- Cholera (yellowBookCh4-Cholera.aspx) (from *CDC Health Information for International Travel 2008*)
- Safe food and water (contentSafeFoodWater.aspx) (CDC Travelers' Health website)

For more information about cholera, see the following CDC links:

- Cholera (http://www.cdc.gov/nczved/dfbmd/disease_listing/cholera_gi.html) (from CDC, Division of Foodborne, Bacterial, and Mycotic Diseases)
- Cholera (yellowBookCh4-Cholera.aspx) (from *CDC Health Information for International Travel 2008*)

To find medical care in Zimbabwe:

- On the web: List of local medical specialists (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292L21lZGljYWxfaW5mb3JtYXRpb24uaHRtbA%3d%3d-U8dFKbSICao%3d) (Embassy of the United States, Harare, Zimbabwe)
- By phone: 263-4-250593/4 Consular section of the United States Embassy, Harare, Zimbabwe: American Citizen Services

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  National Center for Preparedness, Detection, and Control of Infectious Diseases

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Centers for Disease Control and Prevention 1600 Clifton Rd. Atlanta, GA 30333, USA
800-CDC-INFO (800-232-4636) TTY: (888) 232-6348, 24 Hours/Every Day - cdcinfo@cdc.gov

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 2009年1月21日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	①～③、⑥～⑧人血清アルブミン ④⑨人血液凝固第 XIII 因子 ⑤フィブリノゲン加第 XIII 因子	研究報告の公表状況	*Babesia* Infection through Blood Transfusions: Reports Received by the US Food and Drug Administration, 1997–2007 Clinical Infectious Diseases, 1 January 2009, Vol. 48, No. 1: pp. 25-30	公表国 米国	
販売名（企業名）	①アルブミン－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ベリプラスト 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

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

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 ($\geq$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/biodev/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.