Monday: Parallel Sessions S1 - Pathogen Reduction/ Inactivation

2A-S01-01

PATHOGEN REDUCTION: AN AMERICAN VIEW

Klein H
NIH, Bethesda, MD, USA

Blood transfusion is extremely safe in the United States. The risks of known viral infections are now so low that they must be calculated from donor data rather than measured directly. Nevertheless, measures for interdicting bacterial contamination remain imperfect, a variety of known pathogens, including viruses and parasites, are not screened out of the blood supply, and the risk of emerging infections transmitted by blood remains a concern of the public, the regulatory agencies, and the medical establishment. Following the HIV epidemic of the early 1980's, the plasma fractionation industry adopted pathogen reduction technology and has improved the process continuously; no transmission of major pathogens has since been reported when proper validated plasma fraction production has been performed, and transmission of some newly recognized agents, such as West Nile virus has been prevented. The blood collection services and the regulatory agencies have remained wedded to the reactive strategy of surveillance, screening, and testing as an approach to new infectious threats. The result has been an accepted disease burden prior to introduction of screening methods and a continued loss of blood donors. Barriers to adopting pathogen reduction technology include concerns about product safety, reduced therapeutic dose, absence of a single technique to treat all blood components, recognition that no technology inactivates all pathogens, and the added cost and complexity of the inactivation process. In January 2008, the Advisory Committee on Blood Safety and Availability recommended to the US Secretary of Health and Human Services that the potential benefits of pathogen reduction warrant a commitment and concerted effort to add this technology as a broadly applicable safeguard to the nation's blood supply. Pathogen reduction was seen as a pro-active and pre-emptive strategy to address the residual risk of known agents and to prevent emerging agents from becoming transfusion risks. The Committee recognized that to achieve this goal, govenment, industry, blood organizations, and public stakeholders must work in concert to commit the required financial and technical resources.

2A-S01-02

EUROPEAN VIEW ABOUT PATHOGEN INACTIVATION IN LABILE BLOOD PRODUCTS

Cazenave JP
EFS-Alsace, Strasbourg, France

Increased safety and efficiency of blood, blood components and drugs derived from plasma remain a major concern. Blood transfusion in Europe is tightly regulated. The demand for blood has continually increased as health care and life expectancy have increased. The safety of labile blood products [red blood cell concentrates (RBCC), platelet concentrates (PC) and plasma] is currently ensured by medical and biological donor selection measures. Nonetheless, in addition to the residual risk of viral, bacterial and parasitic infection, there is the emerging danger associated with new viruses. PI based on chemical or photochemical genomic modifications is a broad-spectrum and pro-active approach. A number of PI techniques have been use with success to inactivate plasma derived products. The solvent-detergent (SD) and the methylene blue (MB) methods are used in many countries in Europe, increasing the safety of the products and without side effects. Unfortunately, SD and PI technologies cannot be applied to RBCC and PC. New PI methods, amotosalen (Intercept, Cerus) and riboflavin (Mirasol, Gambro) have received CE marking and are being implemented in Europe. A PI process (Mirasol PRT, Gambro) is being developed for PC, plasma and possibly RBCC, using riboflavin, UV and visible light. The procedure inactivates a wide range of pathogens. Toxicity is reduced. A phase III clinical study to evaluate the efficacy and safety of Mirasol PC in thrombocytopenic patients is to be reported. Amotosalen hydrochloride and UVA (Intercept, Cerus) inactivate a broad spectrum of pathogens in PC and plasma. Intercept PC (both apheresis and buffy-coat derived) have been implemented in several centres in Europe (more than 15, 000 units transfused). In France Intercept PC have been implemented during an epidemic of Chikungunya virus in the Ile de la Réunion in 2006 and in EFS-Martinique and EFS-Guadeloupe-Guyane in 2007 (dengue and Chagas disease). EFS-Alsace, a pilot region, has introduced Intercept PI for PC (40% apheresis and 60% buffy coat derived PC, about 15 000 units/year) in May 2006 and Intercept PI for plasma (about 15 000 units/year) in July 2007. The distribution of both products is universal to patients. As of January 2008 more than 22 000 Intercept PC and 8,000 Intercept plasma have been transfused. For all patients, clinical haemostasis provided by Intercept PC is equivalent (same platelet dose) to conventional non treated PC and transfusion adverse reactions are reduced by about 50%. Intercept plasma has been used for current indications with equivalent effects as quarantine plasma. Inactivation of RBCC is a major undertaking. The use of FRALE S-303 (Cerus) is in the more advanced stage of development. In 2007, the Consensus Conference of Toronto concluded with statements that will guide the ultimate implementation of PI for all labile blood products: (1) active surveillance cannot account for the risk of an emerging transfusion-transmitted pathogen; (2) such risks require a proactive approach; (3) PI should be implemented when feasible and safe methods are available; and (4) costs and benefits should be assessed. Universal inactivation of all labile blood products should be possible in future.

