白血病ウイルス感染者108万人　大都市圏で割合増

母乳を通じて母子感染し、白血病などを引き起こす可能性がある成人T細胞白血病ウイルス（HTLV1）について厚生労働省研究班が約20年ぶりに実施した調査で、感染者の地域別割合がもともと高かった九州で減少し、関東や中部、近畿の大都市圏で増加したことが27日、分かった。

国内の感染者数は約108万人と推計。旧厚生省研究班が1988～90年度にまとめた調査の約120万人と比べ大きな変化はなかった。これまで全国的な対策は取られておらず、子供への感染を防ぐ取り組みが急務となりそうだ。

研究班班長の山口一成国立感染症研究所客員研究員は大都市圏での割合増加について、感染者が多い九州からの人の移動が背景にあると指摘。「妊婦への抗体検査や授乳指導を実施している自治体は一部に限られ、感染者総数もあまり減少していない」と話した。

HTLV1はATLと呼ばれるタイプの白血病や、歩行障害などが出る脊髄症（HAM）の原因となる。ATLの発症率は3～5%。根本的な治療法はなく、年間約千人が亡くなっている。

今回の調査は、2006～07年に初めて献血した全国の約119万人を対象に実施、3787人の感染が確認された。

感染者の地域別割合は、九州が前回調査の50・9%から41・4%に減少。一方、関東は17・3%（前回10・8%）、中部8・2%（同4・8%）、近畿20・3%（同17・0%）で、いずれも前回より増加した。

2009/08/27 18:03 【共同通信】

ホーム 共同ニュース

最47ニュース アクセスランキング一覧へ

別紙様式第2-1

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
				2009. 8. 18	該当なし	
一般的名称	新鮮凍結人血漿				公表国	
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) 新鮮凍結血漿-LR「日赤」成分採血（日本赤十字社）	研究報告の公表状況	Euro Surveill. 2009 May 14;14(19).		オランダ	

研究報告の概要		使用上の注意記載状況・その他参考事項等
○オランダ南部におけるQ熱の持続的集中的伝播、2009年 オランダは、2007年と2008年のアウトブレイク後再びQ熱報告の急増に直面している。もっとも影響が大きいのは大規模なヤギ農場が集中しているNoord Brabant県であり、流産の増加している農場が発生源と疑われる。複数の専門分野にわたる大規模な調査研究により、疾患の伝播や予防手段に関する知見が得られることが期待される。 Q熱症例数は2009年4月以降急増し、1月1日から5月11日までの間に345例(可能性例13例を含む)が報告された。11例は2008年、1例は2007年に発症していたため、2009年に発症した症例は合計333例という結果となった。男女比は約1.7:1で、年齢の中央値は49才(38-61才)であった。過去の2年と比べて4-5月に患者数が急増しており、流行の規模は2008年と同程度以上になることが示唆されている。ほとんどの患者が、2007年、2008年と同様Noord Brabant県民であったが、感染区域に拡大傾向が見られている。 主な症状は肺炎で、2008年に報告された患者では、545名が肺炎、33名が肝炎、115名が他の発熱性疾患を発症した。2009年の症例のうち、データの得られた226例中59例(26%)が入院した。これは2008年度と同程度の割合だが、2007年(49%)よりは少なかった。 Noord Brabant県を中心に、少なくとも10件の独立した流行クラスターがあることが明らかになってきた。一部のクラスターでは、家畜のQ熱が発生し流産が増加している小型反芻動物農場との明確な疫学的関連性があった。動物のワクチン接種キャンペーンが始まっており、2010年には効果を発揮する見込みである。	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	新鮮凍結血漿「日赤」 新鮮凍結血漿-LR「日赤」 新鮮凍結血漿-LR「日赤」成分採血
報告企業の意見	**今後の対応**	
オランダ南部においてQ熱の患者が急増しており、一部では家畜のQ熱が発生している農場との疫学的関連性があったとの報告である。	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、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。	

(12)

Rapid communications

Sustained intensive transmission of Q fever in the south of the Netherlands, 2009

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3. Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands
4. Municipal Health Service South Limburg, Sittard-Geleen, the Netherlands
5. Municipal Health Service Brabant-Southeast, Helmond, the Netherlands
6. Municipal Health Service "Hart voor Brabant", 's Hertogenbosch, the Netherlands

The Netherlands is again facing a sharp increase in Q fever notifications, after the unprecedented outbreaks of 2007 and 2008. The most affected province of Noord Brabant has a high density of large dairy goat farms, and farms with abortion waves have been incriminated. Mandatory vaccination of small ruminants has started and should have an effect in 2010. A large multidisciplinary research portfolio is expected to generate better knowledge about transmission and additional control measures.

Introduction

Q fever is a zoonosis caused by the obligate intracellular bacterium *Coxiella burnetii*. Cattle, sheep and goats are the primary animal reservoir, but the causative agent has also been noted in many other animal species. Infected goats and sheep may abort, mainly in late pregnancy. The bacterium is shed in urine, faeces, milk and in especially high concentrations in placentas and birth fluids of infected animals. Bacteria are transmitted to humans mainly through the aerosol route, resulting in subclinical infection, a flu-like syndrome with abrupt onset of fever, pneumonia or hepatitis, after an incubation period of two to three weeks [1]. People with underlying conditions, especially heart valve lesions, are more susceptible to developing chronic Q fever. Endocarditis, the most common form of chronic Q fever is estimated to occur in about 1% of acute Q fever cases.

Since 1978, when Q fever in humans became a notifiable disease in the Netherlands, until 2006, the number of notifications had ranged between 1 and 32 cases annually, with an average of 17 cases per year [2]. However, in 2007, Q fever emerged as an important human and veterinary public health challenge with large epidemics in the southern part of the Netherlands [3]. In 2007, 168 human cases were notified and in 2008 exactly 1,000 human cases were registered (Figure 1). Notification criteria for acute Q fever are a clinical presentation with at least fever, or pneumonia, or hepatitis and confirmation of the diagnosis in the laboratory. Currently, the laboratory criteria are a fourfold rise in IgG antibody titre against *C. burnetii* in paired sera or the presence of IgM-antibodies against phase II antigen. Identification of *C. burnetii* in patient material with a PCR test will soon be added to the notification criteria. Notification of probable cases, defined as clinical signs with a single high antibody titre is voluntary.

