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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
西ナイルウイルス(WNV)は 1999 年に初めて合衆国に現われ、2002 年までにウイルスが輸血によって伝達されることが明確になったが、2003 年中頃、基本的にすべての献血は核酸増幅テスト(16 人ミニプール)で WNV RNA についてスクリーニングされた。 米国赤十字の 2003 年と 2004 年のルーチンテストの結果、WNV RNA が陽性の 540 の供血者の内、362 (67%)は IgM 抗体陰性で感染の可能性が最も高かった。 540 の陽性ドナーのうち、148 (27%)は個別テストでのみ検出可能で、148 のうち 15 (10%)は IgM 抗体陰性であった。 流行期間のにおける WNV RNA 陽性の供血者数は、2003 年は 1.49/10000 人、2004 年では 0.44/10000 人でした。2004 年における陽性供血の 52%は南カリフォルニアの 4 つの郡の供血者からであった。 核酸増幅テストを早く実施したことが、米国赤十字社の血液供給から WNV RNA 陽性であった 519 人の供血者の身元確認と、1000 以上の潜在的に感染性のある血液成分を除くことに貢献した。検査された血液の受血者では、WNV 感染は確認されていない。	

報告企業の意見	今後の対応
血漿分画製剤での WNV 感染伝播の報告はなく、製造工程中に WNV と同じフラビウイルスであるウシ下痢症ウイルス(BVDV)の不活化除去が確認された工程を設けているが、今後とも関連情報に注意していく。	今後とも WNV に関連する情報の収集に努めていく。

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West Nile Virus among Blood Donors in the United States, 2003 and 2004

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ABSTRACT

BACKGROUND

West Nile virus first appeared in the United States in 1999 and has since spread throughout the contiguous states, resulting in thousands of cases of disease. By 2002, it was clear that the virus could be transmitted by blood transfusion, and by the middle of 2003, essentially all blood donations were being tested for West Nile virus RNA with the use of investigational nucleic acid amplification tests; testing was performed on individual samples or on "minipools" of up to 16 donations.

METHODS

We analyzed data from the West Nile virus testing program of the American Red Cross for 2003 and 2004 to identify geographic and temporal trends. In areas with a high incidence of infection, individual donations were tested to increase the sensitivity of testing. Donors with reactive results participated in follow-up studies to confirm the original reactivity and to assess the natural history of infection.

RESULTS

Routine testing in 2003 and 2004 identified 540 donations that were positive for West Nile virus RNA, of which 362 (67 percent) were IgM-antibody–negative and most likely infectious. Of the 540 positive donations, 148 (27 percent) were detectable only by testing of individual donations, but only 15 of the 148 (10 percent) were negative for IgM antibody. The overall frequencies of RNA-positive donations during the epidemic periods were 1.49 per 10,000 donations in 2003 and 0.44 per 10,000 in 2004. In 2004, 52 percent of the positive donations were from donors in four counties in southern California.

CONCLUSIONS

Rapid implementation of a nucleic acid amplification test led to the prospective identification of 519 donors who were positive for West Nile virus RNA and the removal of more than 1000 potentially infectious related components from the blood supply of the Red Cross. No cases of transfusion-transmitted infection were confirmed among recipients of the tested blood.

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ALTHOUGH WEST NILE VIRUS WAS FIRST isolated in 1937 from a patient in Uganda,[1] it was not seen in the Western Hemisphere until 1999, when 62 cases of West Nile virus encephalitis were reported.[2,3] Biggerstaff and Petersen estimated that, during the peak of the 1999 outbreak in Queens, New York, the maximal and mean risks of transmission of West Nile virus by blood transfusion were 2.7 and 1.8 per 10,000 units, respectively.[4] In September 2002, the Centers for Disease Control and Prevention (CDC) announced that three of four recipients of transplanted organs from a single donor had acquired meningoencephalitis and were positive for West Nile virus. The fourth recipient was subsequently confirmed to have West Nile virus infection. The organ donor acquired West Nile virus infection through the transfusion of blood from 63 donors two days before organ harvest.[5,6] Subsequently, 23 cases of transfusion-transmitted West Nile virus infection were confirmed in 2002.[7] As a result, on September 20, 2002, major blood organizations, diagnostic companies, the CDC, the American Association of Blood Banks, and the Food and Drug Administration (FDA) agreed that blood-screening tests for West Nile virus RNA were needed by the 2003 season of West Nile virus infection. The FDA provided guidance for the assessment of donor suitability and the safety of blood and blood products in cases of known or suspected West Nile virus infection in October 2002,[8] with revisions in May 2003[9] and April 2005.[10]

In the United States, routine screening of blood donors for West Nile virus RNA started in the summer (June through August) of 2003. We describe the results of the American Red Cross program of laboratory testing in 2003 and 2004 and compare the yield in those years with the preclinical yield obtained in 2002.[11] The dynamics of viral replication, the serologic profiles of seroconverting donors, and the associated clinical symptoms in infected donors are reported in detail elsewhere.[12-14]