2A-S01-03

A RANDOMIZED, CONTROLLED, 2-PERIOD CROSSOVER STUDY OF RECOVERY AND LIFESPAN OF RADIOLABELED AUTOLOGOUS 35-DAY-OLD RED BLOOD CELLS PREPARED WITH A MODIFIED S-303 TREATMENT FOR PATHOGEN INACTIVATION

Cancelas JA[1], Dumont L[2], Herschel L[2], Roger J[2], Rugg N[1], Garratty G[3], Arndt P[3], Propst M[4], Laurence L[4], Sundin D[4], AuBuchon J[2]
[1]University of Cincinnati, Cincinnati, USA [2]Dartmouth-Hitchcock Medical Center, Lebanon, USA [3]American Red Cross Blood Services, Pomona, USA [4]Cerus Corporation, Concord, USA

Background: The S-303 Treatment System for Red Blood Cell concentrates (RBC) developed by Cerus Corporation uses S-303, a frangible anchor-linker-effector compound, to irreversibly inactivate contaminating bacteria, viruses, protozoa, and leukocytes. Following observations of antibodies specific for S-303 treated RBCs in a Phase three trial the treatment process was modified to reduce S 303 binding to treated RBCs.
Aims: The present study was conducted to evaluate recovery/lifespan of 35-day old autologous RBCs prepared with the modified S-303 process.
Study Design: This was a proof-of-concept, radiolabeled, crossover Phase I study conducted in 28 healthy subjects (10 male, 18 female). The study was divided into three periods: screening and enrollment, Treatment Period 1, and Treatment Period 2. In each treatment period, subjects underwent autologous blood donation on Day 0 and infusion of double-label (51Cr/99mTc) autologous RBCs on Day 35. All whole blood units were processed into AS-3 solution, and leukocyte reduced. In random sequence, one unit (Test) from each subject was treated with the modified pathogen inactivation process (0.2 mM S-303 and 20 mM GSH) and stored at 4°C for 35 day. The other unit (Control) was prepared as conventional RBC and stored at 4°C for 35 day. Following infusion, blood samples were obtained over a 24 hour period (for single and double radio-isotope determinations of post-transfusion recovery). Additional samples were collected for 35 day post-infusion to determine lifespan. Biochemical assessments of study units (e.g. ATP, 2,3-DPG, PCV) were performed on days 0 and 35 of storage. Crossmatch reactivity to S303 treated RBC was conducted during the study using conventional gel cards.

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医薬部外品　　研究報告　調査報告書
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識別番号・報告回数			報告日	第一報入手日 2008年8月27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乾燥抗HBs人免疫グロブリン ②ポリエチレングリコール処理抗HBs人免疫グロブリン	研究報告の公表状況	ProMED/20080826.2660	公表国 中国
販売名 （企業名）	①ヘブスブリン（ベネシス） ②静注用ヘブスブリンーIH（ベネシス）			

