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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 2003⁹ 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 writ-

ten 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.

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)
<i>no. of confirmed positive samples</i>					
+	–	–	0	10	5
+	+	–	16	283	64
+	+	+	0	36	9
+	–	+	30	107	26
Total			46	436	104
<i>rate (no./10,000 donations)</i>					
			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.

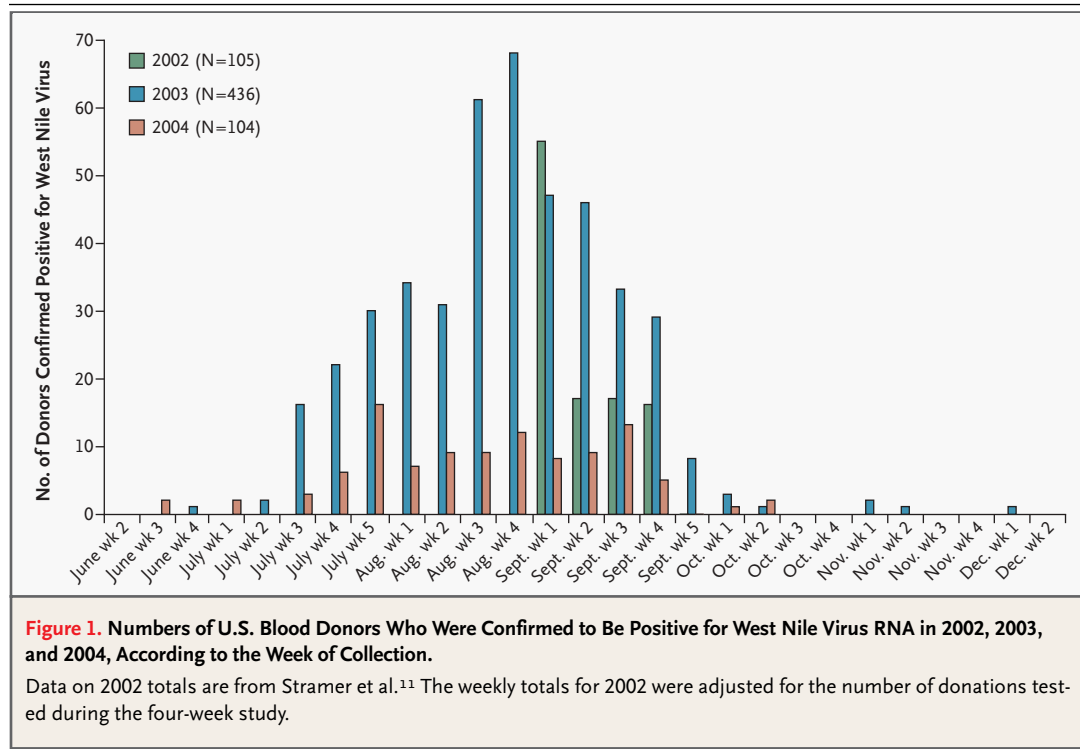
Figure 1 shows the frequency of confirmed positive donors identified in 2002, 2003, and 2004, according to week of donation. Although all positive

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-



itive, IgM-negative) sample detectable only by nucleic acid amplification testing of individual donations for every four such samples detected by minipool testing.¹¹ For 2003 and 2004, we therefore chose to initiate testing of individual donations in any blood-collection region after the identification of four RNA-positive donations and consequent calculation of a detection frequency of 1 in 1000 (the epidemic frequency documented in 2002^{11,19}), on the basis of the date of collection of the first reactive donation. Once nucleic acid amplification testing of individual donations had been initiated, a seven-day period with no RNA-reactive donations was required before a collection region could revert to the use of minipool testing.

NUCLEIC ACID AMPLIFICATION TESTING AND IgM AND IgG TESTING OF INDIVIDUAL DONATIONS

In 2003, 30,501 Red Cross donations from Kansas residents (August 19 to September 27) and Nebraska residents (August 25 to October 4) underwent individual nucleic acid amplification testing. Prospective testing identified 181 confirmed positive donations. Of these, 96 (53 percent) were nonreactive at a 1:16 dilution, of which 88 (92 percent) were IgM-positive and 8 (8 percent) were IgM-negative. In addition, as requested by the FDA, individual nucleic acid amplification testing was performed retrospectively on frozen samples from 18,049 donations collected from July 10 (the date of the first confirmed positive donation identified by minipool testing) to August 22 from donors who lived in Nebraska to determine whether donations that were nonreactive on minipool testing and had therefore been released for transfusion would be identified as reactive on testing of individual donations. This retrospective evaluation identified 21 additional confirmed positive donations: 19 were IgM-positive samples and 2 were IgM-negative samples. During the same period, minipool testing had previously identified 80 confirmed positive donations (or 79 percent of the total detected during this period): 7 were IgM-positive samples and 73 were IgM-negative samples.