Current situation

From April 2009, a sharp increase in Q fever was observed again, and a total of 345 cases (including 13 probable) were notified between 1 January and 11 May 2009 (Figure 1). For 11 cases, the date of illness onset was in 2008 and one case fell ill in 2007, resulting in a total of 333 cases with confirmed or presumed illness onset in 2009. The overall male-to-female ratio for these 333 cases was 1.7:1 with a median age of 49 years (IQR 38-61 years).

The epidemic curve for 2009 shows an even steeper increase in case numbers in April-May, than in the previous two years, suggesting that an epidemic of at least the same magnitude as the one in 2008 is imminent. While most cases reside in the same region in the province of Noord-Brabant as the cases reported in 2007 and 2008 (see map in reference 3), the geographic area seems to be expanding (Figure 2).

Clinical features and diagnostics

Pneumonia is the predominant clinical presentation of the Q fever cases in the Netherlands. For those patients notified in 2008 for whom clinical details were available, 545 presented with pneumonia, 33 with hepatitis, and 115 with other febrile illness (data not yet analysed in detail). Of the 226 cases in 2009 where data regarding hospitalisation were available, 59 (26%) had been admitted to a hospital, a percentage comparable to figures in 2008, but lower than the proportion of patients hospitalised in 2007 (49%). Clinical follow-up of patients that were diagnosed with acute Q fever in 2007, shows that Q fever is not always a mild disease of short duration, as many cases still suffered from persisting fatigue several months after disease onset [4]. We have no clear information about the occurrence of other chronic sequelae, such as endocarditis at this stage.

The medical microbiology laboratories in the affected region have jointly formulated diagnostic recommendations. Cases are currently diagnosed with immunofluorescence assays (Focus Diagnostics), in-house complement fixation tests or ELISA. Real-time polymerase chain reaction (PCR) tests were developed by eight medical microbiology laboratories and the most sensitive (98%) PCR has been selected and has proven a valuable additional tool for early diagnosis of acute Q fever in the time window before seroconversion.

Increased alertness of general practitioners together with easy availability of diagnostic services certainly has an impact on the number of notifications. The current epidemic curve based on week of notification reflects a more real time situation than in previous years, as the interval between date of illness onset and date of diagnosis has decreased from a median of 77 days in 2007 (IQR 40-121) and 29 days (IQR 19-45) in 2008 to 17 days in 2009 (IQR 12-24 days).

Separate clusters with multiple sources

It is becoming increasingly clear that the overall outbreak consists of at least 10 separate clusters with multiple sources, mainly in the province of Noord Brabant. For some clusters a clear epidemiological link could be established to small ruminant farms with clinical Q fever cases in animals presented as abortion waves. For other clusters such a link was less obvious. An example of the latter is a medium sized city (87,000 inhabitants) that experienced a second Q fever outbreak in 2009 similar to the one in 2008. In 2008, a dairy goat farm with abortions due to Q fever was suspected as the source, but in 2009 there were no veterinary notifications from the area. The 73 notified human cases residing in the city were clustered in the same part of the city as the cases that were notified in 2008. It remains unclear whether the same source is involved, whether the bacteria have persisted and survived in the local environment, whether the primary source in 2008 has resulted in secondary sources in 2009, or whether there is increased awareness among health professionals in this part of the city based on the 2008 experience.

In March 2009, the Animal Health Service reported a Q fever-positive farm in the province of Limburg with more than a thousand goats. The place also serves as a care farm for young people with mental disabilities who work there as part-time farmhands. Prompted by this notification, the municipal health service (MHS) South Limburg performed active laboratory screening by ELISA of the individuals affiliated to this goat farm. The screening, which involved a total of 96 people, has resulted in 28 notified symptomatic cases to date.

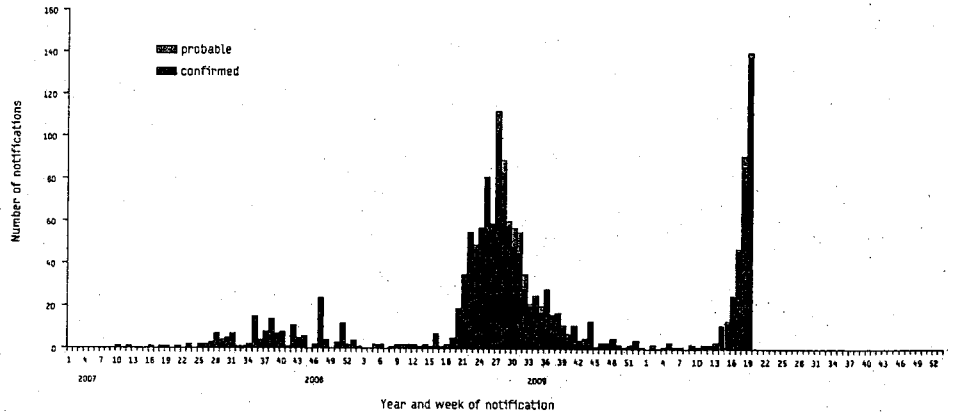
Veterinary situation

The total number of registered small ruminant farms in the Netherlands is 52,000, of which 350 are professional dairy goat farms with more than 200 adult goats and 40 are professional dairy sheep farms. In 2005, Q fever was diagnosed for the first time as a cause of abortion at a dairy goat farm, using immunohistochemistry on sections of placenta [5]. A second case was diagnosed later in 2005. In 2006, 2007 and 2008, six, seven and seven new cases at dairy goat farms were confirmed, respectively, mainly in the same area where human cases occurred. In the same period, two cases of abortion caused by *C. burnetii* were confirmed at dairy sheep farms, one in the southern and one in the northern part of the country but these two cases do not seem to be related to human cases. Analyses of abortion outbreaks showed that the average number of goats per farm was 900 of which 20% aborted, ranging from 10-60%. The average number of sheep on both infected sheep farms was 400 and the abortion rate was 5%.

Abortion outbreaks before June 2008 were reported on a voluntary basis to the Animal Health Service and also confirmed by immunohistochemistry. Since June 2008, notification of Q fever in goats and sheep is mandatory in the Netherlands. There is a legal requirement for farmers and their private veterinary surgeons to notify the occurrence of abortion in small ruminants held in deep litter houses. For large farms (>100 animals) the notification

FIGURE 1

Q fever notifications by week of notification, 1 January 2007 - 11 May 2009, the Netherlands (2007: n=168, 2008: n=1000, 2009 [week 1-week 19]: n=345)



criterion is an abortion wave defined as an abortion percentage higher than 5% among pregnant animals. For smaller holdings, a criterion of three or more abortions in a 30-day period is used.