研究報告の概要

中国の新しい研究が、狂犬病感染が劇的に急増していることを報告した。この報告によると、中国のいくつかの省においてヒトの狂犬病の症例数が、2000年以降急に跳ね上がったという。
報告者らが調査したのは、中国保健省のサーベイランス・データベースから得た、1990年1月から2007年7月までの22,527のヒト狂犬病症例のデータである。報告者らは、ヒトの狂犬病は1990-1996年に下火になり、このときはわずか159の症例が報告されただけであったが、この数字は、2006年に3,279症例に跳ね上がったことを見出した。
さらに、狂犬病に遭遇する頻度が多いのは、中国の南西部および南部の省、特に人口密度の高い地域であることを見出した。
報告者の1人は、「狂犬病流行のこの4つの省では、イヌの狂犬病を排除する厳しい強制的措置が欠けているか、またはヒトへ投与する最新技術による細胞培養の狂犬病ワクチンがないのです」と述べた。報告者らによると、最も影響が大きかった広東省では、患者の62.5%が、受けた傷への適切な治療を受けておらず、92.5%が曝露後に十分なワクチン接種を受けていなかったという。また91.25%が抗狂犬病免疫グロブリンの投与を受けなかった。
この報告者らは、現在の狂犬病の管理プログラムを、監督を強化することによって改善し、これによって地方と政府との人的交流を改善し、狂犬病への意識を高め、都市の計画立案と開発を変更してヒトと動物とのふれ合いのバランスを図るべきであると勧告している。
（本研究はin pressであり、'Rabies trend in China (1990-2007) and post-exposure prophylaxis in the Guangdong province'と題され、BMC Infectious Diseasesに掲載される予定である。）

使用上の注意記載状況・その他参考事項等

代表として静注用ヘブスブリンーIH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血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2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高力価の抗HBs抗体を含有する血漿を原料として、Cohnの低温エタノール分画で得た画分からポリエチレングリコール4000処理、DEAEセファデックス処理等により抗HBs人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びろ過膜処理（ナノフィルトレーション）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。

報告企業の意見	今後の対応
中国における狂犬病が2006年に急増したとの報告である。 血漿分画製剤からの狂犬病ウイルス伝播の事例は報告されていない。また、万一原料血漿に狂犬病ウイルスが混入したとしても、BVDをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・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。

39

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Subject PRO/AH/EDR> Rabies - China: increased incidence

RABIES - CHINA: INCREASED INCIDENCE
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ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Date: Fri 22 Aug 2008
Source: Science Daily [edited]
<http://www.sciencedaily.com/releases/2008/08/080820194839.htm>

A new Chinese study has reported a dramatic spike in rabies infections. The research shows that in some provinces of China the number of human rabies cases has jumped since the new millennium.

Jia-Hai Lu, from the School of Public Health at Sun Yat-Sen University, China, led a team of researchers who studied the rabies trend in China between 1990 and 2007. Lu describes how things have changed in the last 8 years: "In China, human rabies was largely under control during the years 1990-1996, via nation-wide rabies vaccination programmes. Since the end of the century, however, cases of human rabies have jumped high enough to trigger a warning sign for control and prevention."

Rabies, an infection of the nervous system transmitted by animal bites, causes over 50 000 deaths each year around the world. During recent years, most of the research on control of rabies has concentrated on the development of post-exposure prophylaxis (preventative treatment — in this case, preventing the worsening of an infection). According to the researchers, "The use of human and equine rabies immunoglobulins (HRIG/ERIG) has saved the lives of countless patients who would have died if treated with vaccine alone. However, both products are often in short supply worldwide and are virtually unaffordable in developing countries." [See ProMED post 20080826.2659 Announcements (03): Rabies vaccine supply limited - USA (CDC)].

Data from 22 527 human rabies cases from January 1990 to July 2007 were obtained from a surveillance database from the Ministry of Health of China. The authors found that human rabies was under control from 1990 to 1996, when only 159 cases of rabies were reported, but this figure had leapt to 3279 cases in 2006.

The authors found that rabies was most frequently encountered in the southwestern and southern territories of China, especially in highly populated areas. Lu said, "The 4 rabies-endemic provinces lacked strictly enforced measures to eliminate dog rabies or an ample supply

of modern cell culture rabies vaccines for humans." Most of the patients were children or teenagers, and most contracted the disease after being bitten by a dog, usually on the head and neck. According to the authors, "In the worst-affected province, Guangdong, 62.5 percent of patients did not receive proper treatment on their wounds, 92.5 percent did not receive adequate post-exposure vaccination, and 91.25 percent did not receive any anti-rabies immunoglobulin."

