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Original Articles

Keeping Blood Transfusion Safe From West Nile Virus: American Red Cross Experience, 2003 to 2012

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ABSTRACT

West Nile virus (WNV) appeared for the first time in the United States in 1999 and rapidly spread across the Western hemisphere within a few years causing hundreds of thousands of human infections and significant disease. In 2002, it was found to be transmissible by blood transfusion, and within less than a year, nucleic acid testing for WNV RNA was in place for all US donations. The American Red Cross (ARC) collects approximately 40% of blood donations in the United States and closely monitors the results of such testing and evaluates donors found to be reactive. This review describes the 10-year results of the ARC testing program during the period 2003 to 2012. Overall, more than 27 million donations were tested during the transmission periods with 1576 RNA-positive donations identified. The temporal and geographic distributions of the infected donors are described. Methods to initiate and discontinue periods of individual donation testing were developed and validated to maximize safety. The nature of WNV infection among donors was investigated, and the distribution of viral titers was defined and was found to be no greater than 720 000 RNA copies per milliliter. The distribution of titers by time sequence of appearance of antibodies was determined. Donors who were identified as being in the earliest stages of infection were evaluated for the appearance of symptoms, and 26% developed at least 3 characteristic symptoms. The testing program has been successful in preventing transmission of WNV by transfusion, and only 1 of the 13 reported cases since the initiation of testing was attributable to the Red Cross; it was from a granulocyte product transfused before availability of the test result.

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Until 1999, the West Nile virus (WNV), a mosquito-borne *Flavivirus*, was endemic to many parts of Africa, Southern Europe, the Middle East, Southwest Asia, India, and Australia (Kunjin strain). However, in that year, an unexpected outbreak occurred in Queens, New York, marking the first autochthonous cases in the Americas. A total of 17 confirmed and 20 probable human cases, with 4 deaths, had been reported by September 28, 1999 [1]. West Nile virus spread rapidly throughout the east coast and as far west as the Rocky Mountains [2], with a total

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of 4305 clinical human cases reported by the end of 2002. Subsequently, WNV spread throughout the Western hemisphere. It is generally recognized that the US outbreak is unique and that, in other areas of endemicity, outbreaks are usually geographically and temporally restricted and do not bear comparison to the US situation. The bases for the explosive and sustained nature of the US epidemic remain unclear; likely multiple factors are at play including climate; migratory bird patterns; and hybrid (human and bird) feeding patterns of the primary mosquito vector, *Culex pipiens*, in the United States [3]. Although it was recognized that WNV infection was almost always acute, the size and rapid expansion of the epidemic in the United States led to concerns that transfusion transmission was possible. In 2002, Biggerstaff and Petersen [4] estimated that the mean potential risk of transfusion transmission in Queens, NY, at that time was 0.18 to 0.27 per 1000 component units. The model was applied again during the 2002 outbreak with 6 high-incidence metropolitan areas estimated with a risk of 0.15 to 1.23 infections per 1000 units [5]. The initial publication was immediately followed by a report of the first 23 cases of transfusion-transmitted WNV infection and disease [6]. To date, 2002 was the year with the highest overall number of human WNV infections nationally, closely followed by 2003 and subsequently 2012 (as estimated by WNV neuroinvasive disease [WNND] cases reported to the Centers for Disease Control and Prevention) (Table 1).

As a result of these findings, blood organizations, the diagnostics industry, regulators, and public health agencies worked together to develop and implement nucleic acid tests (NATs) for WNV-RNA in donated blood. Methods became available and were broadly implemented under Investigational New Drug protocols by the summer of 2003. The testing program, relying on a combination of testing minipools (MP-NAT) and individual donations (ID-NAT), has been remarkably successful and has been credited with the identification and interdiction of 4355 WNV-positive donations through the end of 2014, many of which are considered to be infectious (Table 1).

Early experience revealed that there continued to be a small number of breakthrough WNV infections among blood recipients and that they were attributable to low-level donor viremia that escaped detection by MP-NAT (involving 6 or 16 samples) during outbreak periods. Accordingly, criteria were developed to convert from MP-NAT to periods of ID-NAT referred to as triggering; resumption of MP-NAT occurs at the conclusion of outbreak activity, as determined by a variety of measures discussed in a recent AABB Association Bulletin [7]. These approaches were validated and modified as needed; their proper use has been shown to have essentially eliminated transfusion-transmitted WNV risk nationally.

