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販売名（企業名）	①アルブミンーベーリング②アルブミナー5% ③アルブミナー25%④フィブロガミン P⑤ベリブラスト P コンビセット⑥アルブミン-ベーリング 20%静注 10.0g/50mL⑦アルブミナー5%静注 12.5g/250mL⑧アルブミナー25%静注 12.5g/50mL⑨フィブロガミン P 静注用（CSL ベーリング株式会社）				

研究報告の概要

問題点（輸血によるバベシア感染による死亡報告）

FDA は血液収集や輸血の合併症疑いに関する情報を、供血者及び受血者の死亡報告、副作用報告システム（MedWatch を含む）、生物学的製剤逸脱報告システム（Biological Product Deviations Reporting System: BPDR）の安全性調査システムにより入手している。FDA は 1996 年 10 月 1 日から 2007 年 12 月 31 日に報告されたバベシア症の傾向を評価するため、これらのシステムを照会し、分析した。

FDA は 2005 年に 2 例、2006 年に 3 例、2007 年に 3 例の供血者及び受血者のバベシア症による死亡報告を受けていた。臨床経過は、無脾症患者、免疫不全患者や他の内科の慢性疾患患者に発症したダニ媒体バベシア感染症と一致していた。全員が B.microti に感染し、赤血球輸血を受けていた。受血者は輸血後 2.5-7 週で症状が進展し、輸血後 2 ヶ月以内に死亡した。

FDA は各死亡例が医学的な検討で輸血によるバベシア症であるとしている。

BPDR において、輸血関連のバベシア感染疑い例と供血後のバベシア症感染は 1999 年の 0 件から 2007 年の 25 件に増加していた。副作用報告システムでは 1997 年から輸血によるバベシア感染は報告されていなかった。

各死亡例を蛍光抗体法で測定すると B.microti 抗体価は 128 倍以上であった。これらデータにより輸血によるバベシア感染は増加していることが示唆された。バベシア種は血液銀行の製造工程である冷凍、白血球除去やろ過の工程で生存できるため、赤血球、脱グリセル赤血球や血小板の輸血により病原体が感染する。症状発現から死亡まで短期間（5-17 日）であることを考慮して、輸血後の最初の数週間に起きる原因不明の発熱を評価するため、特に無脾症患者や免疫不全患者では、末梢血塗抹標本の試験などでバベシア種を早期に検討すべきである。バベシア症はアメリカで届出義務はないが、輸血によるバベシア感染を当局に報告することにより感染供血者を特定し、残存している血液の使用を禁止することができる。

血液収集者は、潜在的に感染している使用期限内の血液成分を速やかに廃棄するため、直ちに供血後のバベシア症について輸血を実施する施設に報告すべきである。また血液事業者は、死亡報告及び BPDR を FDA に報告すべきである。

以上のことから、輸血によるバベシア感染は増加していることが示された。

報告企業の意見	今後の対応
バベシア症は赤血球等内にバベシア原虫が寄生するため発症するが、本剤は血漿を原材料にしているため感染はないと考えられる。	今後とも新しい感染症に関する情報収集に努める所存である。

使用上の注意記載状況・その他参考事項等

(19)

87

Babesia Infection through Blood Transfusions: Reports Received by the US Food and Drug Administration, 1997–2007

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Background. Human babesiosis is an illness with clinical manifestations that range from asymptomatic to fatal. Although babesiosis is not nationally notifiable, the US incidence appears to be increasing. *Babesia* infection is a transfusion-transmissable disease. An estimated 70 cases were reported during 1979–2007; most of these cases were reported during the past decade.

Methods. We queried the 3 following US Food and Drug Administration safety surveillance systems to assess trends in babesiosis reporting since 1997: fatality reports for blood donors and transfusion recipients, the Adverse Event Reporting System (which includes MedWatch), and the Biological Product Deviations Reporting system. We analyzed fatality reports for time frames, clinical presentations, and patient and donor demographic characteristics.

Results. Eight of 9 deaths due to transfusion-transmitted babesiosis that were reported since 1997 occurred within the past 3 years (2005–2007). Four implicated donors and 5 patients lived in areas where *Babesia* infection is not endemic. Increasing numbers of Biological Product Deviations Reports were submitted to the US Food and Drug Administration over the past decade; the Adverse Event Reporting System received no reports.

Conclusions. After nearly a decade with no reported death due to transfusion-transmitted babesiosis, the US Food and Drug Administration received 8 reports from November 2005 onward. The increased numbers of deaths reported and Biological Product Deviations Reports suggest an increasing incidence of transfusion-transmitted babesiosis. Physicians should consider babesiosis in the differential diagnosis in immunocompromised, febrile patients with a history of recent transfusion, even in areas where *Babesia* infection is not endemic. Accurate and timely reporting of babesiosis-related donor and transfusion events assists the US Food and Drug Administration in developing appropriate public health–control measures.

Human babesiosis is a protozoal zoonotic illness that is transmitted primarily by *Ixodes scapularis* ticks in North America. Of >100 *Babesia* species that infect vertebrate hosts, *Babesia microti*, *Babesia divergens*–like organisms, *Babesia duncani* (previously known as WA-1), CA-1, and MO-1 infect humans in the United States [1]. The majority of US babesiosis cases are attributed to *B. microti*, which is found mostly in the northeastern and upper midwestern states.

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Data in this article are based on information provided to the US Food and Drug Administration in required reports of potentially transfusion-related deaths.

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Clinical manifestations range from mild, self-limited flu-like symptoms to severe malaise, fatigue, fever, anorexia, arthralgia, myalgia, depression, vomiting, and anemia. Complications can include acute respiratory failure, congestive heart failure, and renal failure [2, 3]. Patients who are immunocompromised, asplenic, coinfected with other tick-transmitted infectious pathogens, and/or elderly are at risk of increased disease severity [1, 4, 5].

After acquiring *Babesia* parasites from a tick bite, infected individuals may develop symptoms within 1–4 weeks. Most cases are probably not reported, because many infections are asymptomatic; symptoms are mild, or a patient may be coinfected with *Borrelia burgdorferi* (with *Babesia* infection remaining undiagnosed) [6–8]. In addition to a probable lack of clinical awareness, especially in areas of nonendemicity, many states have

88

no reporting requirement [6, 9, 10], and babesiosis, unlike Lyme disease, is not nationally notifiable. Infected patients can harbor circulating parasites for months or years without symptoms; patients with chronic low-level parasitemia may unknowingly transmit the organisms through donating blood [7, 8]. There is no licensed test for *Babesia* screening of donated blood products.

