Joint UKBTS / HPA Professional Advisory Committee **(*)**

Position Statement

West Nile Virus

22 March 2013

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1. Background

West Nile Virus (WNV), a mosquito-borne flavivirus recognised since 1937 and widely distributed in Africa, Western Asia, Europe and Australia, emerged for the first time in the Northeast of the United States (US) in 1999. WNV case numbers increased in the US in following years, and WNV is now found across the whole of the US and into Canada.

In 2002, cases of transfusion and transplant-transmission of WNV were recognised in the US. The definitive strategy adopted in the US to deal with this issue was the implementation of WNV NAT in 2003. As travel to the USA and Canada is common in UK blood donors, a deferral policy for such donors was adopted by UKBTS in June 2003 as a precautionary measure. In April 2004 this deferral policy was updated to take account of the availability of WNV NAT tests for donation screening and such screening was applied in NHSBT for the relevant periods of 2004 and 2005.

The EU Blood Safety Directive (and the Blood Safety and Quality Regulations) requires that travellers from an area with ongoing transmission of WNV in humans should be deferred for 28 days. There is no provision within the Directive for WNV NAT testing in place of deferral, as a strategy for travellers returning from an affected area. The directive became UK statutory law as the Blood Safety and Quality Regulations 2005. Thereafter UKBTS deferred travellers returning from areas affected by West Nile Virus.

Outbreaks of WNV infection in a number of areas within Europe in 2010/11 led to the introduction of WNV NAT testing of donations in affected areas, in order to maintain a sufficient blood supply. The recommendation for NAT testing was included in the “WNV Preparedness Plan” produced in 2011 by a working group with representatives from DG SANCO: European Commission's Directorate General for Health and Consumer Policy, the European Communicable Disease Centre (ECDC) and experts from affected areas. At a meeting in January 2012 to review the Preparedness Plan it was agreed that WNV NAT testing could be applied by blood establishments in non-affected areas to donations from travellers returning within 28 days from an affected area, if donor deferral would threaten the sufficiency of the blood supply[12].

The EU Blood Safety Directive makes no recommendations about the management of donors who have had symptoms of WNV during, or shortly after, a visit to a WNV affected area, referring instead to the “Guide to the Preparation, Use and Quality Assurance of Blood and Blood Components of the Council of Europe 16th Edition, 2011”. This document states that individuals who have had WNV should be deferred for 120 days. UK Guidelines include the requirement for a negative WNV test before reinstatement.

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1.1. The recommended deferral criteria for UK donors are:

Donors who have visited a WNV risk area*:	Defer for 28 days from date of leaving the affected area unless WNV NAT screening is in place to maintain a sufficient blood supply
Donors who have visited a WNV risk area* and have either:	
a history of symptoms suggestive of WNV whilst there or shortly following their return to the UK	Defer for 120 days unless WNV RNA screening is in place. Donors who are found not to have had WNV may be re-instated.
or	Donors diagnosed with WNV may be re-instated 120 days after their return from an affected area providing no longer WNV NAT reactive.
had a laboratory diagnosis of WNV whilst there or following their return to the UK.	
Donors who are WNV NAT tested and have NAT reactive samples.	Do not use the donation. Defer. Refer for clinical microbiology follow-up as appropriate. May be re-instated 120 days after return from affected area providing no longer WNV NAT reactive.

***A WNV risk area** is defined as:

- any part of North America (USA and Canada) during the risk period. FDA CBER specified the “typical WNV season” as falling between **1 May and 30 November** although isolated cases may occur at any time, and the majority of cases occur in the months July to October.

- any other area with ongoing transmission of WNV (”affected area”) that does not attract a malaria travel deferral of 6 months and which meets the definition accepted by the European Commission/ European Centre for Disease Control.

1.2. Post- donation illness (donor) and post-transfusion infection (recipient) reporting

Both types of reporting are routine in the UKBTS and standard UKBTS procedures should be followed:

- In the case of a donor becoming ill with WNV or suspected WNV within 14 days of donation, relevant blood donations are those 14 days prior to and 120 days after the onset of illness.

- In the case of a recipient becoming ill with WNV/suspected WNV within 120 days of transfusion.

2. West Nile Virus

Background [2,3,4]

WNV is an arthropod borne flavivirus, first isolated in 1937. The principal vectors are mosquitoes and the principal hosts are wild birds. Humans and other animals e.g. horses, are infected via mosquito bites. They are considered to be "incidental hosts" as they do not develop sufficient viraemia to maintain transmission cycles.

