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Directorate C - Public Health and Risk Assessment
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SCIENTIFIC COMMITTEE ON NEWLY IDENTIFIED AND EMERGING HEALTH RISKS

(SCENIHR)

Updated Opinion on

"The Safety of Human Blood and Organs with Regard to West Nile Virus"

Adopted by the SCENIHR
during the 4th plenary of 17 February 2005

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1. INTRODUCTION

Commission Directive 2004/33/EC [1], in particular Annex III, sets out eligibility criteria for donors of whole blood and blood components. Section 2.2 on Temporary deferral criteria for donors of allogeneic donations details the following deferral period for West Nile Virus (WNV) – 28 days after leaving an area with ongoing transmission of WNV to humans.

The first reported clinical cases of WNV disease acquired in Portugal were registered in July 2004. The Commission was advised in July 2004 by the National Blood Transfusion Service of Ireland that it was implementing this four week deferral criteria for donors after leaving the Algarve; this is the same deferral as is practised in Ireland for people who have been to North America. This deferral came into force on 28th July 2004 and will be continued at least until October 2004. Several other Member States are also implementing this requirement for visitors to the Algarve while others are not. The Commission conducted a survey on the measures taken by Member States regarding the prevention of transmission of WNV by blood [2].

One Member State reported to the Commission findings by the American Red Cross. The findings presented in The America's Blood Centers Newsletter July 30, 2004, p.5, shows that infectious WNV particles may linger in the blood of the infected person for up to 49 days after the first signs of infection. If this finding is correct, changes to the 28 day deferral period to e.g. a 56 day deferral period in Directive 2004/33/EC may need to be considered. The Committee for Proprietary Medicinal Products (CPMP) of the EMEA concluded in its "*Position Statement on West Nile Virus and Plasma-Derived Medicinal Products*" (EMEA/CPMP/BWP/3752/03) that the virus is effectively inactivated or removed during the manufacture of plasma-derived medicinal products. It also notes clearly that this statement is not applicable to whole blood and labile blood products, which were not included in the scope of the Position Statement.

In the light of an increase in the incidence of WNV infections in humans in Portugal and potential similar situations in other European areas, the inclusion for these areas of a time-limited donor deferral pursuant to Directive 2004/33/EC and the introduction of testing for WNV may need to be re-evaluated.

2. BACKGROUND

The Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) adopted an opinion on the impact of arthropod borne diseases (including the West Nile Virus, (WNV)) on the safety of blood and organs used for transplantation with recommendations of 16th October 2003 [3]. The first of these recommendations stated that:

> *Since the WNV epidemic in the USA (and Canada) appeared at levels similar to the 2002 epidemic also in 2003, the temporary exclusion of travellers from WNV affected regions from blood donation is considered a well-balanced measure with a four weeks interval between the last day spent in an endemic region and the possible date of a blood donation being considered sufficient.*

In Commission Directive 2004/33/EC of March 2004 with respect to certain technical requirements for blood and blood components, Section 2.2 of Annex III specifically referred to the temporary deferral criteria for donors of allogeneic donations and defined this period for persons leaving an area with ongoing transmission of WNV to humans as 28 days, in line with the SCMPMD recommendation.

However, the pattern of outbreaks of WNV in animals and the occurrence of cases of WNV in humans has changed to some extent recently, and questions have been raised over the maximum period of viremia. In the light of this new information, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has been asked to re-visit this subject, with the terms of reference as described in point 2.

3. TERMS OF REFERENCE

- *WNV transmission risks in blood donors having visited the Algarve:*

In the light of recent evidence, the SCENIHR is requested to review the previous scientific opinion of the Scientific Committee on Medicinal Products and Medical Devices "*on the impact of arthropod borne diseases (including WNV) on the safety of blood used for transfusion as well as organs used for transplantation in the European Community*" as adopted on 16 October 2003 (SANCO/SCMPMD/2003/00025) in the light of the new information. The Committee is also asked to assess:

- The potential impact on the blood supply of introducing additional deferral criteria.

- The impact on the use of tissues and cells used in therapy.

- *WNV transmission risks in relation to the prolonged presence of virus in the blood of the infected persons:*

The SCENIHR is also requested to examine new scientific evidence and adopt an opinion on the impact of the risk of transmission of WNV through blood transfusion from infected donors beyond the current deferral period of 4 weeks.

4. ASSESSMENT

4.1. Current Evidence Concerning West Nile Virus

In deriving an opinion on the scientific justification for further actions with respect to WNV and blood transfusion deferral, it is necessary to consider the evidence for the spread of WNV and for any change in the understanding of the maximum period of viremia.