Overall, 117 of the 436 confirmed positive donations identified in 2003 (27 percent) were detected only by individual nucleic acid amplification testing (although this may be an underestimate, since not all donations were tested by this method), and of these 117, 10 (9 percent) were IgM-negative (Table 1). Of the remaining 319 donations

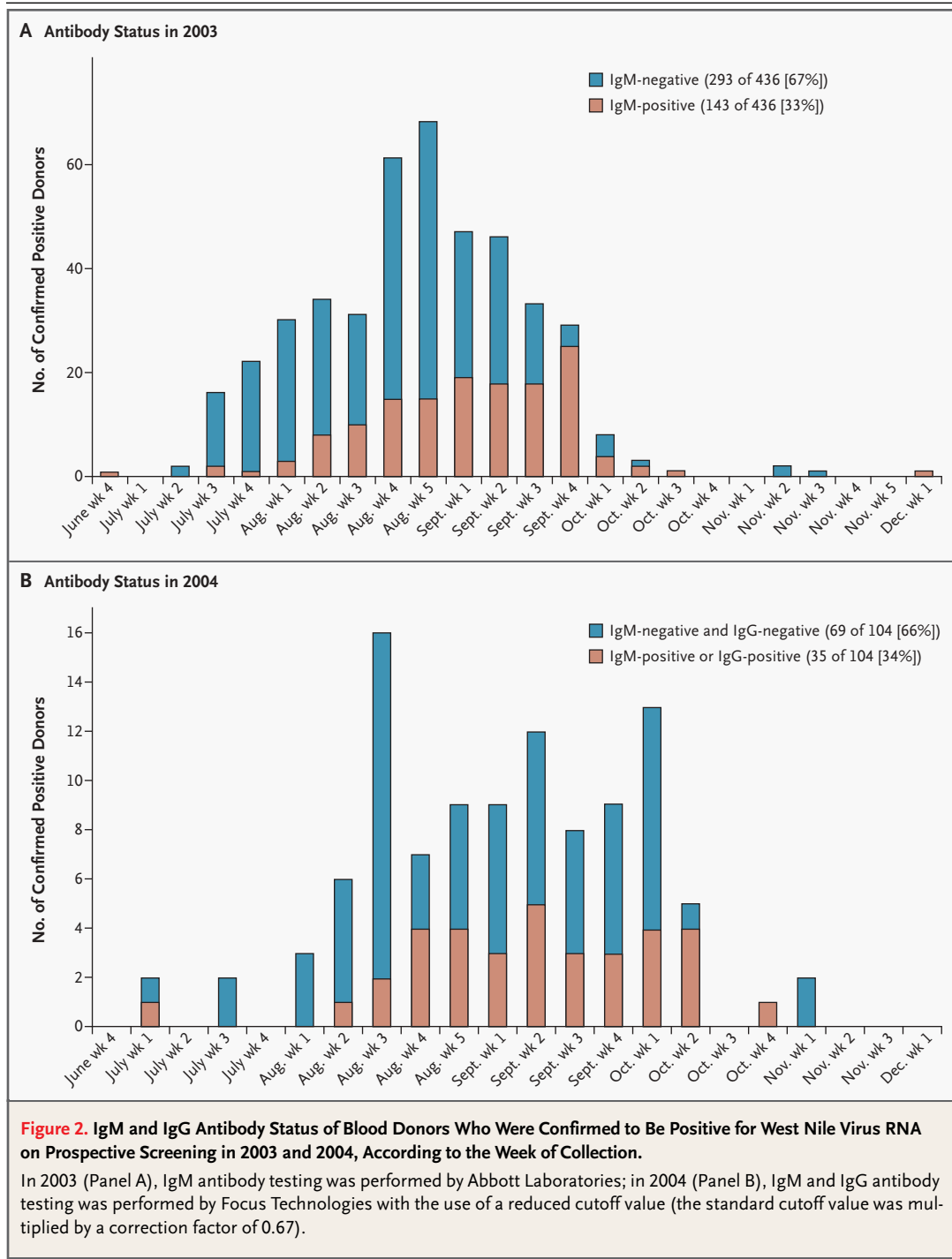
that were reactive on minipool testing, 283 (89 percent) were IgM-negative (Table 1). For the 143 IgM-positive donations, the median viral load was below 100 copies per milliliter (range, less than 5 to 14,000), as compared with 5800 copies per milliliter (range, less than 5 to 580,000) for the 293 IgM-negative donations ($P < 0.001$ by the Wilcoxon rank-sum test). Donations that were positive for West Nile virus RNA and IgM were identified more frequently as the season progressed (Fig. 2A).