From January to April 2009, this new regulation has led to notification of three dairy goat farms with clinical cases of Q fever. One farm is located in the province of Overijssel (notified in February), one in the south of the province of Limburg (notified in March), and one in the province of Noord-Brabant (notified in April).

This veterinary notification can potentially facilitate the detection of related human cases or clusters. Veterinarians, physicians and the public are informed through targeted mailings, publications and the media. The exact location of animal farms with clinical Q fever is now reported to the municipal health service. In February 2009, a nationwide stringent hygiene protocol became mandatory for all professional dairy goat and sheep farms, independent of Q fever status.

Vaccination campaigns

In the fall of 2008, a voluntary vaccination campaign was implemented in the province of Noord Brabant. In total, about 36,000 small ruminants were vaccinated in an area with a radius of 45 kilometer around Uden, a small town in the centre of the high-risk area.

Another, mandatory vaccination campaign led by the Animal Health Service (GD) started on 21 April 2009. From April to October 2009, 200,000 small ruminants will be vaccinated in an area which includes the province of Noord-Brabant and parts of the provinces of Gelderland, Utrecht and Limburg.

Ongoing research

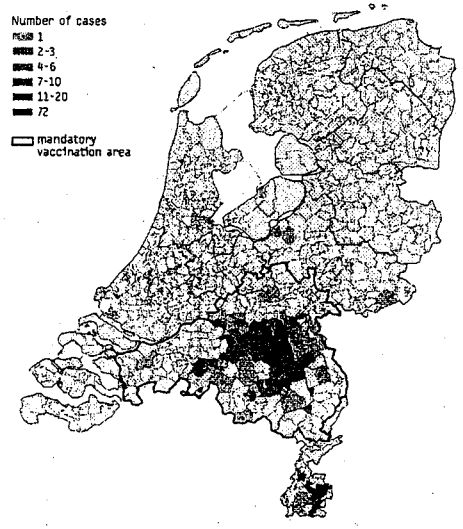
Ongoing studies address the factors involved in the 2008 epidemic at a national, regional and local level, the efficacy of the 2008 voluntary vaccination campaign in small ruminants and the nationwide occurrence of *C. burnetii* antibodies in the community and in small ruminants. From the human epidemiological perspective, a case control study is currently underway in the two main affected MHS regions of 2009, 'Hart voor Brabant' and Brabant-Southeast. Routinely collected sera of pregnant women from the affected regions over the period June 2007 to July 2008 are retrospectively screened for Q fever to study the effect of infection on pregnancy outcome (registered in a national database). An integrated human-veterinary study was started, in which small ruminant farmers and their animals will be screened for presence of *C. burnetii* antibodies. In addition, environmental samples will be obtained from a subset of these farms and the role of particulate matter in relation to *C. burnetii* transmission will be further investigated.

Conclusion

For the third consecutive year the Netherlands is facing a large outbreak of Q fever. The new upsurge in Q fever cases in 2009 is alarming. The mandatory vaccination campaign among small ruminants that was started in April 2009, if effective, is expected to reduce the occurrence of abortion waves and excretion of *Coxiella* in the lambing season 2010. There is a large portfolio of ongoing multidisciplinary research, but it will take some time before results become available that eventually will lead to the implementation of extended and improved control measures.

FIGURE 2

Notified cases of acute Q fever in the Netherlands by three-digit postal code area, 1 January – 11 May 2009 (n=344*). The black line indicates the mandatory vaccination area covering the province of Noord Brabant and parts of the provinces of Gelderland, Utrecht, and Limburg.



Source: OSIRIS notification system. Map compiled by Ben Bom, Expertise Centre for Methodology and Information Services, RIVM
* For one case the information on postal code is missing

References

1. Maurin M, Raoult D. Q fever. Clin Microbiol Rev. 1999;12(4):518-53.
2. Gageldonk-Lafeber AB van, Koopmans MPG, Bosman A, Heijnen MA. Het vóórkomen van Q-koorts in Nederland [Occurrence of Q fever in the Netherlands]. [Article in Dutch]. Infectieziekten Bulletin. 2003;14(5):173-177. Available from: http://www.rivm.nl/infectieziektenbulletin/bul1405/art_qkoorts.html
3. Schimmer B, Morroy G, Dijkstra F, Schneeberger PM, Weers-Pothoff G, Timen A, et al. Large ongoing Q fever outbreak in the south of the Netherlands, 2008. Euro Surveill. 2008;13(31):pii=18939. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18939
4. Nabuurs-Franssen MH, Limonard G, Horrevorts AM, Weers-Pothoff G, Besselink R, Wijkmans C, et al. Clinical follow-up after acute Q fever. Scientific Spring Meeting of the Dutch Society for Medical Microbiology and the Dutch Society for Microbiology, 20-22 April, Arnhem, the Netherlands. International Journal of General and Molecular Microbiology. 2009;95(Supplement 1).
5. Wouda, W, Dercksen D. [Abortion and stillbirth among dairy goats as a consequence of Coxiella burnetii] [Article in Dutch]. Tijdschr Diergeneeskd. 2007;132(23):908-11.