METHODS

SELECTION AND QUALIFICATION OF TEST KITS

In 2002, a total of 383 retrieved units of frozen plasma, including plasma corresponding to blood components transfused to 11 of the 23 patients with confirmed transfusion-transmitted infection,[7] were tested with the use of five different investigational and research-based assays for West Nile virus RNA and three research-based or FDA-cleared assays for viral IgM antibody.[15] On the basis of these studies, the Gen-Probe Procleix West Nile virus assay (Gen-Probe and Chiron) was deemed qualified for routine screening of blood donations involving "minipools" of 16 samples. In this test, West Nile virus–specific RNA is amplified by transcription-mediated amplification. Also on the basis of these studies, the qualitative and quantitative polymerase-chain-reaction (PCR) assays (National Genetics Institute) and IgM antibody test (Abbott Laboratories) were selected for use in confirmation and follow-up studies.

SAMPLE COLLECTION AND LABORATORY TESTING

Plasma samples to be screened for West Nile virus RNA were obtained from the collected Plasma-Preparation Tubes (Becton Dickinson) used for routine screening for human immunodeficiency virus type 1 (HIV-1) RNA and hepatitis C virus RNA.[16] Testing for West Nile virus was performed under an FDA-approved Investigational New Drug application. All studies were approved by the institutional review board of the American Red Cross.

Routine screening for West Nile virus RNA of minipools of plasma from 16 donations was implemented on June 23, 2003, and is ongoing at five American Red Cross laboratories. The testing process is identical to that used for routine screening of blood for HIV-1 and hepatitis C virus RNA.[16] Samples from reactive minipools were tested individually to determine which were reactive. Routine nucleic acid amplification testing of individual donations was substituted for minipool testing in areas in which reactive donations exceeded the defined threshold.[17] In 2003, nucleic acid amplification testing of individual donations was also retrospectively performed on samples collected in Nebraska that had been nonreactive on minipool testing to determine whether any reactive donations had gone undetected with the use of minipool testing.

All reactive samples and samples of the corresponding plasma components manufactured from the index donations were further tested for West Nile virus RNA by transcription-mediated amplification and PCR. Samples from the retrieved plasma components from donors with reactive samples on nucleic acid amplification testing in 2003 were tested for IgM antibodies to the virus. Manufacture of the Abbott IgM assay was discontinued in 2004; the use of another test was necessary. Thus, beginning

in 2004, FDA-cleared assays for West Nile virus IgM and IgG antibodies (Focus Diagnostics) were used.[18] Use of this IgM assay required multiplication of the cutoff value by a correction factor of 0.67 and coupling of the assay with the company's IgG assay so that sensitivity was similar to that of the Abbott IgM assay. Donations that were positive for West Nile virus RNA on minipool or individual nucleic acid amplification testing were considered to be confirmed if the index donation sample, retrieved plasma-component sample, or donor follow-up samples were reactive on repeated nucleic acid amplification testing (transcription-mediated amplification or PCR), were positive for West Nile virus–specific antibodies, or met both criteria. The viral loads (expressed as the number of copies of West Nile virus RNA per milliliter) of PCR-positive index or follow-up samples were determined. According to the manufacturers, the 50 percent detection rate of transcription-mediated amplification is 3 to 4 copies per milliliter, and the sensitivity of the qualitative PCR is 5 copies per milliliter; the sensitivity of quantitative PCR is 100 copies per milliliter.

APPROACH TO BLOOD DONORS, COMPONENTS, AND RECIPIENTS

Donors with either confirmed positive or false positive results on nucleic acid amplification tests for West Nile virus RNA were notified, and they were prevented from making further donations according to FDA guidelines.[8,9] Demographic information about these donors (including ZIP Code of residence, sex, and age and whether they were first-time or repeat donors) was collected for analysis. Donors with reactive specimens who provided written informed consent participated in the follow-up study by providing additional blood samples for repeated RNA and antibody testing.

On identification of an RNA-reactive donation, all components associated with the index donation were quarantined and the plasma unit was retrieved for further testing. We traced recipients of transfused components from confirmed positive index donations identified through retrospective nucleic acid amplification testing of individual donations in 2003.

STUDY DESIGN AND ANALYSIS

The authors are jointly responsible for the study design, the integrity and analysis of the data, and the content of the article. Data on nucleic acid amplification testing were collected and verified by an independent clinical-research organization (Medical Marketing Consultants).

RESULTS

PREVALENCE OF WEST NILE VIRUS AMONG BLOOD DONORS, 2002 THROUGH 2004

Studies conducted on samples collected in September 2002 from six areas with a high incidence of West Nile virus infection yielded a confirmed positive rate of 0.095 percent, or 1 in 1057 samples.[11] This rate, even late in the 2002 season, remained high and similar to the average risks of transfusion-transmitted West Nile virus infection estimated by the CDC for 2002 for the same metropolitan areas.[19] Table 1 shows the prevalence rates of West Nile virus infection in 2002 in comparison with the rates in 2003 and 2004.