The authors recommend that the current rabies control programme be improved by increasing supervision, improving the interaction between local and national authorities, increasing rabies awareness, and altering urban planning and development to balance the interaction between humans and animals.

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Adapted from materials provided by BMC Infectious Diseases (<http://www.biomedcentral.com/bmcinfectdis/>) via EurekAlert!, a service of AAAS (<http://www.eurekalert.org>).

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Communicated by:
Shamsudeen Fagbo, DVM
<oloungbo@yahoo.com>

[It is useful to read the full article, not so much for the summary of incidence trends or methods but to fully appreciate the application of potential control mechanisms. The authors emphasize the need for improved availability and timely application of anti-rabies biologicals and the undertaking of dog vaccination programs for the control of rabies in dogs as critical elements for success in reducing the rate of occurrence of rabies in China. Such strategies have worked in other countries around the world and have even previously worked in China in the 1990s. The failure of effective dog vaccination programs in China is a step back.

CDC's (US Centers for Disease Control and Prevention) Advisory Council on the subject agrees with the importance of vaccination in dogs in the following introduction:

"As a result of improved canine vaccination programs and stray animal control, a marked decrease in domestic animal rabies cases in the United States occurred after World War II. This decline led to a substantial decrease in indigenously acquired rabies among humans. In 1946, a total of 8384 indigenous rabies cases were reported among dogs and 33 cases in humans. In 2006, a total of 79 cases of rabies were reported in domestic dogs, none of which was attributed to enzootic dog-to-dog transmission, and 3 cases were reported in

humans. The infectious sources of the 79 cases in dogs were wildlife reservoirs or dogs that were translocated from localities where canine rabies virus variants still circulate. None of the 2006 human rabies cases was acquired from indigenous domestic animals. Thus, the likelihood of human exposure to a rabid domestic animal in the United States has decreased substantially."

See "Human Rabies Prevention – United States, 2008, Recommendations of the Advisory Committee on Immunization Practices" at <http://www.cdc.gov/mmwr/pdf/rr/rr57e507.pdf>.

WHO's introduction to their section on rabies from the "WHO recommended standards and strategies for surveillance, prevention, and control of communicable diseases" includes 3 main control strategies: post-exposure prophylaxis, pre-exposure immunization in high risk groups, and control of the disease in dogs.

WHO provides further information in the introduction as follows:
"Rabies is a vaccine-preventable disease, and it is still a significant public health problem in many countries of Asia and Africa, even though safe, effective vaccines for both human and veterinary use exist. Most of the 55 000 deaths from rabies reported annually around the world occur in Asia and Africa, and most of the victims are children: 30–50 percent of the reported cases of rabies — and therefore deaths — occur in children under 15 years of age. The main route of transmission is the bite of rabid dogs. Most of the children who die from rabies were not treated or did not receive adequate post-exposure treatment. Although the efficacy and safety of modern cell culture vaccines have been recognized, some Asian countries still produce and use nervous tissue vaccines, which are less effective, require repeated visits to the hospital, and often have severe side-effects. Moreover, these patients do not receive the necessary rabies immunoglobulin, because of a perennial global shortage and because of its high price, so that it is unaffordable in countries where canine rabies is endemic.

"Due to complete absence of any successful medical treatment for clinical rabies and the horrific nature of the disease, most rabies victims die at home rather than being admitted to a hospital in abysmal conditions. These circumstances add to the notorious lack of surveillance data. Underestimating the health implications of rabies leads many high ranking decision-makers in public health and animal health to perceive rabies as a rare disease of humans resulting from a bite of an economically unimportant animal (the dog). Therefore, rabies usually falls between 2 stools and is not dealt with appropriately either by the Ministry of Health or the Ministry of Agriculture."
See "Human and Animal Rabies" at <http://www.who.int/rabies/en/>. – Mod.PC]

[see also:
Rabies, canine – China: compulsory vaccination 20080120.0254
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.....pc/mj/jw

