study we assessed the field test version of the new WHO JE surveillance standards. We applied the clinical case definition of acute encephalitis syndrome (AES), laboratory diagnostic criteria and case classifications to patients with suspected central nervous system (CNS) infections in southern Vietnam. 380 patients (149 children) with suspected CNS infections were recruited and evaluable, of whom 296 (96 children) met the AES case definition: 54 children were infected with JE virus (JEV), of whom 35 (65%) had AES, giving a sensitivity of 65% (95%CI 56-73%), and specificity 39% (30-48%). 9 adults with JEV all presented with AES. The 19 JEV-infected children missed by the surveillance included 10 with acute flaccid paralysis, 2 with a flaccid hemiparesis, and 6 with meningism only. Altering the case definition to include limb paralysis and meningism improved the sensitivity to 89% (83-95), whilst reducing the specificity to 23% (15-30). An acute serum sample diagnosed 41(68%) of 60 JEV positive patients; an admission CSF diagnosed 33(72%) of 46 patients with this sample, including 7 that were serum negative. Examining a 2nd sample at day 10 diagnosed 61 of 62 patients. 5 patients with neurological manifestations of dengue infection had JEV antibodies in serum, and would have been misdiagnosed had we not tested for dengue antibodies in parallel. In conclusion, the case definitions detected about two thirds of the children infected with JEV, missing those presenting with acute flaccid paralysis. A modified case definition which included acute paralysis and meningism detected nearly 90% of children. An acute CSF sample is more sensitive and specific than an acute serum sample. This formal evaluation of surveillance standards during their development provides an evidence base to support their recommendation, and should be encouraged for future WHO standards.

1043

EPIDEMIC CHIKUNGUNYA FEVER, INDIA AND INDIAN OCEAN, 2006: LABORATORY-BASED SURVEILLANCE FOR IMPORTED CASES, UNITED STATES

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Chikungunya virus (CHIKV) is a mosquito-borne alphavirus endemic to Africa and Asia. Chikungunya fever (CHIKF) is characterized by fever, rash, arthralgia, and sometimes arthritis; joint symptoms can be severe and prolonged. In 2005-2006, an unprecedented outbreak of CHIKF occurred on islands in the Indian Ocean and in India. Viremic travelers from epidemic areas could introduce CHIKV to the United States (U.S.) through infection of competent local mosquito species, including *Aedes aegypti* and *Aedes albopictus*, which are distributed throughout the southeastern U.S. and Hawaii. We investigated all cases of CHIKF among U.S.-bound travelers in 2006 that were confirmed at CDC. We searched the CDC Arboviral Diagnostic and Reference Laboratory's database for all patients with laboratory-confirmed CHIKF with onset in 2006, and abstracted demographic and travel information. Cases were confirmed using serology (IgM enzyme-linked immunosorbent assay and plaque reduction neutralization test), viral culture, and reverse transcriptase-PCR (RT-PCR). Thirty-eight people from 16 states and the District of Columbia had laboratory evidence of recent CHIKV infection. Their median age was 49 years (range, 22-78 years); 55% were female. India was the travel destination most frequently reported (87%), followed by Sri Lanka (11%), Réunion (3%) and Zimbabwe (3%). One person reported travel to both India and Sri Lanka. Evidence of recent infection was found by serology in 31 (82%), by viral culture and RT-PCR in 5 (13%), and by RT-PCR alone in 2 (5%). In contrast, only 3 cases of CHIKV infection among U.S.-bound travelers were diagnosed at CDC during the preceding 15-year period from 1991-2005. An unprecedented number of CHIKF cases were confirmed at CDC among travelers to the U.S. in 2006. The 5 culture-positive travelers, and others who might have had undetected viremia, posed a risk of introducing CHIKV into local mosquito populations. There was no evidence of local CHIKV transmission in the U.S. in 2006, but the potential for introducing CHIKV to the U.S. from areas with ongoing transmission still exists. Travelers to tropical areas of Asia and Africa should take precautions against mosquito bites. Travelers returning from epidemic or endemic areas with fever and joint symptoms should be tested for CHIKV infection, and positive cases reported promptly to local public health authorities.