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別紙様式第 2-1
番号 15

医薬品
医薬部外品　研究報告　調査報告書
化粧品

識別番号・報告回数		報告日	第一報入手日 2009年6月29日	新医薬品等の区分	厚生労働省処理欄
一般的名称	①②③④人血清アルブミン ⑤乾燥濃縮人血液凝固第Ⅷ因子 ⑥⑦乾燥濃縮人血液凝固第Ⅸ因子				
販売名（企業名）	①献血アルブミン 25%静注 5g/20mL「ベネシス」（ベネシス） ②献血アルブミン 25%静注 12.5g/50mL「ベネシス」（ベネシス） ③献血アルブミン 5%静注 5g/100mL「ベネシス」（ベネシス） ④献血アルブミン 5%静注 12.5g/250mL「ベネシス」（ベネシス） ⑤コンコエイト-HT（ベネシス） ⑥クリスマシン M 静注用 400 単位（ベネシス） ⑦クリスマシン M 静注用 1000 単位（ベネシス）	研究報告の公表状況	FDA (Vaccines, Blood & Biologics)/2009/06/12	公表国 アメリカ	
研究報告の概要	FDAは、全血および成分血の製造施設、ヒト細胞・組織・それら由来製剤（HCT/Ps）のドナーの適性判定施設において、Trypanosoma cruzi（T. cruzi）抗体を検出するための酵素免疫反応試験（EIA）の承認申請（BAL）がFDAにより承認されたことを通知する。この検査は輸血に使用される全血および成分血、およびHCT/Pドナー（生体および死後（心停止））を含む個別ドナー血漿およびの血清サンプルにおけるT. cruzi抗体検出により、T. cruziの伝播リスクを低減させることを目的とする。このガイダンス文書は、分画製剤用原料血漿の採集には適用されない。FDAはこのガイダンスの最終版発行後1年以内にこのガイダンスに記載の推奨事項を実施するよう推奨する。 1989年9月のBlood Products Advisory Committee（BPAC）の会合で、委員会は適当な検査が利用可能になったとき、全血および成分血のドナーにシャーガス病の検査をすることを勧めた。2006年12月、FDAは血液及びHCT/Ps ドナーにおけるT. cruzi抗体の検出のためのELISA検査システムを製造業者1社に許可した。2007年1月の末以来、米国血液センターの多くは、この許可された測定法を使用してドナーを検査した。2009年2月、FDAは死んだ（心停止）HCT/Ps ドナーにおける、T. cruzi抗体の検出のためにこのELISA検査システムを認可した。 1990年代半ばの米国の血液ドナーの血清陽性率は1/5400～1/25000であった。しかし、最近の研究ではこれより増加していることを示唆している。例えば、Los Angeles大都市圏で最近では1/2000であることがわかった。 伝播経路として垂直感染、経口感染、粘膜感染、粘盤感染があり、適切なスクリーニング及び/又は検査を実施する有用性について報告をすることが記載されている。				
	報告企業の意見		今後の対応		
	米国における全血、血液成分及びHCT/Psにおけるトリパノソーマ症感染伝播のリスク低減のためのドナースクリーニングについての業者向けガイダンス（案）である。 血漿分画製剤からのトリパノソーマ原虫伝播の事例は報告されていない。また、万一原料血漿にTrypanosoma cruziが混入したとしても、除菌ろ過等の製造工程において十分に除去されると考えている。		本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。		
	使用上の注意記載状況・その他参考事項等				
	代表として献血アルブミン 25%静注 5g/20mL「ベネシス」の記載を示す。 2. 重要な基本的注意 (1) 本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-1抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohnの低温エタノール分画で得た画分から人アルブミンを精製し、アルブミン濃度 25w/v%に調整した製剤であり、ウイルス不活化を目的として、製造工程において 60℃、10時間の液状加熱処理を施しているが、投与に際しては、次の点に十分注意すること。		

(13)

Guidance for Industry

Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2009

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Guidance for Industry

Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

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I. INTRODUCTION

We, FDA, are notifying you, establishments that manufacture Whole Blood and blood components intended for use in transfusion, and establishments that make eligibility determinations for donors of HCT/Ps, about FDA approval of a Biologics License Application (BLA) for an enzyme-linked immunosorbent assay (ELISA) test system for the detection of antibodies to *Trypanosoma cruzi* (*T. cruzi*). This test is intended for use as a donor screening test to reduce the risk of transmission of *T. cruzi* infection by detecting antibodies to *T. cruzi* in plasma and serum samples from individual human donors, including donors of Whole Blood and blood components intended for use in transfusion, and HCT/P donors (living and cadaveric (non-heart beating)). This guidance document does not apply to the collection of Source Plasma.

In addition, we are providing you with recommendations for unit and donor management, labeling of Whole Blood and blood components, and procedures for reporting implementation of a licensed *T. cruzi* test at your facility or at your contract testing laboratory, as required for blood establishments under Title 21 Code of Federal Regulations 601.12 (21 CFR 601.12). For establishments that make donor eligibility determinations for HCT/P donors, we are notifying you that we have determined *T. cruzi* to be a relevant communicable disease agent under 21 CFR 1271.3(r)(2), and are providing you with recommendations for testing and screening donors for antibodies to *T. cruzi*.

The recommendations made in this guidance with respect to HCT/Ps are in addition to recommendations made in the document entitled "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated August 2007 (Ref. 1).

We recommend that you implement the recommendations provided in this guidance within one year after a final guidance is issued.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Chagas disease is caused by the protozoan parasite, *T. cruzi*. The disease is found primarily in Mexico and Central and South America; the pathogenic agent has rarely been reported to cause human infection in the United States (U.S.) by natural vector transmission (Ref. 2). Natural infections are transmitted mainly when the feces of certain blood sucking insects (triatomine bugs, commonly referred to as kissing or chinch bugs) that harbor the infection are rubbed into a bug bite, other wound, or directly into the eyes or mucous membranes. Other primary forms of transmission include congenital (mother to unborn infant), organ transplantation, and blood transfusion. Current estimates are that at least 11 million persons in Mexico and Central and South America carry the parasite chronically and could present a potential source of infection should they become donors. The presence of the pathogenic agent in U.S. and Canadian donors is increasing due to immigration of infected individuals from endemic areas. Some experts estimate that there may be as many as 100,000 persons unknowingly infected with *T. cruzi,* who reside in the U.S. and Canada.

Vector-borne infections are mostly mild in the acute phase and then persist throughout life, usually without symptoms. Acute infection in patients with compromised immune systems, for example, from cancer therapy or organ transplantation, can be very serious and sometimes fatal. Treatment options are limited, but are most effective early in the infection. The lifetime risk of severe cardiac complications (cardiomegaly, heart failure and arrhythmias) or intestinal disorders (megacolon, megaesophagus) in infected individuals averages about 30% (range of 10 to 40% depending on a variety of factors) and may occur many years after the initial infection. During the acute phase of vector-borne Chagas disease, parasites are found in skin lesions at the site of transmission. The parasites are then spread through the bloodstream to various tissues, particularly skeletal muscle (Ref. 3). During the chronic stage of Chagas disease, most persons who harbor the parasite are asymptomatic and unaware of their infection. During this phase, parasites have been demonstrated in muscle (especially cardiac muscle), nerves, and digestive tract, but there has been very little investigation of tissue distribution during that phase (Refs. 3 through 10).