別紙様式第2-1

No. 14

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	機構処理欄
				2008. 7. 3	該当なし	

一般的名称	(製造販売承認書に記載なし)	研究報告の公表状況	Dujardin JC, Campino L, Cañavate C, Dedet JP, Gradoni L, Soteriadou K, Mazeris A, Ozbel Y, Boelaert M. Emerg Infect Dis. 2008 Jul;14(7):1013-8.	公表国
販売名(企業名)	合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)			ヨーロッパ

研究報告の概要

○ヨーロッパにおける生物媒介性疾患の拡大とリーシュマニア症に対する軽視(ネグレクト)

リーシュマニア症は南ヨーロッパ各国に定着しており、毎年700例近く、トルコを含めると3,950例の地域内感染症例が報告される。

ヒトでのリーシュマニア症の発現率は100,000人当り0.02～0.49(トルコを含むと8.53/100,000)である。無症候症例は、臨床症例1例に対して30～100例程度発生すると見られている。これは、血液事業に重大な影響を及ぼす可能性がある。南フランスとギリシャの流行地域に住む供血者由来の血液の血清陽性率は、それぞれ3.4%、15%であった。スペインの高流行地域の供血者の22.1%は、PCR法でリーシュマニア症陽性であった。また、無症候感染は、エイズ患者などの免疫不全者で重度の臨床型に進行する場合がある。飼い犬のリーシュマニア症血清陽性率は最高25%と推定されている。薬剤耐性*L. infantum*は、イヌを介してヨーロッパ国外に輸出されるかもしれない。

薬剤耐性の出現などの問題があるにもかかわらず、全ヨーロッパレベルでの協調的な疾患調査は行われていない。リーシュマニア症は、睡眠病やシャーガス病などと同様に、発展途上国で最も軽視された疾患の1つであり、有効で安価で使用簡便な薬剤の開発、調査や対策は行われてこなかった。この主な理由の1つには、リーシュマニア症が発展途上国の貧しい者の疾患であるということがある。

2001年以降、複数の研究チームが欧州—地中海諸国から科学者を集め、リーシュマニア症研究者のネットワークが形成された。今後研究者は、基礎研究を進めると共に、結果を発表することで政策決定に影響を与え、生物媒介性疾患の1つとして対策が行われるよう働きかけなくてはならない。

報告企業の意見	今後の対応
リーシュマニア症は南ヨーロッパ各国に定着しており、毎年700例近くの症例が報告されているが、全ヨーロッパレベルでの調査や対策が行われていないとの報告である。リーシュマニア症をはじめとするダニ媒介性疾患の対策は難しく、流行状況に注意が必要である。	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。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とともに、ヨーロッパにおける輸血感染症の動向等に注意する。

使用上の注意記載状況・その他参考事項等

合成血-LR「日赤」
照射合成血-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

Spread of Vector-borne Diseases and Neglect of Leishmaniasis, Europe

Jean-Claude Dujardin,* Lenea Campino,† Carmen Cañavate,‡ Jean-Pierre Dedet,§ Luigi Gradoni,¶ Ketty Soteriadou,# Apostolos Mazeris,** Yusuf Ozbel,†† and Marleen Boelaert*

The risk for reintroduction of some exotic vector-borne diseases in Europe has become a hot topic, while the reality of others is neglected at the public health policy level. Leishmaniasis is endemic in all southern countries of Europe, with ≈700 autochthonous human cases reported each year (3,950 if Turkey is included). Asymptomatic cases have been estimated at 30–100/1 symptomatic case, and leishmaniasis has up to 25% seroprevalence in domestic dogs. Even though leishmaniasis is essentially associated with *Leishmania infantum* and visceral leishmaniasis, new species, such as *L. donovani* and *L. tropica*, might colonize European sand fly vectors. Drug-resistant *L. infantum* strains might be exported outside Europe through dogs. Despite this possibility, no coordinated surveillance of the disease exists at the European level. In this review of leishmaniasis importance in Europe, we would like to bridge the gap between research and surveillance and control.

