, 119 cases (2.1 percent) had their onset more than one year after the patient had traveled to a malarious area. Among 4229 cases in foreign-born residents for which information was available, 7 cases (0.2 percent) had their onset more than three years after the patient left a malarious area. In U.S. surveillance data, we found transfusion-transmitted cases of P. vivax, P. ovale, and P. falciparum infections in which donors had reportedly left malarious areas five, seven, and nine years, respectively, before the diagnosis of malaria in the recipient. We also found 9 case reports in the literature of transfusion-transmitted infections by species other than P. malariae with more than three years between the donor’s departure from a malarious area and the diagnosis of malaria in the recipient or the transfusion.

The longest periods between the reported exposure to malaria and the donation of blood products that transmitted the infection were 13 years in the case of a P. falciparum infection, 27 years in the case of a P. vivax infection, and 7 years in the case of a P. ovale infection. In our series, the longest interval between travel to a malarious area and transmission of malaria through a blood transfusion was 44 years in the case of a P. malariae infection, 5 years in the case of a P. falciparum infection, 2.5 years in the case of a P. vivax infection, and 7 years in the case of a P. ovale infection. Because P. malariae parasites can persist for decades, rare cases of transfusion-transmitted malaria will continue to occur despite the use of current exclusion guidelines. The guidelines aim to strike a balance between minimizing the risk of malaria and excluding as few uninfected donors as possible.

One possible option for reducing transfusion-transmitted malaria is laboratory screening. Among potential screening tests, diagnosis on the basis of a blood-smear examination is not sensitive enough, since donors who have transmitted the infection typically have a low level of parasitemia that may not be detected even by careful examination of a blood smear. In their current stage of development, antigen-detection tests have an even higher limit of detection (in terms of the number of parasites per cubic millimeter) than blood-smear examination and would be of limited usefulness in screening.

Figure 1. The Number of Cases and the Incidence of Transfusion-Transmitted Malaria in the United States, 1963 through 1998. The incidence is the number of cases per 1,000,000 units of whole blood and packed red cells transfused.
Another screening option is the detection of plasmodium DNA or RNA by the polymerase chain reaction (PCR), which is more sensitive and specific than microscopic examination and has been used on donor blood. In a recent case, one implicated donor had negative results on the examination of blood smears but had parasite DNA detectable by PCR. PCR, however, is relatively cumbersome, and data to date are insufficient to show that it is sensitive enough to detect the lowest parasite densities that can cause malaria.

Serologic tests, another option, could be applied either selectively (to high-risk donors) or universally. Since the presence of antibodies does not necessarily indicate the presence of parasitemia, serologic screening would result in the exclusion of some uninfect ed donors but overall would probably increase the amount of blood available, as was noted in several European countries where serologic testing was used to screen donors who had traveled to malarious areas.

Although transfusion-transmitted malaria is reported rarely, current exclusion practices in the United States result in the loss of many potential donors. Among the 535,211 donations excluded in 1998 by blood-collection centers affiliated with America’s Blood Centers (a national network of nonprofit, independent community blood centers that collect 47 percent of the U.S. blood supply), 15,338 (2.9 percent) were excluded because of the potential risk of malaria. If these proportions are extrapolated to the entire U.S. blood supply, an estimated 50,000 donations annually (of approximately 13 million donations) are excluded because the donor had a history of travel to a malarious area. An analysis of the cost and benefits of various screening procedures, which takes into account the strengths and limitations of screening tests, the rates of seropositivity for malaria in the donor population, and the proportion of blood donors with a history of travel to malarious areas, will be a useful step toward addressing this problem.

We are indebted to Dr. Phuc Nguyen-Dinh for technical advice and helpful suggestions; to Marianna Wilson, Katharine Grady, Dr. Norman Pietrzkiewicz, and Susan Slamenda for laboratory support at the CDC; to Kay Gregory at the American Association of Blood Banks for assistance in obtaining prior editions of the donor-exclusion guidelines; and to Drs. Mark Heintzelman, Jay Epstein, and Chang Sun at the FDA for their collaboration. 

REFERENCES

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