The majority of an estimated 70 transfusion-transmitted *Babesia* infections since 1979 involved *B. microti*; most of these infections were reported in the past decade (D. Leiby, personal communication) [7]. The national standard blood donor questionnaire includes questions about prior babesiosis infection and general donor health [11]. Individuals with previously diagnosed babesiosis are indefinitely deferred (ineligible to donate blood). However, mild *Babesia* infections may remain unrecognized, and infected individuals may not recall recent tick bites [12].

The purpose of this article is to alert clinicians and the public health community of reported deaths related to transfusion-transmitted babesiosis; to describe the US Food and Drug Administration's (FDA's) surveillance systems for adverse events and product manufacturing deviations related to donor blood collection, distribution, and transfusion; and to encourage the reporting of suspected cases of transfusion-transmitted babesiosis.

METHODS

The FDA's surveillance systems. The FDA receives information about suspected complications of blood collection and transfusion via the 3 following systems: fatality reports for blood donors and transfusion recipients, the Adverse Event Reporting System (AERS; which includes the FDA MedWatch program), and the Biological Product Deviations Reporting (BPDR) system (table 1).

Blood establishments are required to notify the FDA "when a complication of blood collection or transfusion is confirmed to be fatal" [13, p. 58]. Center for Biologics Evaluation and Research medical officers review documentation from the reporting facility and reports from FDA investigators to assess the relationship, if any, to the blood donation or transfusion.

Biologics manufacturers are required to submit reports of adverse experiences to the AERS, the FDA's computerized database for postmarketing safety surveillance. The voluntary MedWatch program allows health care professionals and consumers to report adverse events to the AERS.

The FDA's BPDR system receives reports of "any event...associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product or blood or blood components... in which the safety, purity, or potency of a distributed product may be affected" [14].

Data query. We queried these systems for babesiosis-related blood donation or transfusion events reported from 1 October 1996 (FDA fiscal year 1997) through 31 December 2007 (first quarter of fiscal year 2008). We analyzed fatality reports for time frames, clinical presentations, and patient and donor demographic characteristics. Babesiosis-related reports to the BPDR system typically describe either possible transfusion-transmitted disease or postdonation illness, with potential implications for the safety of the donated blood units. We categorized cases reported to the BPDR system as postdonation illness and potential transfusion transmission–related events. To avoid distortion of BPDR trends, we excluded reports of infected donors identified prospectively through antibody assay research [7].

RESULTS

Reported deaths of blood donors and recipients. Before 2005, the FDA received the last fatality report of transfusion-transmitted babesiosis in 1998; there were 2 reports in 2005, 3 in 2006, and 3 in 2007. Clinical presentations (table 2) were consistent with natural tick-borne *Babesia* infection in asplenic, immunocompromised, or other patients with serious comorbid chronic disease [12]. All were infected with *B. microti* and had received RBCs; 1 death was attributable to a unit of frozen deglycerolized RBCs. Recipients developed symptoms in 2.5–7 weeks and died within 2 months after transfusion of the implicated blood units (table 3). FDA medical review verified that transfusion-transmitted babesiosis contributed to each death.

BPDR. Figure 1 summarizes 10 years of BPDRs for potential transfusion-transmitted *Babesia* infection and postdonation babesiosis. The numbers that were received range from 0 in fiscal year 1999 to 25 in fiscal year 2007.

AERS. Since 1997, the AERS has not received any report of transfusion-transmitted babesiosis.

Laboratory and blood establishment investigations. All fatal cases (in blood recipients) reported here were initially diagnosed with use of a thin peripheral blood smear. For each fatality, subsequent donor testing by immunofluorescence antibody assay revealed elevated *B. microti* antibody titers (≥1:128). All implicated donors were indefinitely deferred from donating blood.

DISCUSSION

Babesiosis has gained attention as an emerging zoonotic disease with an expanding known geographical range [6, 9, 15, 16]. Since November 2005, the FDA learned of 8 deaths involving transfusion-transmitted babesiosis and has received increasing reports of nonfatal cases and postdonation illness. Because of the likelihood of underreporting to the FDA's surveillance systems, these data suggest that the incidence of transfusion-transmitted babesiosis may be increasing.

Table 1. US Food and Drug Administration (FDA) surveillance systems for biologics.

Surveillance system	Regulatory authority	Products covered	Reporting entity	Additional information	Publicly accessible data
Fatalities	Required per 21 CFR 606.170(b)	Blood and blood-product collection and transfusion	Blood establishments	Guidance: "Notifying the FDA of Deaths Related to Blood Collection or Transfusion" (http://www.fda.gov/cber/gdlns/bldfatal.htm)	Annual summaries (http://www.fda.gov/cber/blood/fatal0506.htm)
AERS	Required per 21 CFR 600.80	Drugs and therapeutic biologics	Manufacturer	http://www.fda.gov/cder/aers/default.htm	Quarterly data files (http://www.fda.gov/cder/aers/extract.htm)
MedWatch	Voluntary	Blood, blood products, biologics, and drugs	Health care professionals and consumers	http://www.fda.gov/medwatch/report/hcp.htm	Quarterly data in AERS files (http://www.fda.gov/cder/aers/extract.htm)
BPDR	Required per 21 CFR 600.14 and 21 CFR 606.171	Blood and blood products	Blood establishments	http://www.fda.gov/cber/fhiodev/biodev.htm	Annual summaries (http://www.fda.gov/cber/biodev/reports.htm)

NOTE. AERS, Adverse Reporting System; BPDR, Biological Product Deviations Reports; CFR, Code of Federal Regulations.

Table 2. Summary of deaths attributed to transfusion-transmitted *Babesia* infection that were reported to the US Food and Drug Administration.