O 1044

PERSISTENT SEROPREVALENCE OF *ANAPLASMA PHAGOCYTOPHILUM* IN NEW ENGLAND BLOOD DONORS

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The incidence of human granulocytic anaplasmosis (HGA) has doubled since 1999. The causative agent, *Anaplasma phagocytophilum*, is transmitted to humans primarily by the ixodid tick, *Ixodes scapularis*, endemic in New England. *A. phagocytophilum* causes an illness that ranges from asymptomatic to severe. There has been one reported case of transfusion-transmitted *A. phagocytophilum*, but blood donors are not currently screened for HGA. To determine the potential blood safety risk posed by this agent, we determined its seroprevalence in Connecticut (CT) and Massachusetts (MA) blood donors. Consenting CT and MA blood donors were enrolled in a comprehensive tick-borne disease study. Blood samples were collected during the late spring to early winter (2001-2005) and year round beginning in 2006. Serum collected from participating donors was tested for human IgG antibodies to *A. phagocytophilum* using an indirect immunofluorescent assay (IFA). A donor was considered positive if their IFA titer result was ≥ 1:64. Of 15, 828 donor sera tested by IFA, 432 (2.7%) were positive by IFA for *A. phagocytophilum* antibodies. The distribution of titers was as follows: 256 (59%) donors at 1:64, 115 (27%) at 1:128, 42 (9.7%) at 1:256, 14 (3.2%) at 1:512 and 5 (1.2%) at ≥1:1024. MA donors had a seroprevalence rate of 2.2% (30/1346), while the rate of CT donors was slightly higher, 2.8% (402/14,482). Seroprevalence peaks occurred in the following months: February (4.7%), December (3.7%) and September (3.4%). Overall, the seroprevalence data demonstrated variable yearly rates with a low of 1.7% in 2004 and a high of 4.1% in 2001. Observed fluctuations in yearly seroprevalence rates are likely the result of climactic and environmental factors that influence the complex lifecycle of *A. phagocytophilum*. The observed persistence of relatively high seroprevalence rates reinforces the need to examine the possible impact that *A. phagocytophilum* may have on blood safety. Limited transmission evidence to date may be attributable to the agent's short bacteremic phase, the effect of leukoreduction on this intra-granulocytic organism, or to transmission of primarily sub-clinical infection and resultant under-recognition.

(ACMCIP Abstract)

1045

FAILURE OF STANDARD BABESIOSIS THERAPY IN IMMUNOCOMPROMISED HOSTS

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別紙様式第2-1

No. 3

医薬品　研究報告　調査報告書

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研究報告の概要

○血液安全パネルはHHSに病原体低減技術の開発を急ぐよう要請
血液安全・安定供給諮問委員会は、米国保健社会福祉省（HHS）事務局に対し、安全で効果的な輸血用血液製剤の病原体低減技術（不活化）の早急な開発を優先して進め、開発され次第実施するよう勧告した。
委員会はまた、HHSに低減技術の開発とバリデーションの障害を取り除くための手段を提供するよう要請した。現在、スクリーニング検査にかかる費用とその複雑さは、血液の安全性の革新を妨げている。これは、製造販売業者の血液安全技術への積極的な投資継続に見合うようなビジネスモデルがないためである。
2008年1月9日と10日の会合では、「病原体低減の効果と安全性を示すエビデンスの蓄積は、今後蔓延する可能性のある感染症に対し広く適応できるセーフガードとして、この技術の導入を保証する」という決議を採択した。こうした新しい技術の例は、血漿分画製剤では世界的に使用され、血液成分製剤ではヨーロッパで導入されている病原体低減システムである。
委員会はこの勧告の根拠として、受血者への既知の感染症の脅威をより低減する必要性を挙げた。また、感染性因子の特定後にドナーの検査を導入するという現行の方式では、新たな病原体が特定される前に感染が拡大する可能性があると指摘した。病原体低減技術の費用は高額になると予想されるが、ガンマ線照射、白血球除去、細菌培養、マラリア予防のための渡航歴による供血制限など、導入後に不要となる現行の血液安全対策の削減によって相殺されると委員会は考えている。また、病原体低減技術の導入で、検査の偽陽性や精度の低い渡航歴による供血制限のためのドナー喪失が減るため、血液の供給量が増加すると推測している。

報告企業の意見	今後の対応
血液安全・安定供給諮問委員会は、米国保健社会福祉省事務局に対し、安全で効果的な輸血用血液製剤の病原体低減技術（不活化）の早急な開発を優先して進め、開発され次第実施するよう勧告したとの報告である。	日本赤十字社では8項目の安全対策の一つとして、不活化技術の導入について、各不活化技術の効果、血液成分への影響、製造作業への影響などについて評価検討を行っている。外国での不活化実施状況や効果、新たな技術、副作用等の情報収集も含め総合的に評価し、導入について関係機関と協議する予定である。

使用上の注意記載状況・その他参考事項等

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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

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Blood Safety Panel Urges HHS to Speed Development of Pathogen Reduction Technologies

The Advisory Committee on Blood Safety and Availability recommended this week that the secretary of the Department of Health and Human Services (HHS) give priority to the urgent development of safe and effective pathogen reduction technologies for blood transfusion products and implement them as they become available.