WNV has caused sporadic cases and outbreaks of human and equine disease in Europe since the 1960s. Outbreaks have occurred in Romania (1996 and 2008), Russia (1999), Israel (2000), Hungary and Italy (both 2008). During 2010, sporadic human cases were reported in a number of European countries, including Hungary, Spain, Italy, Romania and Russia. A larger outbreak occurred in Italy (2008) and northern Greece (2010), and during 2010 both Greek and Italian blood services introduced WNV NAT screening for blood donations collected from affected areas in their own countries. During 2012, Croatia, Macedonia, Kosovo, Serbia and Tunisia were all added to the list of WNV-affected areas. There were a total of 237 human cases reported in the EU, predominantly in Greece, and 670 in neighbouring countries, chiefly in the Russian Federation.

In the USA, WNV was first identified in 1999, and during 2000-2001 spread to over half the country. In 2002 a major epidemic peaked in August – late September; 99% of the human cases occurred between 1 July and 31 October. Since cases are mosquito-related, numbers are expected to decline over the winter. In 2003 there were 9858 human cases with 262 deaths. Thereafter there was a steady decline in cases until 2009, when there were 663 human cases with 30 deaths and 109 presumptive viraemic blood donors, but there was an increase in cases in 2010, and a large rise in 2012 leading to the highest number of cases and deaths seen since 2003. The number of human WNV cases, deaths and viraemic blood donors, in USA 1999 – 2012* is represented in the table:

Year	Case numbers	Deaths	Presumptive viraemic blood donors
1999	62	7	
2000	21	2	
2001	66	9	
2002	3893	254	
2003	9862	264	818
2004	2539	100	224
2005	3000	119	417
2006	4269	177	361
2007	3630	124	326
2008	1356	44	174
2009	720	32	109
2010	1021	57	117
2011	712	43	137
2012	5387	243	597

*Data source: www.cdc.gov/ncidod/dvbid/westnile/surv&control.htm

In Canada a similar pattern has been seen, with a dramatic decrease in cases from a peak of 2215 (2007) to 36 cases in 2008 with the last case reported in mid-September. Number of cases continued to fall to a low of 5 in 2010. Mirroring the situation in USA, there was a rise to 101 cases in 2011, and provisional 2012 data showed an increase to 450 cases.

The incubation period of WNV in humans is reported to be 3-15 days. Most human infections are either asymptomatic (76%), or result in only mild flu-like symptoms with full recovery (24%)[12], but 1 in 150 –200 develop a more severe form of the disease which may culminate in fatal encephalitis, particularly if elderly or immunosuppressed.

In general, the risk of transmission by transfusion relates to a few days of viraemia starting 1-3 days after infection. Viraemia lasts a mean of 6 days. During the 2002 epidemic in the USA 23 patients were confirmed to have acquired WNV through transfusion of red cells, platelets or fresh frozen plasma. Transmission has also been reported following organ transplantation from a donor who initially acquired the infection through a blood transfusion. Information from the US has shown that, depending on the sensitivity of the NAT assay used, the virus may take up to 104 days to clear[1]. Additionally, it was reported that live virus can be demonstrated in some individuals who are seropositive for WNV antibodies. It was also noted that symptoms of headache and fever were poor indicators of WNV infection.
A 2005 report from the US of WNV in organ transplant recipients indicated that WNV transmission through solid organ transplantation can occur from donors who are seropositive for WNV (IgM and IgG antibodies) and WNV NAT negative[5] but there had been no such reports of transmission from blood donations.

There is a report[10] from the US of two cases of probable transfusion-transmitted WNV from a common blood donor in 2006 despite a negative MP-NAT result at the time of donation. The source of infection could not be proven because blood samples or co-components from the implicated donation were unavailable for testing; however, evidence of WNND in two recipients of blood products from a common donor with serologic evidence of recent infection (IgM antibody) at follow-up makes WNV transfusion-transmission probable. Because the two transfusion recipients were hospitalized for at least 2 weeks each before onset of WNND, neither patient was likely to have acquired infection from a mosquito bite. Furthermore, for the recipient who also underwent transplant surgery, transmission through the transplanted kidney is unlikely, given that neither the organ donor nor the other organ recipient had evidence of WNV infection.