Patient	Age, years	Sex	State of residence	Medical history	Presenting complaint	Clinical course	Donor information
1	81	Female	Maryland	Hypercholesterolemia, hypertension, severe nosebleeds requiring transfusion but otherwise in good health	Severe fatigue and lethargy	CBC showing a hemocrit of 21%, a platelet level of 21,000 platelets/mL, BUN level of 80 mg/dL, and a creatinine level of 2.5 mg/dL, indicating renal failure; examination for anemia and fatigue identified *Babesia* species on PB smear (positive PCR result); treated with quinine and clindamycin; developed signs of adult respiratory distress syndrome; experienced thrombotic cerebrovascular accident on day 5 of treatment with high fever	Resident of Maryland; traveled to New York (Long Island); positive PB smear result; *B. microti* IFA titer of 1:512
2	88	Male	Rhode Island	Chronic myelomonocytic leukemia with chronic anemia (transfusion dependent) and GI bleed	4-Day history of progressive weakness, fatigue, and anorexia with low-grade fever	*Babesia* species identified by PB smear; treated with atovaquone and azithromycin; died on hospital day 12 with persistent parasitemia, progressive renal failure, anemia, and altered mental status	Resident of Rhode Island; *B. microti* IFA titer of 1:1024
3	57	Male	Texas	Recent history of melena and previous hepatitis B and C virus infection, cirrhosis, coronary artery disease, congestive heart failure, receipt of coronary artery bypass grafts, and GI bleed requiring transfusion	10–12-Day history of fever, night sweats, chills, and other complaints of melena, weakness, dizziness, anorexia, and increasing ascites	*Babesia* species identified by PB smear; treated; developed altered mental status, respiratory distress and GI bleed	Resident of Texas; history of travel to Massachusetts; *B. microti* IFA titer of 1:256
4	76	Male	Minnesota	Transfusion-dependent acute myelocytic leukemia, rheumatoid arthritis, steroid-induced immunosuppression, and history of splenectomy, coronary artery disease, idiopathic thrombocytopenia, and multiple other medical problems	Several-day history of fever, cough, weakness, and dyspnea	Sepsis examination and broad-spectrum antibiotics started at hospital admission, with *Babesia* infection diagnosed (by PB smear) and treated on hospital day 2; death due to multiple medical problems	Resident of Minnesota; *B. microti* IFA titer of 1:256; negative PCR result
5	71	Female	Connecticut	Chronic liver disease (portal hypertension with gastroesophageal varices and hepatorenal syndrome), chronic transfusion-dependent anemia and diabetes, splenectomy, and cholecystectomy	Low-grade fever, complaints of chills and weakness for several days, with hemocrit decreasing from 29% to 23% at routine outpatient CBC monitoring	*Babesia* species identified by PB smear; treated; developed acute tubular necrosis, altered mental status, and progressive hypotension	Resident of Connecticut; *B. microti* IFA titer of 1:256; positive Western Blot result; negative PCR result
6	82	Female	Ohio	Receipt of coronary artery bypass grafts and aortic valve replacement with transfusion, atrial fibrillation, cerebrovascular accident, and hyperlipidemia	Several-day history of fever and chills, with anemia and thrombocytopenia diagnosed at hospital admission	*Babesia* species identified by PB smear; treated with clindamycin and quinine *plus* automated RBC exchange by apheresis, which reduced parasitemia from 26% to 5%; developed altered mental status; the patient died of multiple-organ failure, *Staphylococcus aureus* pneumonia, and acute myocardial infarction	Resident of Ohio; traveled to Connecticut 2 months before donating blood; *B. microti* IFA titer of 1:256
7	74	Female	New Jersey	Insulin-dependent diabetes, end-stage renal disease (receiving dialysis), coronary artery disease (receipt of coronary artery bypass graft), GI bleeding, and polyp removal with transfusion	Nausea, cough, vomiting, weakness, and fever	Low platelet count on CBC with 8% *Babesia* species found by manual PB smear; confirmed by PCR as *B. microti*; atovaquone, clindamycin, and quinine failed to prevent respiratory failure, hypotension, cardiac complications, and progressive shock	Resident of New Jersey; *B. microti* IFA titer of 1:128
8	61	Female	Indiana	End-stage renal disease (receipt of hemodialysis), congestive heart failure, GI bleed requiring transfusion at previous hospital admission	Nausea with fever while receiving hemodialysis	Initially treated for bacterial sepsis (vancomycin and ceftazidime), then parasitemia was treated with exchange transfusion; originally received a misdiagnosis of malaria; treated with clindamycin and quinidine; developed altered mental status and disseminated intravascular coagulation and died; positive PCR results and an IgG titer of 1:2048 for *B. microti*	Resident of Indiana; traveled to wooded areas of Wisconsin 2 months before donating blood; no known tick bite; IgG titer of >1:256 and IgM titer of 1:20 for *B. microti*; negative PCR result after donation
9	43	Female	Delaware	Congenital hypoplastic anemia (Diamond-Blackfan syndrome), splenectomy, hepatitis C virus infection, pulmonary hypertension, iron overload, and multiple transfusions	Fatigue, "shakes" for 4 days without fever, decreased appetite and loose bowel movements for 1 week, chronic dry cough with infiltrates on chest radiograph	Treated for pneumonia with levaquin, vancomycin, and oseltamivir; previous PB smear reexamined as positive for *Babesia* species treated with clindamycin and quinine and transferred to ICU because of respiratory distress	Resident of New Jersey; traveled to Rhode Island but no known tick bite; *B. microti*; IFA titer of 1:1024; negative PCR result; donated RBC unit was frozen and deglycerolized before transfusion

NOTE. The information in this table was reported through a passive surveillance system; we report here the information provided. BUN, blood urea nitrogen; CBC, complete blood count; GI, gastrointestinal; ICU, intensive care unit; IFA, indirect immunofluorescence antibody assay; PB, peripheral blood.

Table 3. Timing of clinical events in fatal cases involving transfusion-transmitted *Babesia* infection reported to the US Food and Drug Administration.

Timing	Patient								
	1	2	3	4	5	6	7	8	9
Date of implicated blood unit transfusion	9 April 1998	16 November 2005	6 December 2005	24 August 2006	20 September 2006	6 September 2006	17 September 2007	20 September 2007	26 November 2007
Latency period,[a] days	35	38	50	30	18	30	29	43	41
Time to diagnosis,[b] days	43	42	50	34	19	36	31	57[c]	45
Time to death, days	49	55	57	42	26	41	34	50	47

[a] Periods from the date of implicated transfusion to the onset of symptoms are approximate (based on available estimated dates of symptom onset).
[b] Posttransfusion diagnosis of *Babesia* infection.
[c] The patient died prior to diagnosis of *Babesia* infection.

Babesia infection should be considered among potential etiologies for otherwise unexplained fever in patients who have recently received blood products. Because of the mobility of donors and transportation of blood products, babesiosis should be considered even beyond geographical regions with naturally occurring disease. As noted in table 2, several donors did not live in areas of endemicity but had traveled to these regions before donating blood.