A. Donor Screening Tests for Chagas Disease in the United States

At the September 1989 Blood Products Advisory Committee (BPAC) meeting, the committee recommended testing donors of Whole Blood and blood components for Chagas disease when a suitable test became available. In a 1995 BPAC meeting, the committee considered whether the performance characteristics of the two FDA-approved tests then available for diagnosis of Chagas disease would be suitable for blood donor screening. The committee concluded that the tests discussed were not suitable for blood donor screening. Furthermore, the committee sought clarification of the criteria that FDA would use to license a Chagas test for donor screening. At the September 2002 meeting of BPAC, FDA presented its current considerations on the regulatory pathway and standards for licensing a donor screening test for Chagas disease and encouraged manufacturers to develop tests based on those considerations (Ref. 11).

In December 2006, FDA granted a license to one manufacturer of an ELISA test system for the detection of antibodies to *T. cruzi* in individual living blood and HCT/P donors. Since the end of January 2007, a number of blood centers representing a large proportion of U.S. blood collections have been testing donors using this licensed assay. In February 2009, FDA licensed this ELISA test system for the detection of antibodies to *T. cruzi* in cadaveric (non-heart beating) HCT/P donors.

Blood donor testing by an ELISA test system identifies donors that are repeatedly reactive for antibodies to *T. cruzi*. The presence of antibodies to *T. cruzi* is strong evidence that a donor is infected with this parasite. Most donors that are repeatedly reactive by an ELISA test system for antibodies to *T. cruzi* have chronic, asymptomatic infections acquired years earlier during residence in areas endemic for *T. cruzi*. Therefore, prior donations from a donor who is repeatedly reactive on an ELISA test system were likely to harbor *T. cruzi* parasites.

At the April 2007 BPAC meeting, FDA requested comments on scientific issues related to the implementation of blood donor testing for infection with *T. cruzi* (Ref. 12). Issues discussed by the committee included the need for additional data on the incidence and risk of transmission of *T. cruzi* by transfusion, the severity of Chagas disease, the performance of the antibody test, and, the lack of a licensed supplemental test for confirmatory testing.

The committee also commented on the design of research studies to validate a strategy for selective testing of repeat blood donors. The committee noted that a period of universal testing of all blood donors would generate critical data on the prevalence of *T. cruzi* infections in donors and that donor questions for selective donor screening needed validation.

B. Risk of *T. cruzi* Infection from Transfusion of Whole Blood and Blood Components

Blood donations from individuals from endemic areas are the primary source of risk for *T. cruzi* infection from transfusion. Studies in the mid-1990s (Ref. 1) estimated that the rate of seropositive blood donors in the U.S. ranged from 1 in 5400 to 1 in 25,000, depending on where the studies were conducted. However, more-recent studies suggest that these rates have increased in the areas where donor testing has been performed over a period of time. For example, a rate of 1 in 2000 was found recently in the Los Angeles metropolitan area (Ref. 14). Transfusion transmission in endemic areas has been a major public health concern, and many countries considered endemic for *T. cruzi* infection screen blood donors for the presence of antibody. Therefore, in response to changes in donor demographics, we are now recommending blood donor testing in the U.S.

In the U.S. and Canada, only seven cases of transfusion-transmitted *T. cruzi* infections (Refs. 15 through 19) and five cases of infection from organ transplantation (Refs. 20 and 21) have been documented. However, transmission in immunocompetent patients is not likely to be apparent, and in many cases, even if symptoms appear, infection may not be recognized (Ref. 22).

Studies in blood centers which question donors about birth and/or residence in a *T. cruzi*-endemic country have shown such questions to be incompletely effective at identifying the seropositive donors. Studies also have looked at the rate of transfusion transmission from *T. cruzi* antibody-positive individuals. Published lookback studies in the U.S. and in Mexico of 22 transfusion recipients of seropositive donations, identified five of these recipients (22.7%) who later tested positive for antibodies suggesting transfusion transmission of *T. cruzi* (Refs. 18, 23 and 24). This transmission rate of 22.7% is consistent with the literature from Latin America on rates of blood-borne transmission from seropositive donors in Mexico and Central and South America (Ref. 25). However, we are aware that lookback studies conducted using the licensed ELISA test indicate that the risk of *T. cruzi* by transfusion of a seropositive unit in the U.S. may be much lower risk than previously thought. We note that these studies have confirmed the demographic characteristics of the typical seropositive donor as described in the first two paragraphs of section II. However, the data also suggest that there are seropositive individuals who acquired their infections within the U.S. (Ref. 26). Despite this new data, the rate of transfusion transmission of *T. cruzi* in the U.S. continues to be uncertain because of the limited number of studies conducted to date and the rate of transfusion transmission remains under investigation.

C. Risk of *T. cruzi* Infection to Recipients of Donated HCT/Ps

Based on the risk of transmission, severity of effect, and availability of appropriate screening measures and/or tests, we have determined *T. cruzi*, the agent for Chagas disease, to be a relevant communicable disease agent or disease under 21 CFR 1271.3(r)(2). This determination was based on the following information.

1. Risk of Transmission

There is a risk of transmission of *T. cruzi* by HCT/Ps and there has been sufficient incidence and/or prevalence to affect the potential donor population.

Recognizing the risk of transmission from donated HCT/Ps, countries endemic for *T. cruzi* infection have instituted various practices to minimize transmission through transfusion or transplantation including screening donors for the presence of *T. cruzi* antibodies. Further, when human leukocyte antigen-matched bone marrow is obtained from an infected individual, the donor receives anti-parasitic treatment before the bone marrow is taken for transplantation. The World Health Organization recommends that:

- a heart from an infected donor not be transplanted;
- a liver from an infected donor only be transplanted to recipients already positive for Chagas disease, except in emergency cases; and
- when other organs are transplanted from a Chagas-positive donor, the recipient should receive prophylactic treatment for Chagas disease (Ref. 3).