In 2004, the trigger for nucleic acid amplification testing of individual donations was reached for collections tested by the Red Cross in three areas: southern California (July 25 to October 8), Kansas (September 12 to 27), and Arkansas (August 28 to September 6), for a total of 92,460 donations tested individually. No reactive donations were identified by individual testing of Arkansas donors. However, 48 of 54 confirmed positive donations from southern California residents (89 percent) and 3 of 7 confirmed positive donations from Kansas residents (43 percent) were identified during the period of individual testing, for a combined positive rate of 0.056 percent, or 1 in 1791 donations. Of the 51 confirmed positive donations identified by nucleic acid amplification testing of individual donations, 31 (61 percent) were nonreactive on minipool testing. These 31 donations represented 30 percent of the total 104 positive donations identified in 2004; 26 (84 percent) were positive for IgM or IgG, and 5 (16 percent) were negative for IgM and IgG (Table 1). Figure 2B shows that the identification of confirmed positive donations with IgM or IgG antibody reactivity increased as the 2004 season progressed; this increase was less than that observed for 2003. For the 35 IgM- or IgG-positive donations, the median viral load was below 100 copies per milliliter (range, less than 5 to 47,000), as compared with 3200 copies per milliliter (range, less than 5 to 160,000) for the 69 IgM- and IgG-negative donations ($P < 0.001$ by the Wilcoxon rank-sum test).

In both 2003 and 2004, two thirds of all viremic donors were negative for West Nile virus antibody, according to two different IgM-antibody testing strategies: the Abbott Laboratories IgM assay (Fig. 2A) and the Focus Technologies IgM and IgG assays (Fig. 2B).

DEMOGRAPHIC CHARACTERISTICS OF DONORS

Among the confirmed positive donors, as compared with the group of donors with false positive



results, there were more male than female donors in 2002,¹¹ 2003, and 2004 (Table 2). In 2003, 50 percent of the overall donor population of the American Red Cross was male. Combining the confirmed positive donors from 2002 through 2004, 13 percent were first-time donors, with a mean age of 46 years (range, 16 to 83). These observations did not

differ significantly from those observed for the donors with false positive test results.

FOLLOW-UP OF DONORS AND RECIPIENTS

In 2003, 350 of 415 confirmed positive donors identified prospectively participated in the follow-up study, of whom 335 (96 percent) were IgM-positive

Table 2. Demographic Characteristics of Blood Donors with Reactive Nucleic Acid Amplification Tests.

Period	No. of Donors	Male Donors	1st-Time Donors	Age	
				Mean	Range
		no. (%)		yr	
Sept. 3–28, 2002*					
Confirmed positive	46	24 (52)	9 (20)	43.8	17–77
False positive	52	23 (44)	10 (19)	42.7	17–73
June 29–Dec. 1, 2003					
Confirmed positive	436	258 (59)†	43 (10)†	46.5	17–83
False positive	382	187 (49)	58 (15)	47.5	13–89‡
June 16–Oct. 16, 2004					
Confirmed positive	104	62 (60)	24 (23)	44.9	16–83
False positive	73	37 (51)	12 (16)	41.8	17–75

* Retrospective nucleic acid amplification testing was performed on frozen samples of individual donations from six high-incidence regions.¹¹

† $P < 0.05$ for the comparison with the false positive group during the same period.

‡ Frozen plasma was obtained from a 13-year-old repeat autologous donor.

or seroconverted during follow-up. Of 186 donors who participated in long-term follow-up, 166 (89 percent) retained specific IgM reactivity for 100 days or longer. However, of the 17 of 46 confirmed positive donors identified in 2002 for whom follow-up data were available,¹¹ 10 (59 percent) had IgM reactivity for more than 398 days, consistent with the observations of Roehrig and coworkers.²¹ Of 104 confirmed positive donors identified in 2004, 82 (79 percent) participated in follow-up studies.

Only two recipients of donations confirmed to be positive on retrospective testing of individual donations in 2003 could be identified and consented to follow-up studies. Both were seronegative for West Nile virus and had had no reported symptoms associated with West Nile virus infection during the year after transfusion. In the case of both recipients, the transfused component was IgM-positive and had an RNA level that was too low to quantitate. In contrast, a 2002 recipient of an IgM-negative unit with a viral load of 6300 copies per milliliter had West Nile virus–related symptoms and antibody seroconversion.¹¹ Although these numbers are small, the data are consistent with reports of seroconversion and disease related to West Nile virus infection only among recipients of viremic, IgM-negative blood components.^{7,22–25}

DISCUSSION

In 2002, transfusion-transmitted West Nile virus infection was confirmed in 23 recipients of blood

components, with the true number of transmissions believed to be much higher. By early summer of 2003, blood-collection agencies had implemented blood-donor testing for West Nile virus RNA, identifying and reporting a total of 1041 RNA-positive donations to the CDC through Arbonet for the 2003 and 2004 seasons.^{19,26} The Red Cross program identified 540 of these viremic donations, of which 362 (67 percent) were negative for West Nile virus antibodies and likely infectious. The major epidemic focus in 2003 was the upper Plains states, moving to the Southwest in 2004. Most important, on the basis of prospective screening for West Nile virus RNA performed in 2003 and 2004 in our program, 1023 components manufactured from 519 prospectively screened viremic donations were not released for use and therefore not transfused.