In August through September of 2007, a chikungunya outbreak occurred in the province of Ravenna, Italy (*1*). The risk for reintroduction of vector-borne diseases in Europe as a consequence of global warming was highlighted, although long-distance tourism, travel, and trade could also play major roles in the transcontinental transport of microorganisms (*2*). The European Centre for Disease Control is currently assessing the magnitude and importance of vector-borne diseases in Europe, focusing on Lyme disease, tick-borne encephalitis, leptospirosis, malaria, plague, tularemia, viral hemorrhagic fevers, hantavirus, and West Nile fever. Concern about the impact of global warming and the spread of arthropod-borne diseases and other infectious agents in Europe is justifiable. However, existing autochthonous vector-borne infections should not be forgotten or ignored, which may be the case, as illustrated here for leishmaniasis.

*Instituut voor Tropische Geneeskunde, Antwerp, Belgium; †Instituto de Higiene e Medicina Tropical, Lisbon, Portugal; ‡Instituto de Salud Carlos III, Madrid, Spain; §Université Montpellier 1, Montpellier, France; ¶Istituto Superiore di Sanità, Rome, Italy; #Hellenic Pasteur Institute, Athens, Greece; **National Reference Laboratory for Animal Health, Nicosia, Cyprus; and ††Ege University Medical School, Bornova, Izmir, Turkey

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Leishmaniasis in Europe

Leishmaniasis is a major vector-borne disease, which is endemic to 88 countries and is the only tropical vector-borne disease that has been endemic to southern Europe for decades. In southern Europe, most of the reported cases are due to zoonotic visceral leishmaniasis (VL), which is the most dangerous form and is lethal when untreated. Cutaneous leishmaniasis (CL), which is more benign than VL, is also present. Incidence of leishmaniasis in humans is relatively low, ranging from 0.02/100,000 to 0.49/100,000 (8.53/100,000 including Turkey). We estimate that this corresponds to a total of ≈700 reported new cases per year for southern European countries (3,950 if Turkey is included; Table and Figure). However, autochthonous leishmaniasis appears not to be limited to the Mediterranean region anymore. It has spread northward, as shown by the recent reports of indigenous VL cases in northern Italy and southern Germany (*8*,*9*).

However, these numbers are misleading for several reasons. First, data from patients infected in southern Europe, but diagnosed elsewhere, are not taken into consideration. For instance, a leishmaniasis reference center established on a voluntary basis in Germany identified within 2 years 70 cases of leishmaniasis. Of the 27 VL case-patients, most

Table. Leishmaniasis situation in 7 disease-endemic countries of Europe (including Turkey)*

Country	Human leishmaniasis				Canine leishmaniasis
	Notification status	Current information from reference centers (2000–2006)	VL + CL incidence x 100,000†	Imported cases (VL + CL)	
Portugal‡	Compulsory for VL	≈22 VL cases/y recorded at IHMT	0.07–0.17	≈2 cases/y recorded at IHMT	Average 20% seroprevalence in disease-endemic areas (*3*)
Spain§	Compulsory in 12/17 autonomous communities; 20%–45% underreporting for VL, ≈100% for CL (*4*)	≈100 VL cases/y recorded by National Epidemiologic Surveillance Network, RENAVE	0.18–0.29	≈5 cases/y recorded at ISCIII	Average 8.5% seroprevalence (*5*)
France¶	Not compulsory, but spontaneous reports at UMON	≈24 VL + CL cases/y reported at UMON	0.02–0.19	≈65 cases/y recorded at UMON	Seroprevalence in disease-endemic areas of southern France 4%–20%#
Italy**	Compulsory for both VL and CL, but CL underreported	≈200 VL cases/y recorded at ISS; ≈300 CL cases/y estimated by ISS	0.15–0.38	≈8 cases/y recorded at ISS	Average 15% seroprevalence in peninsular Italy; average 2% seroprevalence in continental Italy (*6*)
Greece††	Compulsory for both VL and CL, but underreported	≈21 VL cases/y notified	0.06–0.49	Unknown	Average seroprevalence 25% in disease-endemic areas (*7*)
Cyprus‡‡	Compulsory for both VL and CL, but underreported	5 VL + CL cases recorded in 2006	0.25–0.47	Unknown	Average seroprevalence 20% in disease-endemic areas
Turkey§§	Compulsory for both VL and CL	≈37 VL cases/y and ≈2,300 CL cases/y notified	1.6–8.53	Unknown	Average 15.7% seroprevalence