The panel also urged HHS to provide resources to overcome current barriers to the development and validation of such technologies. Currently, the cost and complexity of individual screening tests is itself becoming a barrier to further blood safety innovations because business models do not appear to favor manufacturers' continued aggressive investments in blood safety technologies

Meeting in Washington, DC, on Wednesday and Thursday, the panel approved a resolution asserting that "accumulating evidence for the efficacy and safety of pathogen reduction warrants a commitment and concerted effort to add this technology as a broadly applicable safeguard against potential emerging infectious diseases." Examples of such emerging technologies are pathogen reduction systems used worldwide for plasma derivatives and being introduced for cellular blood components in Europe.

> **The committee based its recommendation on the need to further reduce known infectious threats to transfusion recipients from infectious agents. The Committee also indicated that the current strategy of implementing donor testing after the identification of new infectious agents may allow widespread transmission of disease before a new agent is recognized.**

Although the cost of pathogen reduction technologies are expected to be high, the committee felt that they likely will be offset by the elimination of current blood safety interventions that would be rendered redundant. These might include gamma irradiation, leukoreduction, bacterial cultures, and travel deferrals for malaria. The Committee also suggested that pathogen reduction could increase the availability of blood by reducing donor loss due to false positive test results and low specificity travel deferrals.

The tone of the meeting was set by Chairman Arthur Bracey, MD, from the St. Luke's Episcopal Hospital, Houston, Texas, who asked speakers to discuss

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Quick Test for Staph (continued from page 11)

Staph infections most frequently occur in hospitals and healthcare facilities among patient with weakened immune systems. Distinguishing between the two sources of infection is critical to successful treatment. The more common, less dangerous strain of staph results in infections that are generally mild and affect the skin with pimples or boils that can be swollen, painful and drain pus.

However, the MRSA staph bacterium is difficult to treat with ordinary antibiotics and can cause potentially life-threatening conditions such as blood stream infections, surgical site infections or pneumonia.

FDA cleared the BD GeneOhm StaphSR assay based on the results of a clinical trial at five locations. The new assay identified 100 percent of the MRSA-positive specimens and more than 98 percent of the more common, less dangerous staph specimens.

The FDA cautions that the test should be used only in patients suspected of a staph infection. The test should not be used to monitor treatment for staph infections because it cannot quantify a patient's response to treatment. Test results should not be used as the sole basis for diagnosis as they may reflect the bacteria's presence in patients who have been successfully treated for staph infections. Also, t he test will not rule out other complicating conditions or infections. (Source: FDA press release, 1/2/08)♦

Pathogen Reduction Technologies (continued from page 1)

"how safe is safe," what are the needs, what are the barriers to achieve an acceptable level of transfusion and transplantation safety and what are the pathways to be considered?

Roger Dodd, PhD, from the American Red Cross' Holland Laboratories, emphasized the current safety of the blood supply and the low risk of transfusion when compared to other medical procedures. Dr. Dodd challenged the committee to consider whether members could find a framework for appropriate decision-making instead of continuing to seek a zero-risk blood supply.

Dr. Dodd was followed by Marc J. Roberts, PhD, from the Harvard School of Public Health, who presented a review of the ethics of blood safety. According to Dr. Roberts, it would be unethical to adopt every possible increase in protection regardless of cost because that would put lower-income individuals at significantly higher risk than higher income individuals.

Celso Bianco, MD, executive vice president of America's Blood Centers, reviewed the current landscape of blood donor screening assays in the context of FDA's "five layers of safety" for the blood supply. These are: medical history, donor deferrals, product testing, quarantine of unsuitable products, and monitoring of collecting facilities. Dr. Bianco noted that the only layer that clearly contributes to safety is testing. He expressed his concern, however, that further development of donor screening tests is being threatened by a lack of investment on the part of assay manufacturers because they find investment in other diagnostic areas and pharmaceuticals much more profitable. Dr. Bianco's point of view was reinforced by Brian McDonough, vice president of World Wide Marketing for Ortho Clinical Diagnostics, who noted that "the market attractiveness" of assays for cardiovascular and metabolic diseases and for oncology is much higher than the "no growth" market of blood donor screening.

David Leiby, PhD, from the Holland Laboratories, and Mark Brecher, MD, from the University of North Carolina showed the need for assays and procedures that address infections like babesia, and malaria, for which blood centers do not test,

(continued on page 13)

Pathogen Reduction Technologies (continued from page 12)

and bacteria, for which screening is not completely effective. David Asher, MD from the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) reviewed the current epidemiology of variant Creutzfeldt Jakob disease (vCJD) and the status of assays being developed to detect vCJD and other prion diseases. He said that none of the tests under development produce satisfactory results.