Table 1. Results of Tests of Blood Donations for West Nile Virus.*

Individual NAT	Minipool NAT	IgM or IgG Antibody	Sept. 3–28, 2002 (N=48,620)†	June 29–Dec. 1, 2003 (N=2,935,249)	June 16–Oct. 16, 2004 (N=2,386,630)
			no. of confirmed positive samples		
+	–	–	0	10	5
+	+	–	16	283	64
+	+	+	0	36	9
+	–	+	30	107	26
	Total		46	436	104
			rate (no./10,000 donations)		
			9.46	1.49	0.44

* NAT denotes nucleic acid amplification test. Plus signs denote a positive result, and minus signs a negative result.
† Retrospective nucleic acid amplification testing was performed on frozen samples of individual donations from six high-incidence regions.[11]

In 2003, the first confirmed positive donation was identified on June 26 in Los Angeles from a donor who had returned from a trip to Colorado on the day before donation. The last positive donation was identified on December 1 in Georgia. Overall, 436 confirmed positive donations were identified from a total of 2,935,249 donations screened, for a rate of 0.015 percent, or 1 in 6732 (Table 1). Of these positive donations, 328 (75 percent) were collected from Kansas and Nebraska residents, for a combined rate of 0.68 percent, or 1 in 147, which was 45 times as high as the systemwide rate.

The first confirmed positive donor in 2004 was identified on June 16 in Phoenix, Arizona, and the last was identified on October 16 in Los Angeles. During this period, 104 confirmed positive donations were identified from a total of 2,386,630 screened, for a rate of 0.004 percent, or 1 in 22,948 (Table 1). Of these positive donations, 54 (52 percent) were identified from residents of four southern California counties (Los Angeles, Orange, Riverside, and San Bernardino), for a rate of 0.064 percent, or 1 in 1566, which was 16 times as high as the systemwide rate.

Figure 1 shows the frequency of confirmed positive donors identified in 2002, 2003, and 2004, according to week of donation. Although all positive donors in both 2003 and 2004 were identified between June and December, the peak season for 2003 was from mid-August to mid-September, whereas for 2004, the peak season started in late July and continued through late September, but at a lower frequency. The absence of any West Nile virus RNA–positive donations during the week before the initiation of prospective screening in 2003 (from retrospective testing of samples retained from the prior week that had been frozen) suggests that the onset of routine screening preceded the 2003 epidemic.

Our data indicate that the areas of highest incidence of confirmed positive donors moved westward from 2002 to 2004. The Cleveland and Detroit metropolitan areas had higher rates in September 2002 than at any time during 2003 and 2004. Kansas and Nebraska had higher rates in 2003 than in 2004, and southern California had the highest rates in 2004. These findings are in agreement with the pattern of clinical cases reported to the CDC.[20]

DEVELOPMENT OF THE TRIGGER FOR NUCLEIC ACID AMPLIFICATION TESTING OF INDIVIDUAL DONATIONS

On the basis of data obtained in 2002, we found that there was one potentially infectious (RNA-pos-

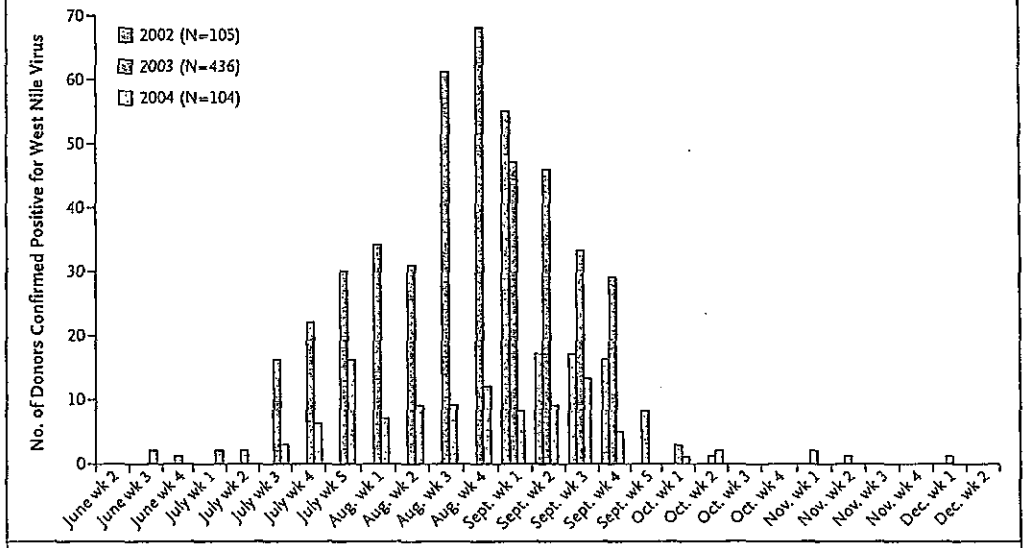

Figure 1. Numbers of U.S. Blood Donors Who Were Confirmed to Be Positive for West Nile Virus RNA in 2002, 2003, and 2004, According to the Week of Collection.

Data on 2002 totals are from Stramer et al.[11] The weekly totals for 2002 were adjusted for the number of donations tested during the four-week study.