Patients presented with symptoms (table 2) that were typical of natural infections. Most developed altered mental status, renal failure, or respiratory distress. The interval from blood transfusion to symptom onset was 2.5–7 weeks (table 3). An earlier article reported a 1–9-week time frame for transfusion-transmitted babesiosis [17]. These ranges of latency periods contrast with the natural infection incubation time of 2–4 weeks.

With 1 exception, all patients received transfusions from August through December, consistent with the seasonality of *Babesia* infection. Chronic parasitemia in the donor may have accounted for the 1 case involving a blood transfusion in April.

Implicated donations were identified in all cases; the donors tested positive by peripheral blood smear or immunofluorescence antibody assay. Four donors' samples also tested by PCR had negative results. They may have been convalescent and no longer parasitemic or were PCR negative because of the small sampling volume. All donors were asymptomatic at donation and remembered no tick bite.

Because many babesiosis cases may escape recognition, questioning donors has limited preventive value [17]. *Babesia* species can survive blood banking procedures, including refrigeration, leukoreduction, and filtration; pathogen transmission through transfusion of RBCs, deglycerolized RBCs, or platelets can occur [1, 18–21]. *Babesia* parasites can survive in frozen RBCs, because the glycerol treatment prevents lysis.

In view of the short periods between symptom onset and death (5–17 days) (table 3), examination of a peripheral blood smear (or other testing, depending on availability and the level of clinical suspicion) for possible *Babesia* species should be considered early in the evaluation of unexplained fever during the first few weeks after transfusions, particularly in aspleni or otherwise immunocompromised patients. Infectious disease consultation may be required to microscopically distinguish *Babesia* species from *Plasmodium* organisms.

Although babesiosis is not nationally notifiable, reporting transfusion-transmitted *Babesia* infections to public health authorities can allow investigators to identify infected donors and interdict remaining units. Investigation of prior donations also allows testing of associated recipients.

Similarly, blood collectors should immediately report postdonation babesiosis to the transfusion facilities to expedite

Figure 1. Summary of babesiosis-related Biological Product Deviation Reports (BPDRs) received by the US Food and Drug Administration (FDA) during fiscal years 1997–2007 (the FDA fiscal year is from 1 October through 31 September). These data do not include reports of infected donors identified prospectively through antibody assay research trials. BPDRs may include >1 recipient unit or donation. Potential implication in transfusion-transmitted disease refers to reports that indicate the safety of a blood component unit that may have been affected (e.g., instances when a blood transfusion recipient received a diagnosis of babesiosis, but the donor could not be contacted for confirmation). Postdonation illness refers to illness in donors who notified the blood collection establishment after donation that they had received a diagnosis of babesiosis. Whether these donors were infected at the time of donation was unknown; all units (not yet transfused) from these donors were withdrawn, and the donors were indefinitely deferred.

prompt withdrawal of potentially infected unexpired blood components. We remind blood establishments of the requirement to submit fatality and BPDRs to the FDA.

Our data cannot distinguish whether the increase in the numbers of deaths and reports to the BPDR system reflect an increasing incidence of babesiosis and/or improved diagnosis and reporting. State Health Departments (e.g., in New York and Connecticut) have also seen an increase in the number of babesiosis case reports over the past 10 years [22–25].

Each year, >5 million recipients receive >14 million transfusions of whole blood or RBCs [26]. Transfusion-transmitted babesiosis appears to be rare, but increased clinician awareness of the possibility of babesiosis in febrile transfusion recipients may facilitate earlier diagnosis and more successful treatment. It will also trigger timely public health investigations to interdict extant infected units and alert other associated recipients, protecting others from this potentially fatal blood-borne pathogen.

Addendum. During final revisions of this article in late September 2008, the FDA received a report of another death associated with transfusion-transmitted babesiosis. An elderly woman in Minnesota died ~3 weeks after receipt of 2 units of RBCs. One of the donated units' retention segments was positive for *Babesia* species by serologic testing and PCR.

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Potential conflicts of interest. All authors: no conflicts.