Published data regarding the transmissibility of *T. cruzi* indicate that vertical transmission (congenitally from mother to infant), oral transmission (through breast milk or contaminated food) and conjunctival transmission (from contact with contaminated hands) have occurred (Ref. 3). In animal studies, *T. cruzi* has been shown to infect multiple tissues, including skeletal muscle, heart, bladder, peripheral nerve, liver, spleen, adrenal gland, brain, adipose tissue, ocular tissue, osteoblasts, chondroblasts, macrophages, and fibroblasts (Refs. 27 through 30). Human placental cells also have been experimentally infected with *T. cruzi* (Ref. 31). As noted previously in this section, *T. cruzi* has been transmitted via blood transfusions and organ transplantation (Refs. 20 through 22, and 32).

At the BPAC meeting of April 26, 2007, the committee noted that, though some HCT/Ps are processed in a manner that might inactivate *T. cruzi* in HCT/Ps from seropositive donors, current data are insufficient to identify specific effective processing methods that consistently render HCT/Ps free of *T. cruzi*. The committee concluded that, absent such data, it would be prudent to test HCT/P donors to decrease the risk of transmitting infection with *T. cruzi* (Ref. 12).

Information about prevalence of *T. cruzi* in the U.S. is provided in section II.B. of this document.

2. Severity of Effect

T. cruzi infections can be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

3. Availability of Appropriate Screening and/or Testing Measures

Appropriate screening measures have been developed for *T. cruzi*, such as the medical history interview. (Screening measures for *T. cruzi* are discussed in section IV.A. of this document.)

A donor screening test for *T. cruzi* has been licensed and labeled for use in testing blood specimens from living and cadaveric donors of HCT/Ps (see section IV.B. of this document). You must use a donor screening test for *T. cruzi* that is specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test when applicable and when available (21 CFR 1271.80(c)). Current FDA-licensed, cleared or approved donor screening tests for use in testing HCT/P donors are listed at http://www.fda.gov/cber/tissue/prod.htm.

III. RECOMMENDATIONS FOR DONORS OF WHOLE BLOOD AND BLOOD COMPONENTS INTENDED FOR USE IN TRANSFUSION

A. Blood Donor Testing and Management

1. Donor Testing

We recommend testing of all donations of allogeneic units of blood using a licensed test for antibodies to *T. cruzi*. You must follow the regulations under 21 CFR 610.40(d) for determining when autologous donations must be tested.

2. Donor Deferral

We recommend that all donors who are repeatedly reactive on a licensed test for *T. cruzi* antibody or who have a history of Chagas disease be indefinitely deferred and notified of their deferral.

3. Confirmatory Testing and Donor Reentry

At this time, there is no FDA licensed supplemental test for antibodies to *T. cruzi* that can be used for confirmation of true positive screening test results. FDA is not recommending reentry criteria for blood donors deferred indefinitely on the basis of a repeatedly reactive screening test for antibodies to *T. cruzi* due to the absence of a licensed supplemental test for antibodies to *T. cruzi*.

4. Donor Counseling and Physician Referral

We recommend that donors who are repeatedly reactive using a licensed test for antibodies to *T. cruzi* be informed about the likelihood and medical significance of infection with *T. cruzi*. Additional medical diagnostic testing may provide information useful in donor counseling.

All repeatedly reactive donors should be referred to a physician specialist. It also may be useful to refer them to their state and local health departments or to other appropriate community resources.

5. Further Testing of Repeatedly Reactive Donors for Cross–Reacting Diseases

Because the licensed test has demonstrated some reactivity in donors infected with pathogens other than *T. cruzi*, we recommend that medical follow up be considered for donors who are repeatedly reactive by the licensed test for antibodies to *T. cruzi* but who have no apparent basis for exposure to *T. cruzi* or who have negative results on more specific medical diagnostic tests. For example, testing for leishmaniasis may be appropriate in persons with geographic risk for exposure to *Leishmania* parasites and who appear to have a falsely reactive screening test for antibodies to *T. cruzi*.

B. Product Management

1. Index Donations

We recommend that blood components from repeatedly reactive index donations be quarantined and destroyed or used for research. Components determined to be unsuitable for transfusion must be prominently labeled: "NOT FOR TRANSFUSION," and the label must state the reason the unit is considered unsuitable (e.g., the component is positive for *T. cruzi* (21 CFR 606.121(f)).

2. Lookback (Product Retrieval and Recipient Notification)

Within 3 calendar days after a donor tests repeatedly reactive by a licensed test for *T. cruzi* antibody, you should:

- identify all in-date blood and blood components previously donated by such a donor, going back either 10 years (or indefinitely where electronic records are available), or else 12 months prior to the most recent time that this donor tested negative with a licensed test for *T. cruzi* antibody, whichever is the lesser period (the lookback period);
- quarantine all previously collected in-date blood and blood components held at your establishment; and
- notify consignees of all previously collected in-date blood and blood components to quarantine and return the blood components to you or to destroy them.

In addition, when you identify a donor who is repeatedly reactive by a licensed test for *T. cruzi* antibodies and for whom there is additional information indicating risk of *T. cruzi* infection, such as geographical risk for exposure in an endemic area, or medical diagnostic testing of the donor, we recommend that you:

- notify consignees of all previously distributed blood and blood components collected during the lookback period; and
- if blood or blood components were transfused, encourage consignees to notify the recipient's physician of record of a possible increased risk of *T. cruzi* infection.

We recommend that when there is additional information indicating risk of *T. cruzi* infection you make such notifications within 12 weeks of obtaining the repeatedly reactive test result.

There currently is no licensed *T. cruzi* supplemental test. When such a test is available, a positive test result will provide additional information indicating risk of *T. cruzi* infection.

Retrospective Review of Records

If you are a blood establishment that implemented screening with a licensed test for antibodies to *T. cruzi* prior to the effective date of this guidance, you may wish to perform a retrospective review of records to identify donors:

- with repeatedly reactive test results by a licensed test for *T. cruzi* antibodies; and
- for whom there is additional information indicating risk of *T. cruzi* infection, such as geographical risk for exposure in an endemic area, or medical diagnostic testing of the donor. There currently is no licensed *T.*

If a donor is identified at risk of infection during the retrospective review, you may want to consider performing all the lookback actions described above.