The emergence of WNV has offered an object lesson in the management of a major emerging infection event in the United States. Analysis of data from blood donor testing has provided information about the distribution of infections, the significance and occurrence of asymptomatic infection, and the limits of infectivity by the intravenous route. It has also supported public health investigations and has demonstrated the value of having available platforms for high-throughput NAT. This review uses the ARC system as an example of success through validation and ongoing hemovigilance.

Emergence of WNV in the United States and development of a national donor testing program

Initially, procedures were established to defer donors and/or recall their donations in the event that they reported symptoms suggestive of WNV. (It was subsequently shown that such a policy had little to no value [8].)

Two manufacturers developed WNV-RNA screening tests, designed to run on existing automated NAT platforms. Gen-Probe (now Hologic) adapted their Procleix transcription-mediated amplification (TMA) method to detect WNV-RNA, Procleix WNV Assay, using the automated TIGRIS platform, marketed by Novartis (now Grifols), whereas Roche developed the cobas Taq-Screen real-time RT-PCR, running on the cobas s201 system. One of these candidate tests was used in a study of plasma samples from donations implicated in the 23 transfusion-transmission cases noted above [9]. In addition, routine surplus donation samples were collected from 6 ARC blood centers during the period September 3 to 28, 2002 [10]. A total of 48 620 samples were selected for evaluation using ID-TMA. Overall, 46 RNA-positive samples were identified, for a frequency of 0.95 per 1000 (similar to the estimated rate described by Biggerstaff and Petersen) [5]. These early data demonstrated that only a minority of RNA-positive samples could be detected by MP-NAT (16/46, 35%; Table 2) with the remainder requiring ID-NAT for detection. A caveat was that all 30 of the ID-NAT-only detectable donations were antibody positive (immunoglobulin M [IgM] and/or immunoglobulin G [IgG]). At that time however, routine programs had already been initiated based on MP-NAT [11].

Routine testing was initiated nearly nationwide in June to July 2003 before the start of the WNV season. Table 1 shows the number of WNV-RNA–positive donations reported each year, 2003 to 2014, along with the number of reported WNND cases; it should be noted that there is a close relationship between these 2 numbers each year. Also shown are 13 identified "breakthrough" infections attributed to transmission by blood transfusion after the implementation of WNV-NAT screening [12-19]. Only 1 of these 13 cases (in 2010) was caused by a component (granulocyte concentrate) from the ARC, which was transfused before the test result was available [18]. Of note, of the 36 total transfusion-transmitted WNV cases, only 2 were WNV IgM positive [9,19].

Materials, Methods, and Results

The Early ARC Testing Program and Its Contributions

The ARC collects approximately 40% of all blood for transfusion in the United States in a coordinated, centrally managed system that includes 35 blood regions in 44 States, Puerto Rico, and Washington, DC. Figure 1A shows the overall pattern of detection of 1576 WNV-RNA confirmed-positive donations that occurred mainly in the June-October period. As noted above, 2003 and 2012 had the greatest number of detected positives, paralleling the number of nationally reported clinical cases. Figure 1B shows the geographic distribution of donors of the 1576 RNA-positive donations by residential zip

Table 1
Yearly statistics for WNV in the US: example of a rapidly emerging agent and a successful intervention, 2002–2014

Year (No.) Reported	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
WNND (18 725)	2946	2866	1148	1309	1495	1227	689	386	629	486	2873	1267	1262[+]
WNV-RNA confirmed-positive donations (4355)[*]	N/A	714	224	417	437	481	218	161	182	139	752	307	303
Transfusion cases[^] (36)	23	6	1	0	2	0	2	0	1[***]	0	1	0	0

WNND, West Nile virus neuroinvasive disease.
N/A, not available; prospective testing not introduced until 2003.
[*] 2003–2005 reported from CDC ArboNet [12]; 2006–2014 reported from the AABB WNV site http://www.aabb.org/research/hemovigilance/Pages/wnv.aspx) [13].
[^] All transfusion-transmission cases were identified from May to October [14–19].
[***] 1 WNV NAT-untested granulocyte [18].
[+] Data available through Dec 16 2014; www.cdc.gov/westnile/StatsMaps/.