References

1. Horner MJ, Aguilar-Delfin I, Telford SR III, Krause PJ, Persing DH. Babesiosis. Clin Microbiol Rev 2000; 13:451–69.
2. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis 2006; 43:1089–134.
3. Hatcher JC, Greenberg PD, Antique J, Jimenez-Lucho VE. Severe babesiosis in Long Island: review of 34 cases and their complications. Clin Infect Dis 2001; 32:1117–25.
4. Hunfeld K-P, Hildebrandt A, Gray JS. Babesiosis: recent insights into an ancient disease. Int J Parasitol 2008; 38:1219–37.
5. Thompson C, Spielman A, Krause PJ. Coinfecting deer-associated zoonoses: Lyme disease, babesiosis, and ehrlichiosis. Clin Infect Dis 2001; 33:676–85.
6. Cable RG, Leiby DA. Risk and prevention of transfusion-transmitted babesiosis and other tick-borne diseases. Curr Opin Hematol 2003; 10:405–11.
7. Leiby DA, Chung APS, Gill JE, et al. Demonstrable parasitemia among Connecticut blood donors with anubodies to *Babesia microti*. Transfusion 2005; 45:1804–10.
8. Krause PJ, Spielman A, Telford SR III, et al. Persistent parasitemia after acute babesiosis. N Engl J Med 1998; 339:160–5.
9. Krause PJ, McKay K, Gadbaw J, et al. Increasing health burden of human babesiosis in endemic sites. Am J Trop Med Hyg 2003; 68:431–6.
10. Kjemtrup AM, Conrad PA. Human babesiosis: an emerging tick-borne disease. Int J Parasitol 2000; 30:1323–37.
11. American Association of Blood Banks. Blood donor history questionnaire. Available at: http://www.aabb.org/Content/Donate_Blood/Donor_History_Questionnaires/AABB_Blood_Donor_History_Questionnaire/. Accessed 11 April 2008.
12. White DJ, Talarico J, Chang H-G, et al. Human babesiosis in New York State—review of 139 hospitalized cases and analysis of prognostic factors. Arch Intern Med 1998; 158:2149–54.
13. US Food and Drug Administration, Department of Health and Human Services. Current good manufacturing practice for blood and blood components. Code of Federal Regulations Title 21, part 606.170(b). 2008:58.
14. US Food and Drug Administration. Biologic Product Deviation Reporting. Available at: http://www.fda.gov/cber/biodev/biodev.htm. Accessed 13 November 2008.
15. Krause PJ. Babesiosis diagnosis and treatment. Vector Borne Zoonotic Dis 2003; 3:45–51.
16. Rodgers SE, Mather TN. Human *Babesia microti* incidence and *Ixodes scapularis* distribution, Rhode Island, 1998–2004. Emerg Infect Dis 2007. Available at: http://www.cdc.gov/EID/content/13/4/633.htm. Accessed 6 June 2008.
17. Leiby DA, Gill JE. Transfusion-transmitted tick-borne infections: a cornucopia of threats. Transfus Med Rev 2004; 18:295–306.
18. Leiby DA. Babesiosis and blood transfusion: flying under the radar. Vox Sang 2006; 90:157–65.
19. McQuiston JH, Childs JE, Chamberland ME, Tabor E. Transmission of tick-borne agents of disease by blood transfusion: a review of known and potential risks in the United States. Transfusion 2000; 40:274–84.
20. Eberhard ML, Walker EM, Steurer FJ. Survival of infectivity of *Babesia* in blood maintained at 25 C and 2–4 C. J Parasitol 1995; 81:790–2.
21. Gerber MA, Shapiro ED, Krause PJ, Cable RG, Badon SJ, Ryan RW. The risk of acquiring Lyme disease or babesiosis from a blood transfusion. J Infect Dis 1994; 170:231–4.
22. New York State Department of Health. Communicable disease annual reports and related information. Available at: http://www.health.state.ny.us/statistics/diseases/communicable/. Accessed 9 April 2008.
23. Connecticut Department of Public Health. Reported cases of disease: 1990–1999. Available at: http://www.ct.gov/dph/lib/dph/CT_Disease_Cases_90_99_FNL.pdf. Accessed 9 April 2008.
24. Connecticut Department of Public Health. Reported cases of disease: 2000–2005. Available at: http://www.ct.gov/dph/lib/dph/CT_Disease_Cases_00_05_FNL.pdf. Accessed 9 April 2008.
25. Connecticut Department of Public Health. Reported cases of disease by county: 2006. http://www.ct.gov/dph/lib/dph/CT_Disease_Cases_by_County_2006_FNL.pdf. Accessed 9 April 2008.
26. Whitaker BI, Sullivan M. The 2005 Nationwide Blood Collection and Utilization Survey Report. U.S. Department of Health and Human Services. 2005. Available at: http://www.hhs.gov/ophs/bloodsafety/index.html. Accessed 27 December 2007.

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No. 10

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2008. 11. 20	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	Seed C, Kee G, Ismay S, Wong T, Keller A.. AABB Annual Meeting and TXPO 2008; 2008 Oct 4–7; Montreal.	公表国 オーストラリア	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)					

研究報告の概要

○マラリア抗体検査-輸血伝播マラリア(TTM)のリスクを最小に抑える安全かつ有効な戦略

背景:マラリアのスクリーニングに関して、オーストラリア赤十字(ARCBS)は2005年7月から、従来の医療歴、渡航歴の収集から、リスクのある供血者に対し、リスクへの暴露を特定したときから最低4ヶ月間のマラリア抗体の検査を実施する代替戦略を導入した。

方法:マラリアに罹患後回復した、あるいは過去3年間にマラリア流行国へ渡航・居住した供血者の血液を、市販のマラリア抗体EIAを用いて検査した。陰性血液は輸血用として供給され、供血者は再度供血可能とされた。EIA反復陽性(RR)の血液は追加検査(リアルタイムプラスモジウムPCR及び 免疫抗原クロマトグラフィー)に供された。追加検査陰性の供血者は現在の感染を示す証拠がない「抗体陽性」と見なされた。追加検査で陽性となった供血者は感染の可能性があると見なされ、直ちに臨床診断に紹介された。

結果:2005年7月～2008年2月に合計122,713の供血血液のEIA検査が実施され、そのうち117,900(96.1%)は陰性であり、ARCBSは159,287本のRBCおよび17,815本の血小板を供給した。EIA RR 4,813(3.9%)のうち1例で、PCRによる低レベルのプラスモジウムDNA が検出された(初回検体31、追加検体50copies/mL)が、抗原は陰性であった。この供血者はリベリア移民で幼少時にマラリアの既往歴があったが、追跡調査時には症状はなかった。

結論:この検査戦略の開始以降、既存の供血者に由来する輸血可能製剤の製造効率は著しく向上し、TTM症例の報告もなかった。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
オーストラリア赤十字(ARCBS)は2005年7月から、マラリア感染のリスクがある供血者に対し、リスクへの暴露を特定したときから最低4ヶ月間のマラリア抗体のスクリーニングを実施する代替戦略を導入した結果、既存の供血者に由来する輸血可能な製剤の製造効率が著しく向上し、輸血伝播マラリア症例の報告もないとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、マラリア流行地への旅行者または居住経験者の献血を一定期間延期している(1～3年の延期を行うとともに、帰国(入国)後マラリアを思わせる症状があった場合は、感染が否定されるまでの間についても献血を見合わせる)。今後も引き続き、マラリア感染に関する新たな知見及び情報の収集、対応に努める。

these findings, and showed both haplotypes have altered h^a and h^b antigen expression, and the associated c and e antigens are altered to the extent that alloanti-c and alloanti-e were produced. We also describe a homozygous proband with an alloantibody to the high-prevalence antigen that is antithetical to JAL. **Methods:** Samples from 15 JAL+ persons (11 probands and 4 family members including two Caucasian, six African American Blacks, one Puerto Rican Black, and six Brazilian Blacks) were tested. Hemagglutination studies were performed by standard methods using reagents from multiple sources. **Results:** The JAL+ status of the RBCs was determined with three anti-JAL (J Pas., Allen, MacD). RBCs from both Caucasian JAL+ probands had the (C)(e) haplotype and altered C, e, h^a, and h^b antigens. RBCs from Black JAL+ persons had the (c)(e) haplotype and expressed altered c, e, f, V, h^a, VS, and h^b antigens. Of six anti-C reagents, all agglutinated the two Caucasian samples moderately. Of nine anti-c reagents tested with RBCs from the non-Caucasian probands, reactivity ranged from strong to negative, notably, clone MS42 reacted strongly, MS33 and BS240 reacted moderately, and Gamma clone 951 was non-reactive. Of 12 anti-e reagents, reactivity ranged from strong to negative; notably, clone MS62 and MS63 reacted moderately, MS69 and HIRO36, 41, and 43 reacted weakly to moderately, and MS16 (depending on the formulation) was weakly reactive or non-reactive. All RBC samples were tested with at least two examples of anti-V, -h^a, -VS, and -h^b; some gave weak reactions while others did not react. Plasma from one proband contained alloanti-c, from another contained alloanti-e, and from a third contained an alloantibody that failed to react with D- - and Rh_{mod} RBCs. This apparent anti-Rh17 recognizes the high-prevalence antigen antithetical to JAL that we have named CES7. **Conclusions:** The presence of the JAL antigen has a quantitative and qualitative effect on the expression of, in Caucasians C, e, h^a, and h^b antigens, and in people of Black African ancestry c, e, f, V, h^a, VS, and h^b antigens. The qualitative effect on two antigens is revealed by two patients who received blood transfusions and made alloanti-c or alloanti-e. This is the first description of an antibody to the high-prevalence antigen antithetical to JAL.