3. Autologous Donations

Although autologous use of blood does not increase a patient's/donor's risk of illness from a pre-existing infection, FDA regulations under 21 CFR 610.40(d) and (e) require testing of autologous blood donors under certain circumstances to prevent inadvertent allogeneic exposures to unsuitable units.

a. We recommend that blood components from autologous donors that are repeatedly reactive by a licensed test for *T. cruzi* antibody be released for autologous use only with approval of the autologous donor's referring physician. Establishments should provide the results of additional testing for antibodies to *T. cruzi*, as available to the autologous donor's referring physician.

b. Each autologous donation must be labeled as required under 21 CFR 610.40(d)(4), as appropriate. Given the seriousness of *T. cruzi* infections, autologous donations that are repeatedly reactive by a licensed test for *T. cruzi* antibody must bear a biohazard label as required under 21 CFR 610.40(d)(4).

4. Circular of Information

Consistent with other donor screening tests, the instruction circular, also known as the "Circular of Information" must be updated to state that a licensed test for antibodies to *T. cruzi* was used to screen donors and that the results of testing were negative (21 CFR 606.122(h)).

5. Biological Product Deviation Report and Fatality Report

Under 21 CFR 606.171, licensed manufacturers, unlicensed registered blood establishments, and transfusion services must report any event and information associated with the manufacturing, if the event either represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of the product; or represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of the product, and it occurs in your facility or another facility under contract with you and involves distributed blood or blood components. For additional information regarding reporting, you may refer to

FDA guidance, "Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments," dated October 2006 (Ref. 33). Also, when a complication of blood collection or transfusion (e.g., involving *T. cruzi*) is confirmed to be fatal, you must notify FDA in accordance with 21 CFR 606.170(b).

C. Reporting the Test Implementation

1. If you are a licensed blood establishment and you begin using a licensed serological test for the detection of antibodies to *T. cruzi* according to the manufacturer's product insert at your facility, then you must notify us of the testing change in your Annual Report (AR), in accordance with 21 CFR 601.12(d). If you already have an approved supplement to your BLA to use a contract laboratory to perform infectious disease testing of blood products, and the contract laboratory will now perform a serological test for antibodies to *T. cruzi*, you must report this change in your AR (21 CFR 601.12(d)).

2. If you are a licensed blood establishment and you use a new contract laboratory to perform a serological test for antibodies to *T. cruzi* (and the laboratory already performs infectious disease testing for blood products), then you must report this change by submission of a "Changes Being Effected" supplement, in accordance with 21 CFR 601.12(c)(1) and (c)(5). If your contract laboratory has not previously performed infectious disease testing for blood products, then you must report this change as a major change in a prior approval supplement, in accordance with 21 CFR 601.12(b).

IV. RECOMMENDATIONS FOR DONORS OF HCT/Ps

A. Donor Screening—Risk Factors or Conditions

Under 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who is identified as having a risk factor for or clinical evidence of relevant communicable disease agents or diseases. Ineligible potential donors include those who exhibit one or more of the following conditions or behaviors.

- Persons who have had a medical diagnosis of *T. cruzi* infection based on symptoms and/or laboratory results.
- Persons who have tested positive or reactive for *T. cruzi* antibodies using an FDA-licensed or investigational *T. cruzi* donor screening test (Ref. 1).

B. Donor Testing

1. You must test blood specimens from all HCT/P donors for antibodies to *T. cruzi* using an FDA-licensed donor screening test (21 CFR 1271.80(c)).

2. Any HCT/P donor whose specimen tests negative (or non-reactive) for antibodies to *T. cruzi* may be considered to be negative (or non-reactive) for purposes of making a donor eligibility determination.

3. Any HCT/P donor whose specimen tests positive (or reactive) for antibodies to *T. cruzi* is ineligible to be a donor (21 CFR 1271.80(d)(1)).

V. REFERENCES

1. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 2007. http://www.fda.gov/cber/tissue/docs.htm

2. Dorn, P. L., L. Perniciaro, M. J. Yabsley, D. M. Roellig, G. Balsamo, J. Diaz and D. Wesson (2007). "Autochthonous transmission of *Trypanosoma cruzi*, Louisiana." Emerg Infect Dis 13(4): 605-7.

3. WHO Expert Committee on the Control of Chagas Disease (2000: Brasilia, Brazil), Control of Chagas Disease: second report of the WHO expert committee, 2002.

4. Bellotti, G., E. A. Bocchi, A. V. de Moraes, M. L. Higuchi, M. Barbero-Marcial, E. Sosa, A. Esteves-Filho, R. Kalil, R. Weiss, A. Jatene and F. Pileggi (1996). "In vivo detection of *Trypanosoma cruzi* antigens in hearts of patients with chronic Chagas' heart disease." Am Heart J 131(2): 301-7.

5. Vago, A. R., A. M. Macedo, S. J. Adad, D. D. Reis and R. Correa-Oliveira (1996). "PCR detection of *Trypanosoma cruzi* DNA in oesophageal tissues of patients with chronic digestive Chagas' disease." Lancet 348(9031): 891-2.

6. Añez, N., H. Carrasco, H. Parada, G. Crisante, A. Rojas, C. Fuenmayor, N. Gonzalez, G. Percoco, R. Borges, P. Guevara and J. L. Ramirez (1999). "Myocardial parasite persistence in chronic chagasic patients." Am J Trop Med Hyg 60(5): 726-32.

7. Jones, E.M., D. G. Colley, S. Tostes, E. R. Lopes, C. L. Vnencak-Jones, and T. L. McCurley (1993). "Amplification of a *Trypanosoma cruzi* DNA sequence from inflammatory lesions in human chagasic cardiomyopathy." Am J Trop Med Hyg 48(3): 348-357.

8. Vago, A. R., L. O. Andrade, A. A. Leite, D. d'Avila Reis, A. M. Macedo, S. J. Adad, S. Tostes Jr., M.C. V. Moreira, G. B. Filho, S. D. J. Pena (2000). "Genetic characterization of *Trypanosoma cruzi* directly from tissues of patients with chronic Chagas disease: Differential distribution of genetic types into diverse organs." American Journal of Pathology 156(5): 1805-1809.

9. Virreira, M., G. Serrano, L. Maldonado, and M. Svoboda (2006). "*Trypanosoma cruzi*: Typing of genotype (sub)lineages in megacolon samples from bolivian patients." Acta Tropica 100(3): 252-255.