Screening of blood donations for West Nile virus RNA was initiated in minipools of 16 samples, leading to concern that donations with low-level viremia might escape detection.^{11,17,23} Our data from the 2002 West Nile virus season suggested that, at the height of the epidemic, there might be one viremic donation undetectable by minipool testing for every four that were detected. Accordingly, in areas with a high prevalence of RNA-positive donations (i.e., more than 1 in 1000 samples), we initiated nucleic acid amplification testing of individual donations after identifying a total of four RNA-positive donations on minipool testing in any given blood-collection region. This policy was supported by the observation of West Nile virus infec-

tions associated with the transfusion of blood units with RNA levels that could not be detected by minipool testing.²²⁻²⁵ In addition, the effectiveness of this evidence-based trigger is demonstrated by the absence of any confirmed cases of transfusion-transmitted West Nile virus infection associated with blood components from our system in 2003 and 2004. An assessment of the effectiveness of various trigger strategies has been published elsewhere.²⁷ The continued use of a trigger strategy for the screening of blood donations for West Nile virus appears justified in order to focus available resources at times and locations of peak incidence. In contrast, at times and locations in which there are few or no identified viremic donations, minipool screening provides adequate safety.

Through careful follow-up studies of all RNA-reactive donors, we were able to establish the natural history of West Nile virus infection, finding that IgM antibodies against the virus were detectable about 11 days after the detection of viral RNA on minipool testing (13 days after the detection of viral RNA on testing of individual samples), followed rapidly by the appearance of IgG antibodies.^{12,13} The transmission of West Nile virus through transfusion has not been linked to an RNA-positive component that is also positive for IgM or IgG antibodies against the virus. Although we identified 148 viremic donations that were detectable only by nucleic acid amplification testing of individual donations, only 15 of them (10 percent), or 1 in 9400 samples, were IgM-negative and thus represent the earliest stages of donor infection. Therefore, in programs dependent on trigger strategies, careful, real-time monitoring is critical; in the absence of timely system readiness and monitoring, breakthrough infection has been documented.²⁴

The vast majority of the yield of nucleic acid amplification testing of individual donations was IgM-positive, demonstrating the long duration of positivity for IgM antibody in the presence of low-level viremia. It is likely that such donations would be noninfectious, especially in the presence of high titers of IgM and IgG, but studies to confirm this possibility have not been performed. Studies tracing recipients of blood components generally have

a low yield, and our study is no exception; however, two recipients of IgM-positive, viremic blood components had no evidence of West Nile virus infection, in contrast to recipients who received IgM-negative, viremic units.^{7,11,22-25}

In future years, will the need to screen blood donors for West Nile virus continue? We have now seen three West Nile virus epidemic seasons in the United States, with an expanding geographic range of viremic blood donors and clinical infections. The number of reported cases of West Nile virus neuroinvasive disease peaked in 2002 and 2003 (2946 and 2866 cases, respectively²⁰) and decreased (to 1108 cases) in 2004.²⁶ This same trend was observed by our identification of 436 viremic blood donors in 2003 and of 104 in 2004, as well as by the total number of viremic blood donors reported to the CDC during these years (818 and 223, respectively).^{20,26} West Nile virus infection may eventually follow the same pattern as St. Louis encephalitis, with only infrequent, localized recurrences.

To our knowledge, the implementation of nationwide testing for West Nile virus RNA has been the most rapidly instituted test-based intervention in the history of transfusion safety, taking only about nine months from the decision to develop a test to its implementation. The program is a model of cooperation among public health agencies, regulators, manufacturers, and the blood-supply system.²⁸ It is to be hoped that this process will be effectively replicated should there be a similar outbreak in the future.

Dr. Stramer reports holding stock in Abbott Laboratories and having received consulting fees from Gen-Probe, Chiron, and Abbott Laboratories. Dr. Fang reports holding stock in and having received consulting fees from Chiron. Ms. Brodsky reports holding stock in Abbott Laboratories. Dr. Dodd reports having received consulting fees from Gen-Probe, Chiron, and Abbott Laboratories.

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