A pragmatic approach is needed in the UK. Donors with a history of WNV and/or a positive WNV NAT should be temporarily deferred pending investigation but may be returned to the donor panel after 120 days with the precaution of a negative WNV NAT test before reinstatement. No UK donors have been found to be WNV NAT positive during the period when routine WNV NAT screening of blood donors with relevant travel history has been performed in the NHSBT.

3. Risk of transfusion-transmitted WNV from blood components produced in the UK

There are two situations to be considered for UK blood services:

- The risk from UK donors who may have been exposed in areas with ongoing transmission of WNV in humans.
- The importation of FFP for further processing for clinical use

3.1. The risk from UK donors

The UK situation is as follows:

- There have been only two human WNV cases reported in the UK (this includes travellers returning from endemic areas). One case each in 2006 and 2007 was reported. The 2006 case was in an UK resident, who was a member of the armed forces and stationed in Canada. The diagnosis was made on his return to the UK. The 2007 case was a Canadian resident who became ill when visiting the UK. No human cases have been reported in the UK since then; although anecdotal evidence suggests that there may have been occasional cases which have not been captured by the Health Protection Agency (HPA) surveillance data.

- There were no WNV viraemic blood donors identified among over 18,000 donations made to NHSBT centres by donors returning from WNV at risk areas (USA and Canada) during 2004 and 2005.

- There were no WNV viraemic donors identified among 28,973 donations made to NHSBT centres by donors returning from WNV at risk areas during 2012.

- Enhanced surveillance of encephalitis patients in England began in November 2005 and no cases of WNV have been reported through this surveillance. http://www.hpa.org.uk/infections/topics_az/encephalitis/study.htm.

- A study of the UK bird population showed the presence of neutralising antibodies in a relatively high proportion of resident birds[8]. The absence of an obvious reduction in the bird population suggests that either the strain detected is avirulent or that birds have been exposed for many years and have developed herd immunity.

- The only known risk is therefore in returning travellers from high incidence areas, in the appropriate season, who may be incubating WNV. However, on this point it is noteworthy that during the period of selective WNV NAT testing of NHSBT donors, out of approx. 18,700 tests performed between 14 June 2004 and the end on November 2005, none were found WNV positive, nor in the testing of over 28,000 donations in 2012. The risk of WNV transmission via blood transfusion in the UK is considered to be very small but cannot be quantified at present. Nevertheless, assessment of the threat to blood safety of this pathogen using criteria developed by SACTTI [9] suggests that the preventative measures adopted to date are appropriate.

- There were no imported cases of WNV reported in the UK in the years 2008 to 2012 inclusive.

3.2. Risk of WNV transmission by imported plasma.

The period of asymptomatic viraemia in WNV infection is short-lived with rapid development of IgG and IgM antibodies to WNV. Methylene blue treatment is applied to imported FFP. It has been shown to reduce the WNV load by at least 6.5^{10} logs to below the detection limit and WNV appears to be one of the most rapidly inactivated viruses studied[6]. The risk of transmission by methylene blue treated FFP of non-UK origin must therefore be considered negligible.

4. Conclusion

4.1 As required by UK Statutory Regulations a 28-day deferral period applies to asymptomatic donors returning from an area with ongoing transmission of WNV in humans. The definition of "ongoing transmission of WNV" was clarified in 2012 as "one autochthonous locally-acquired case of laboratory-confirmed WNV infection". The EU Directive and UK Statutory Regulations do not currently allow for WNV NAT testing as an alternative to donor deferral for returning travellers, although guidance issued in 2010 allowed for the use of WNV NAT testing to release blood donations in areas which are affected by ongoing transmission of WNV. Guidance in 2012 allows WNV NAT testing in place of donor deferral for returning travellers, where deferral will threaten the sufficiency of the blood supply[12].

4.2 The possibility of prolonged WNV viraemia, which may be low-level and not detectable by mini-pool WNV NAT, requires a pragmatic approach in the UK, especially as most available evidence is obtained from the United States and relates to lineage 1 WNV, whereas European cases mainly belong to lineage 2. Donors with a history of WNV and/or a positive WNV NAT should be temporarily deferred pending investigation but may be returned to the donor panel after 120 days with the precaution of a negative WNV NAT test. To date, no UK donors have been found to be WNV NAT positive.

References

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(1) **Joint U**nited **K**ingdom **B**lood **T**ransfusion **S**ervices and **H**ealth **P**rotection **A**gency **Professional Advisory Committee**