Disclosure of Conflict of Interest
Christine Lomas-Francis, Connie Westhoff, Denden Alcantara, Pamela Nickle, Joan Uehlinger: Nothing to Disclose
Marion E. Reid: Not Specified

S36-020D
The JAL Antigen (RH46) is Encoded by an ARG114TRP Mutation
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Background: Two JAL-positive (Rh46+) haplotypes have been described. One, found in Caucasians, has altered C and e antigens ((C)(e)), and the other, found in people of African Black ancestry, has altered c and e antigens ((c)(e)) (Lomas, et al., Vox Sang 1990;59:39). The purpose of this study was to determine the molecular basis associated with expression of the JAL antigen. **Methods:** Samples from fifteen JAL+ probands; two Caucasian, six African American Blacks, six Brazilian Blacks, and one Puerto Rican were included in the study. Hemagglutination studies were performed by standard methods. DNA, extracted from peripheral blood leukocytes, was amplified by PCR and analyzed by sequencing. Reticulocyte RNA isolation and Rh-cDNA analysis was performed by standard molecular methods. **Results:** Samples from Caucasian JAL+ probands had RHCE*Ce, and those from Black JAL+ probands had RHCE*ce, but all had a 340C > T (Arg114Trp) missense mutation in exon 3 of RHCE regardless of the Ce or ce background allele. The JAL-encoding RHCE*ce allele also had 733C > G (Leu245Val) and red cells from informative heterozygotes and homozygotes did not express f, hr^a, or h^a antigens, and had dramatically weakened V and VS antigens. Expression of c antigen was also altered, as the RBCs were non-reactive with one of three monoclonal anti-c tested. In kind, expression of C on the Ce allele was altered, as was the e antigen expressed from both the ce or Ce allele that encoded JAL. **Conclusions:** Expression of the JAL (RH46) antigen results from 340C > T (Arg114Trp) on either a Ce or ce background. Although the Ce allele encoding the JAL antigen has been reported as CeMA by Nolzat-Pirenne et al., (Transfusion 2002;42:627) and the ce allele as ceS(340) by the same authors (Blood 2002; 100:4223), these alleles have not previously been recognized as encoding the JAL antigen. Those samples were studied because of altered expression of C or e antigen, respectively. We show here for the first time that, in addition to altered expression of C or c and e, the 114Trp mutation encodes the low-prevalence Rh antigen, JAL.

Disclosure of Conflict of Interest
Connie Westhoff, Sunitha Vege, Christine Lomas-Francis, Kim Hue-Roye, Lilian Castilho, Marion E. Reid: Nothing to Disclose

Transfusion Transmitted Diseases: Malaria and Chagas Disease

S37-020E
Malaria Antibody Testing—A Safe and Efficient Strategy to Minimize the Risk of Transfusion Transmitted Malaria (TTM)
C Seed, (akeiler@arcbs.redcross.org.au), G Kiel, S Ismay, T Wong, A Keiler, Australian Red Cross Blood Service, Perth, Australia; Sydney, Australia.

Background: Until recently, owing to the lack of a suitable test, screening for malaria in Australian blood donors involved collecting a medical and travel history and excluding the 'cellular' blood components from donors with a potential malaria exposure. This strategy minimised the residual risk of TTM to less than 1 in 10 million but resulted in the unavailability for transfusion of approximately 35,000 red blood cells (RBC) per annum. In July 2005 the Australian Red Cross Blood Service (ARCBS) implemented an alternative strategy based on screening donors with potential malaria exposure for malaria antibodies a minimum of 4 months after their last identified risk exposure. **Methods:** Since July 2005, donations from donors identified as having had malaria and recovered, or having travelled to or resided in a malarial country within the last 3 years are eligible for testing. RBC from these donors were collected, quarantined and samples tested using a commercial malaria antibody EIA. Non reactive (NR) donations were then issued for transfusion and the associated donors re-instated for cellular component manufacture. EIA repeatedly reactive (RR) donations were not issued and subject to supplementary testing (real-time plasmodial PCR and antigen immuno-chromatographic test). Concordantly supplemental test negative donors were considered 'antibody positive' without evidence of current infection. Donors reactive on either or both supplemental tests were considered potentially infected and referred immediately for clinical assessment. **Results:** A total of 122,713 donations were tested by EIA between July 2005 and February 2008, of which 117,900 (96.1%) were NR and the remaining 4,813 (3.9%) repeat reactive (RR). From donors re-instated by a NR EIA, ARCBS issued for transfusion an additional 159,287 RBC and 17,815 platelets representing the combined return from their tested donation, and subsequent donations made during the period of their original restriction. Of the 4,813 EIA RR samples, one had low level but reproducibly detectable plasmodial DNA by PCR (index sample 31 and follow-up sample 50 copies/uL) but was antigen negative. The donor, a migrant from Liberia had a history of malaria during childhood but was asymptomatic at follow up. **Conclusions:** The testing strategy has delivered in excess of 50,000 additional RBC and 5,000 additional platelets annually since inception. This has markedly improved manufacturing efficiency by increasing the proportion of transfusible components from existing donors. The lack of a reported TTM case since implementing the new strategy suggests that this dividend has been achieved without measurably impacting recipient safety.