"The Ultimate Precuationary Principle." The meeting then moved to the concept of pathogen reduction with Harvey Alter, MD from the NIH Blood Bank making an impassionate plea for examination of currently available processes for pathogen reduction and investment in further developments.

"Pathogen reduction is the ultimate precautionary principle by eradicating almost all potential for infectious disease transmission even before risk has been conclusively established, and possibly, even before the agent has been recognized" Dr. Alter said.

Dr. Alter was followed by John Chapman, PhD vice president of Research and Development for Thermogenesis Corp., who said that after many years in the area of pathogen reduction for cellular blood products he believes that various available procedures have acceptable toxicity. This was confirmed by Margarethe Heiden, PhD, from the Paul Erlich Institute in Germany, who spelled out the agency's reasoning in granting a CE mark to the process developed by the Cerus Corporation and the approval by the German regulatory authorities.

Harvey Klein, MD, from the National Institutes of Health's Blood Bank, summarized the conclusions of the panel of the Canadian Consensus Conference on Pathogen Inactivation that took place in March 2007 in Toronto, Canada. Dr. Klein was the chairman of the panel. The summary has been published in the journals *Transfusion* and the proceedings in *Transfusion Medicine Reviews*.

Dr. Klein's was followed by presentations by Larry Corash, MD, from Cerus Corporation, Ray Goodrich, PhD, from Navigant, and Marc Maltas, from Octapharma, about their respective pathogen inactivation processes and clinical trial results.

Finally, Jaroslav Vostal, MD, from CBER, reviewed the current requirements for FDA approval of a pathogen reduction process and provided the detailed reasoning for FDA's refusal to approve the Cerus pathogen reduction process for platelets without submission of additional clinical data. ♦

BRIEFLY NOTED

Hospitals in Vermont are joining those in two other states that have officially formed policies to stop billing patients and insurance companies for certain adverse events. Two more states are considering similar policies as well. The Vermont Association of Hospitals and Health Systems said its policy will cover eight serious events based on the list of 28 so-called "never events" identified by the National Quality Forum as preventable-care errors. Vermont's policy includes: air embolism-associated injury; artificial insemination/wrong donor; incompatible blood-associated injury; medication error injury; retention of foreign object; wrong-patient surgery; wrong-site surgery; and wrong surgical procedure. The hospital association said it expects to complete implementation by the fall. The Minnesota and Massachusetts hospital associations both announced similar policies last year. Minnesota will stop billing for all 28 events, but does not have an implementation schedule in place. Massachusetts, which will stop billing for nine of the 28 events while assessing the others, expects to initiate its policy by the end of January. The Colorado Hospital Association and Michigan Health & Hospital Association are considering non-billing policies as well. (Source: *Modern Healthcare*, 1/6/08)

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医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙 3-7

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2007 年 12 月 5 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	Pathogen inactivation: a new paradigm for blood safety. Mc Cullough, J. Transfusion, 47, 2180-2184 (2007)	公表国 米国	
販売名（企業名）						

研究報告の概要

本論説は，血漿分画製剤業界における病原体不活化（PI）の新たな手法に焦点を当てた報告文献［BYL-2008-0306］と密接に関連している。本稿では，著者が病原体不活化に関するコンセンサス会議［BYL-2008-0306］で得られた結論を考察し，さらに展開している。過去 25 年間で血液の安全性については主要な改善が行われているものの，輸血伝播による感染を低減するための現在のアプローチ法にはいくつかの欠点がある。特に，新規病原体の脅威に対しては対応しきれていない。また，核酸標的薬剤を用いた特有の処理によって，多岐にわたる病原体が不活化されることが明らかになっているものの，この手法は現在ヨーロッパでは利用されているが北米では利用されていない。更に，PI は血液成分の絶対的な安全性を担保するものではないことも念頭に置いておく必要がある。結論として，利害関係者ら（規制当局，医師，血液バンク及び輸血医療業界）が長期的な展望に立って PI を検討し，北米での実施を著者は奨励している。

使用上の注意記載状況・その他参考事項等

BYL-2008-0305

報告企業の意見	今後の対応
著者らは，現在ヨーロッパで普及している PI を北米でも実施することを非常に推奨しており，それによる利点はリスクを上回ると確信している。 弊社のポリグロビン N の製造工程には，コーンの低温エタノール血漿分画法，限外ろ過，S/D 工程及び低 pH インキュベーション処理等の効果的なウイルスが除去・不活化工程が含まれている。	弊社の血漿分画製剤，及び遺伝子組換え製剤の製造工程で使用されている血漿分画製剤の原料が北米であることを考慮すると，本論説で推奨されている PI 法を導入することによって得られる血漿分画製剤の安全性について，検討する必要があると考えられる。

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