*Authors' institutions are national reference laboratories for leishmaniasis diagnosis and surveillance and rely on consolidated countrywide networks of collaborating clinical health centers. Diagnosis records are cross-checked with case notifications to provide more realistic figures and estimates. VL, visceral leishmaniasis; CL, cutaneous Leishmaniasis; WHO, World Health Organization.
†WHO-EURO, WHO Europe, 1996–2005; http://data.euro.who.int/CISID.
‡Instituto de Higiene e Medicina Tropical (IHMT), Lisbon, Portugal.
§Instituto de Salud Carlos III (ISCIII), Madrid, Spain.
¶Université de Montpellier (UMON), data from Centre National de Référence des Leishmania, Montpellier, France.
#Source: retrospective canine leishmaniasis database, Centre National de Référence des Leishmania.
**Istituto Superiore di Sanità (ISS), Rome, Italy.
††Hellenic Pasteur Institute (HPI), Athens, Greece.
‡‡National Reference Laboratory for Animal Health (VS), Nicosia, Cyprus.
§§Ege University (EUMS-DP), Izmir, Turkey.

(17) had been infected within European Union boundaries: Spain, Portugal, Greece, or France (*10*). Five cases were in children. Similarly, a retrospective study in the Hospital for Tropical Diseases in London showed that most of the imported VL case-patients in the United Kingdom were adult men touring the Mediterranean (*11*). Second, in the absence of public health surveillance at the European level, underreporting is common (see the Leishmaniasis and the Globalization of Neglect section). Third, asymptomatic infections may be common in some regions: for 1 clinical case of VL, there may be 30–100 subclinical infections (*12*). This underreporting can have major consequences for blood banks: blood from donors living in areas of endemicity in southern France and Greece had 3.4% and 15% seropositivity, respectively (*13,14*). In addition, 22.1% of blood donors in a highly disease-endemic area from Spain were PCR positive for leishmaniasis (*15*). Furthermore, asymptomatic infections may progress to severe clinical forms in immunocompromised persons, for example, in AIDS patients (*16*). Fourth, the etiologic agent of southern European VL, *Leishmania infantum*, is also infecting dogs (with a seroprevalence of up to 34% in areas of Spain where the disease is highly endemic) (Table). Dogs with leishmaniasis infections are generally very sick, causing a major problem in southern Europe (e.g., ≈5,000 clinical cases occur each year in France) (Table). However, sick as well as asymptomatic dogs also represent a risk for humans, as they constitute the major reservoir of the parasite on which sand fly vectors may feed and transmit the infection.

Import–Export Balance of European Leishmaniasis

In addition to the reality of autochthonous leishmaniasis in Europe, the risk for introduction of new species through travelers or immigrants from countries where

non-European species are endemic should also be considered. However, the probability that these species could enter in a transmission cycle is relatively low. The probability depends on contact between infected persons and sand flies, the capacity of the infected person to act as reservoir, and the susceptibility of European sand flies to the different *Leishmania* species. For most species, humans are generally a transmission dead-end. However, for 2 species, the risk might theoretically be higher: *L. tropica*, which is causing CL in Africa, the Middle East, and Southwest Asia, and *L. donovani*, the etiologic agent of VL in East Africa and the Indian subcontinent. These 2 species are indeed associated with an anthroponotic transmission cycle. On one hand, *L. donovani*, which is transmitted by a different species of sand fly outside Europe, might be hosted by most European sand flies, except *Phlebotomus papatasi* and *P. sergenti* (*17*). On the other hand, *L. tropica*, which has more stringent requirements in terms of vector, would need *P. sergenti*, which was reported in several places in southern Europe, from Portugal (*18*) to Cyprus (*19*). *L. tropica* was indeed encountered in Greece (*20*), and according to a very recent report, the first autochthonous cases of *L. donovani* in Europe have been detected in Cyprus (*21*). The clinical phenotype associated with both species needs also to be considered for an exhaustive risk evaluation. *L. tropica* causes lesions that are generally more difficult to treat with antimonial drugs (*22*), whereas *L. donovani* is considered to be more aggressive than *L. infantum* and often does not respond to treatment with first-line drugs (*23*).