Disclosure of Conflict of Interest
Clive Seed, Glenda Kee, Susan Ismay, Timothy Wong, Anthony Keiler: Nothing to Disclose

S38-020E
Malaria Deferrals: Time to Lessen the Impact of Travel Deferrals
M Nguyen, (gibble@usa.redcross.org), D Leiby, T Goff, J Gibble, American Red Cross, Rockville, MD; American Red Cross, Baltimore, MD; American Red Cross, Blood Services, Baltimore, MD.

Background: Human malaria, caused by five species of the intraerythrocytic protozoan parasite Plasmodium, remains a blood safety concern. However, blood banks are adversely impacted by ongoing donor loss due to an increasing number of malaria deferrals. Among the 1% of donors lost because of malaria deferrals, the majority (91%) were associated with travel to malaria endemic areas. In contrast, the only 2 transfusion-transmitted malaria cases reported in the US since 1998 were attributed to donors with past residence in an endemic region. This study investigated the relationship

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
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一般的名称	新鮮凍結人血漿		研究報告の公表状況	Am J Trop Med Hyg. 2009 Feb;80(2):215-7. Lee KS, Kim TH, Kim ES, Lim HS, Yeom JS, Jun G, Park JW.	公表国 韓国	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)					

研究報告の概要

○韓国におけるクロロキン耐性三日熱マラリア
韓国において、三日熱マラリア(*Plasmodium vivax* malaria)が再興した1993年以降の患者は約100万人と推定される。この状況に対処するため、1997年より韓国軍はヒドロキシクロロキンおよびプリマキンを用いた予防的化学療法を実施している。予防的化学療法を受けた韓国軍兵士の累積者数は、2007年までに140万人を超えた。広範な予防化学療法を実施することで、韓国軍におけるマラリア患者の急増を防ぐことができたが、クロロキン(CQ)耐性*P. vivax*株発現の可能性が高まった。
本調査では、2003～2007年の期間に、韓国の*P. vivax*マラリア患者の治療効果のモニタリングを行い、調査登録患者484名中2名にCQ耐性を確認した。本結果は、アジア温帯地域におけるCQ耐性*P. vivax*の初めての報告である。韓国における*P. vivax*のCQ耐性発現頻度の変動をモニターするには、継続的調査が必要である。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
1997年より韓国軍はヒドロキシクロロキンおよびプリマキンを用いた予防的化学療法を実施し、マラリア患者の急増を防ぐことができたが、調査登録患者484名中2名にクロロキン(CQ)耐性*Plasmodium vivax*を確認したとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、マラリア流行地への旅行者または居住経験者の献血を一定期間延期している(1～3年の延期を行うとともに、帰国(入国)後マラリアを思わせる症状があった場合は、感染が否定されるまでの間についても献血を見合わせる)。今後も引き続き、マラリア感染に関する新たな知見及び情報の収集、対応に努める。

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Short Report: Chloroquine-resistant *Plasmodium vivax* in the Republic of Korea

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Abstract. The number of *Plasmodium vivax* malaria patients in the Republic of Korea and North Korea since the re-emergence of malaria in 1993 is estimated to be approximately one million. To cope with this situation, the Army of the Republic of Korea has performed chemoprophylaxis with hydroxychloroquine and primaquine since 1997. The cumulative number of soldiers in the Army of the Republic of Korea given chemoprophylaxis exceeded 1.4 million by 2007. Extensive chemoprophylaxis contributed to preventing a rapid increase of malaria patients in the Army of the Republic of Korea, but increased the possibility of the occurrence of chloroquine (CQ)–resistant *P. vivax* strains. In this study, treatment responses of *P. vivax* malaria patients in the Republic of Korea monitored during 2003–2007, and CQ resistance was confirmed in 2 of 484 enrolled patients. Our results are the first report of CQ-resistant *P. vivax* in a temperate region of Asia. Continuous surveillance is warranted to monitor the change in CQ resistance frequency of *P. vivax* in the Republic of Korea.

Plasmodium vivax malaria, which was endemic on the Korean Peninsula for many centuries until the late 1970s, re-emerged in 1993 in the Republic of Korea.[1] The malaria-prevalent area has been confined to the area adjacent to the Demilitarized Zone (DMZ) from the early stage of the re-emergence, and malaria occurrence in the Republic of Korea has been directly influenced by the prevalence of malaria in the region of North Korea located near the DMZ.[1–3] The total number of malaria patients in the Republic of Korea and North Korea since the re-emergence likely approaches one million.[1–4] To cope with the situation, the Army of the Republic of Korea has performed chemoprophylaxis with hydroxychloroquine (HCQ) and presumptive anti-relapse therapy with primaquine since 1997.[5] The cumulative number of the soldiers in the Army of the Republic of Korea given chemoprophylaxis exceeded 1.4 million by 2007. This extensive chemoprophylaxis campaign has helped prevent a rapid increase of malaria patients in the Army of the Republic of Korea. However, this success is tempered by the increased possibility of chloroquine (CQ)-resistant *P. vivax* strains.[5]

In this study, 484 patients from 6 hospitals in the Republic of Korea (5 in the malaria-prevalent region and 1 in Seoul) were enrolled during 2003–2007. Blood samples were collected from all patients before HCQ treatment and 24 hours after completion of treatment. Treatment responses were monitored by investigation of fever clearance time and parasite clearance time. Plasma concentrations of HCQ before and 24 hours after completion of treatment were measured by validated reversed-phase high-performance liquid chromatography[6] with slight modifications.[7] Additional examinations or blood collection were not performed. The study protocols were reviewed and approved by the institutional review board of each hospital. All patients enrolled in this study were admitted to the hospitals during HCQ treatment, and HCQ was taken under the physician supervision. There were no problems with HCQ treatment compliance.

Among 484 patients enrolled in the five-year study, HCQ treatment failed in two patients (Table 1). These two patients had not been in malaria-prevalent areas in other nations during the two years prior to their present hospitalization.

Patient A was a 26-year-old man (civilian) who had been discharged from the military in May 1998. Chemoprophylaxis was not performed during his military service. He was admitted to hospital I located in Goyang, a malaria-prevalent area in Kyonggi Province, on July 30, 2003. *Plasmodium vivax* malaria was confirmed and he was administered 2,000 mg of HCQ over a three-day period. More specifically, on day 0, he was given 800 mg of HCQ, with doses of 400 mg administered 6 hours and 24 hours later (day 1), and 48 hours later (day 2). Despite administration of the first cycle of HCQ treatment, fever did not subside until day 6 and *P. vivax* trophozoites were evident in a peripheral blood smear obtained on day 6. Parasite density on day 0 (before the treatment) and day 3 (24 h after completion of HCQ treatment) were 3,500/μL and 300/μL, respectively. Gene amplification by species-specific primers for small subunit ribosomal RNA[8] showed that *Plasmodia* in the patient's peripheral blood was *P. vivax*. The plasma concentration of HCQ 24 hours after the completion of HCQ treatment was 165 ng/mL. The patient was completely cured by administration of an additional cycle of HCQ treatment commencing on day 6.