10. da Silva Manoel-Caetano, F., C.M. Carareto, A. A. Borim, K. Miyazaki, and A.E. Silva (2008). "kDNA gene signatures of Trypanosoma cruzi in blood and oesophageal mucosa from chronic chagasic patients." Trans R Soc Trop Med Hyg 102(11): 1102-1107.

11. Blood Products Advisory Committee, 74th Meeting, September 12, 2002 http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3892t1-03.pdf.

12. Blood Products Advisory Committee, 89th Meeting, April 26-27, 2007 http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4300M.pdf.

13. Leiby, D. A., R. M. Herron, Jr., E. J. Read, B. A. Lenes and R. J. Stumpf (2002). "*Trypanosoma cruzi* in Los Angeles and Miami blood donors: impact of evolving donor demographics on seroprevalence and implications for transfusion transmission." Transfusion 42(5): 549-55.

14. Strong, D. M. and K. Shoos-Lipton (2006). "Information Concerning Implementation of a Licensed Test for Antibodies to *Trypanosoma cruzi*." AABB Bulletin #06-08.

15. Saulnier Sholler, G. L., S. Kalkunte, C. Greenlaw, K. McCarten and E. Forman (2006). "Antitumor activity of nifurtimox observed in a patient with neuroblastoma." J Pediatr Hematol Oncol 28(10): 693-5.

16. Young, C., P. Losikoff, A. Chawla, L. Glasser and E. Forman (2007). "Transfusion-acquired *Trypanosoma cruzi* infection." Transfusion 47(3): 540-4.

17. Cimo, P. L., W. E. Luper and M. A. Scouros (1993). "Transfusion-associated Chagas' disease in Texas: report of a case." Tex Med 89(12): 48-50.

18. Leiby, D. A., B. A. Lenes, M. A. Tibbals and M. T. Tames-Olmedo (1999). "Prospective evaluation of a patient with *Trypanosoma cruzi* infection transmitted by transfusion." N Engl J Med 341(16): 1237-9.

19. Lane, D. J., G. Sher, B. Ward, M. Ndao, D. Leiby, B. Hewlett and E. Bow (2000). "Investigation of the second case of transfusion transmitted Chagas disease in Canada." 42nd Annual Meeting of the American Society of Hematology, San Francisco, CA.

20. CDC. C.F. Zayas, C. Perlino, A. Caliendo, D. Jackson, E. J. Martinez, P. Tso, T. G. Heffron, J. L. Logan, B. L. Herwaldt, et.al. (2002). "Chagas disease after organ transplantation--United States, 2001." MMWR Morb Mortal Wkly Rep 51(10): 210-2.

21. CDC. L. Mascola, B. Kubak, S. Radhakrishna, T. Mone, R. Hunter, D. A. Leiby, M. Kuehnert, A. Moore, F. Steurer, G. Lawrence and H. Kun (2006). "Chagas disease after organ transplantation--Los Angeles, California, 2006." MMWR Morb Mortal Wkly Rep 55(29): 798-800.

22. Leiby, D. A., F. J. Rentas, K. E. Nelson, V. A. Stambolis, P. M. Ness, C. Parnis, H. A. McAllister, Jr., D. H. Yawn, R. J. Stumpf and L. V. Kirchhoff (2000). "Evidence of *Trypanosoma cruzi* infection (Chagas' disease) among patients undergoing cardiac surgery." Circulation 102(24): 2978-82.

23. Leiby, D. A., E. J. Read, B. A. Lenes, A. J. Yund, R. J. Stumpf, L. V. Kirchhoff and R. Y. Dodd (1997). "Seroepidemiology of *Trypanosoma cruzi*, etiologic agent of Chagas' disease, in US blood donors." J Infect Dis 176(4): 1047-52.

24. Kirchhoff, L. V., P. Paredes, A. Lomelí-Guerrero, M. Paredes-Espinoza, C. S. Roni-Guerrero, M. Delgado-Mejia and J. G. Peña-Muñoz (2006). "Transfusion-associated Chagas disease (American trypanosomiasis) in Mexico: implications for transfusion medicine in the United States." Transfusion 46(2): 298-304.

25. Schmunis, G. A. (1999). "Prevention of transfusional Trypanosoma cruzi infection in Latin America." Mem Inst Oswaldo Cruz 94 (Suppl 1): 93-101).

26. Bern, C., S. P. Montgomery, L. Katz, S. Caglioti and S. L. Stramer (2008). "Chagas disease and the US blood supply." Curr Op Infect Dis 21:476–482.

27. Ben Younès-Chennoufi, A., M. Hontebeyrie-Joskowicz, V. Tricottet, H. Eisen, M. Reynes and G. Said (1988). "Persistence of *Trypanosoma cruzi* antigens in the inflammatory lesions of chronically infected mice." Trans R Soc Trop Med Hyg 82 (1): 77-83.

28. Buckner, F. S., A. J. Wilson and W. C. Van Voorhis (1999). "Detection of live *Trypanosoma cruzi* in tissues of infected mice by using histochemical stain for ß-galactosidase." Infect Immun 67(1): 403-9.

29. Morocoima, A., M. Rodriguez, L. Herrera and S. Urdaneta-Morales (2006). "*Trypanosoma cruzi*: experimental parasitism of bone and cartilage." Parasitol Res 99(6): 663-8.

30. Herrera, L., C. Martínez, H. Carrasco, A. M. Jansen and S. Urdaneta-Morales (2007). "Cornea as a tissue reservoir of *Trypanosoma cruzi*." Parasitol Res 100(6): 1395-9.

31. Shippey, S. H., 3rd, C. M. Zahn, M. M. Cisar, T. J. Wu and A. J. Satin (2005). "Use of the placental perfusion model to evaluate transplacental passage of *Trypanosoma cruzi*." Am J Obstet Gynecol 192(2): 586-91.

32. CDC. S. L. Stramer, R. Y. Dodd, D. A. Leiby, R. M. Herron,L. Mascola, L. J. Rosenberg, S. Caglioti, E. Lawaczeck, R. H. Sunenshine, M. J. Kuehnert, S. Montgomery, C. Bern, A. Moore, B. Herwaldt, H. Kun and J. R. Verani (2007). "Blood donor screening for Chagas disease--United States, 2006-2007." MMWR Morb Mortal Wkly Rep 56(7): 141-3.

33. Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments, October 2006, http://www.fda.gov/cber/gdlns/devbld.htm.