In addition to being concerned about importation and spread of exotic *Leishmania* species in Europe, exportation should also be considered. The best known historical example of the spread of leishmaniasis is the migration of *L. infantum* from Europe to Latin America, where it colonized in *Lutzomyia longipalpis* and is now causing a serious public health problem (>3,500 cases of VL per year in Brazil) (*24*). This spread is thought to have been caused by conquistadores' dogs (*25*). Another and current example concerns the *L. major/L. infantum* hybrids recently described in HIV-positive VL patients from Portugal (*26*). Indeed, these hybrids were shown to be able to develop in *P. papatasi* (*27*), a vector that is widespread in Europe, Africa, and Asia. Considering the reservoir role of HIV–coinfected patients and the peridomestic and anthropophilic nature of *P. papatasi*, these hybrid strains might circulate by using this sand fly vector, thereby increasing the risk of their spreading into new foci throughout the broad range of *P. papatasi* distribution (*27*). Finally, the way Europe deals with its leishmaniasis public and animal health problem can still have major consequences for the rest of the world. Miltefosine, one of the few available antileishmania drugs, has been recently launched in the market for canine leishmaniasis treatment in Portugal, Spain, Italy, Greece, and Cyprus. Because dogs are never cured parasitologically and given the long half-life of the drug, the lack of European policy might contribute to the emergence of parasites resistant to miltefosine. This resistance could be a problem for European human patients, as miltefosine is being used on a compassionate basis in several European AIDS coinfected patients unresponsive to amphotericin B or pentavalent antimonials (*28,29*). Furthermore, if dogs infected with miltefosine-resistant strains were to migrate to Latin America, where several countries have registered the drug for human use (currently Colombia, Guatemala, Argentina, Venezuela, Paraguay, Ecuador, and Honduras; *30*), the impact might be greater.

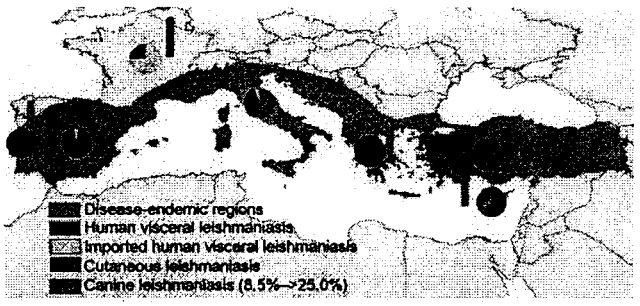

Figure. Leishmaniasis in southern Europe. Distribution of the endemic disease; relative proportion of autochthonous (visceral, cutaneous) and imported human cases and seroprevalence in dogs (from data reported in Table).

Leishmaniasis and the Globalization of Neglect

Twelve million persons have leishmaniasis, and 500,000 new cases of VL occur each year. More than 50,000 die of this disease each year. The disease is spreading because of several risk factors, climate being only one. Humanmade changes to the environment and population movements (for economic or political reasons) may lead to alterations in the range and densities of the vectors and reservoirs, increasing human exposure to infected sand flies. Urbanization of leishmaniasis becomes more common and in conjunction with the ruralization of HIV/AIDS, it contributes to increase the problem of co-infections in contexts where access to highly active antiretroviral therapy is not the same as in industrialized countries. *Leishmania* spp. have already become resistant to antimonial drugs (the first-line drug in many developing countries) in some regions and may soon become resistant to miltefosine (*23*). Despite this increasing resistance, leishmaniasis is one of the most neglected diseases in developing countries, along with others like sleeping sickness or Chagas disease. Leishmaniasis is a disease for which we lack effective, affordable, and easy to use drugs, and the pharmaceutical industry has had few incentives to engage