Patient B was a 72-year-old woman. She was admitted to hospital II located in Seoul on July 24, 2007 (day 0), because of fever and chills. *Plasmodium vivax* malaria was diagnosed and HCQ was administered on July 25–27 (days 1–3). Treatment was unsuccessful in resolving the fever and severe headache, and parasites were evident both microscopically and by small subunit ribosomal RNA amplification until day 4. Parasite density on days 0 and 4 was 3,800/μL and 440/μL, respectively. The plasma concentration of HCQ 24 hours after the completion of HCQ treatment was 150 ng/mL. Salvage treatment with quinine sulfate and doxycycline was carried out for seven days beginning on day 4, followed by administration of primaquine. This regimen completely resolved the infection.

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TABLE 1
Demographic and clinical characteristics of two patients unsuccessfully treated with the conventional HCQ regimen, Republic of Korea*

Patient	Hospital (location)	Period of HCQ administration	Plasma concentration of HCQ† (ng/mL)	Parasite density before/after HCQ treatment (parasites/μL)	Regimen for complete cure
A	I (Goyang)	July 30–August 1, 2003	165	3,500/300	Additional administration of HCQ
B	II (Seoul)	July 25–27, 2007	150	3,800/440	Quinine sulfate and doxycycline

* HCQ = hydroxychloroquine.
† Measured 24 hours after completion of HCQ treatment.

Chloroquine-resistant *P. vivax* strains have been reported from various areas[9–12] since its emergence in Papua New Guinea in 1989.[13] In the Republic of Korea, a large-scale chemoprophylaxis campaign has been performed since 1997. However, prophylaxis has consistently failed in many cases despite attainment of sufficiently high plasma concentrations of HCQ. Moreover, the length of time required for the elimination of *P. vivax* from patients' blood by HCQ treatment has increased in the current decade.[14]

Hydroxychloroquine has been reported to be as active as CQ against malaria parasites,[15,16] and 400 mg of HCQ is the molar equivalent of 309.6 mg of HCQ base and 295.0 mg of CQ base. Therefore, a CQ concentration of 10 ng/mL in plasma, which is the minimum effective concentration against CQ-susceptible *P. vivax*, is equivalent to an HCQ concentration of 10.5 ng/mL of plasma. In this study, treatment with 2,000 mg of HCQ over a three-day period was not effective in 2 (0.4%) of 484 patients. For these two patients, plasma concentrations of HCQ 24 hours after completion of HCQ treatments were much higher than the minimum effective concentration of CQ against *P. vivax*.[17] For the 482 patients with successful therapeutic outcomes, the mean and the standard deviation of plasma concentrations of HCQ 24 hours after completion of HCQ treatments were 220 ng/mL and 121 ng/mL, respectively, which were in not distinct from the two patients in whom HCQ treatment failed. This indicates that HCQ was absorbed and metabolized normally in the two patients, precluding the possibility that the treatment failure was caused by personal factors. In the two patients, parasitemias were reduced markedly, but not cleared, by HCQ administration. Patient A was cured by additional administration of HCQ; this success may have been the result of the infecting *P. vivax* being exposed to an increased trough concentration of HCQ for an extended period because of the cumulative dosage.

The present observations are the first report of CQ-resistant *P. vivax* from a temperate region of Asia. Surveillance activity should be strengthened to monitor the change of CQ susceptibility of *P. vivax* in the Republic of Korea.

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REFERENCES

1. Park JW, Klein TA, Lee HC, Pacha LA, Ryu SH, Yeom JS, Moon SH, Kim TS, Chai JY, Oh MD, Choe KW, 2003. Vivax malaria: a continuing health threat to the Republic of Korea. *Am J Trop Med Hyg 69:* 159–167.
2. Yeom JS, Ryu SH, Oh S, Lee WJ, Kim TS, Kim KH, Kim YA, Ahn SY, Cha JE, Park JW, 2005. Status of *Plasmodium vivax* malaria in the Republic of Korea during 2001–2003. *Am J Trop Med Hyg 73:* 604–608.
3. Yeom JS, Kim TS, Oh S, Sim JB, Barn JS, Kim HJ, Kim YA, Ahn SY, Shin MY, Yoo JA, Park JW, 2007. *Plasmodium vivax* malaria in the Republic of Korea during 2004–2005: changing patterns of infection. *Am J Trop Med Hyg 76:* 865–868.
4. Roll Back Malaria Partnership, 2008. Democratic People's Republic of Korea: country profile. Available at: http://www.rbm.who.int/countryaction/index.html. Accessed July 11, 2008.
5. Yeom JS, Ryu SH, Oh S, Choi DH, Song KJ, Oh YH, Lee JH, Kim YA, Ahn SY, Yang HY, Cha JE, Park JW, 2005. Evaluation of anti-malarial effects of mass chemoprophylaxis in the Republic of Korea Army. *J Korean Med Sci 25:* 707–712.
6. Easterbrook M, 1999. Detection and prevention of maculopathy associated with antimalarial agents. *Int Ophthalmol Clin 39:* 49–57.
7. McChesney EW, 1983. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. *Am J Med 75:* 11–18.
8. Snounou G, Viriyakosol S, Zhu XP, Jarra W, Pinheiro L, do Rosario VE, Thaithong S, Brown KN, 1993. High sensitivity of detection of human malaria parasites by the use of nested polymerase chain reaction. *Mol Biochem Parasitol 61:* 315–320.
9. Marlar T, Myat Phone K, Aye Yu S, Khaing Khaing G, Ma S, Myint O, 1995. Development of resistance to chloroquine by *Plasmodium vivax* in Myanmar. *Trans R Soc Trop Med Hyg 89:* 307–308.
10. Baird JK, Sustriayu Nalim MF, Basri H, Masbar S, Leksana B, Tjitra E, Dewi RM, Khairani M, Wignall FS, 1996. Survey of