West Nile Virus Activity

The US Center for Disease Control (CDC) publishes regular up-dates on the number of human cases of WNV by area. As of January 11th 2005, the number of cases reported in the US in 2004 was 2,470, with 88 reported deaths [4]. These cases

covered 41 states and Washington DC. In 12 states, the numbers were less than 10; the largest numbers were reported in California (771), Arizona (391), Colorado (276) and Texas (158). In most of the states yet to report a case of WNV in humans, cases have been reported in terrestrial animals and avians. The total number of human cases is less than the reported numbers for previous years. The total number of cases and deaths in 2002 were 4,156 and 284, and in 2003, 9862 and 264 respectively. The distribution across the USA has shown a marked change as the epidemic has moved westwards, there being only 3 cases in California and 13 in Arizona in 2003. The incidence is seasonal, with summer (August and September) being the high risk period. The general position in the USA, summarised in the New England Journal of Medicine in 2004 [5], is that WNV can be considered endemic over much of the USA, although the incidence of human neuroinvasive disease appears to have peaked in 2003. The risk of this disease increases with age and appears to be significantly higher among immunocompromised individuals, especially organ transplant recipients, than in the general population.

In Europe, the incidence of WNV is very low [6]. An overview of the spread of WNV in Europe has been published in 2004[7]. In 1996 there was an outbreak in Romania where 352 patients presented with acute central nervous system infection, with 17 fatalities. In 1998 there were 14 cases reported in horses in Italy [8] and in 2000 there were 76 cases reported in horses in Southern France [9]. There were no human cases reported in the French outbreak of 2000 but there were 6 confirmed and 1 suspected cases in 2003, clustered in the Var region of Southern France, presenting with symptoms between August 14th and 28th [10], where also one case was reported in a horse on 10 October 2003 [11]. During surveillance of these regions in 2004, there were 57 suspected cases in horses, of which 32 were confirmed, but none of the 69 suspected human cases were confirmed. Also in 2004, two travellers from Ireland were confirmed to have contracted WNV after visiting the Algarve in Portugal [12] although neither were hospitalised. It is clear that while WNV is endemic at this time in the USA it is not endemic in Europe, although small regional outbreaks are possible.

The Maximum Period of Viremia and Blood Donations

The basis of the decision to control blood donations as a means of limiting the spread of WNV is the known incidence of human – to – human transmission via blood transfusion. According to the CDC, during the 2002 epidemic, a total of 23 persons were reported to have acquired WNV infection after receipt of blood components from 16 WNV-viremic blood donors [13]. The issues of transfusion-transmission of WNV have been reviewed in 2004 by Wullenweber et al [14].

The SCMPMD opinion on WNV was based upon the information available at that time that the typical course of mosquito-borne WNV infection involved a viremic phase of 2-14 days, which preceded the specific humoral response and virus clearance from the blood. The 28 day deferral period was considered to be consistent with this viremic phase.

It is stated in the 2004 Commission request for an opinion that the American Red Cross has presented findings that 'infectious WNV particles may linger in the blood

of the infected person for up to 49 days after the first signs of infection'. This statement was actually contained in the ABC Newsletter, July 30th 2004 [15]. This did not give any data but merely stated that The American Red Cross conducted lookback studies on samples from the 2003 West Nile epidemic, which indicates that viremia may persist for longer periods of time in individual cases. However, in the view of the strength of the data in the literature concerning the widely held view of the 2-14 day viremia period [16], the possibility of a few cases with a period longer than 28 days is not judged to be a significant risk.
Because of its endemic nature in that country, the USA has adopted procedures for blood donations to be screened for WNV using Nucleic Acid Testing methods (NAT). When a sample tests positive the donor is temporarily deferred for 28 days, consistent with the currently known duration of the viremic period. In the light of the possibility that the viremic period could be longer, as noted above, the Food and Drug Administration (FDA) have, in October 2004 asked their Blood Products Advisory Committee to advise on the implications of this in the context of the FDA current practice of deferral in association with NAT testing [17] .

It is difficult to determine the effect that policies of deferral have on donated blood supply, especially since there are numerous unquantifiable factors. Custer et al, who have recently discussed the general effects of donor deferral on blood supply [18], confirmed the difficulties involved in this analysis. There are many reasons why potential donors presenting for donation are deferred. Disease-marker-reactive donations represented 0.9% of donor outcomes. A deferral policy in Europe based on travel to the USA will obviously have seasonal and geographical implications. It is possible that even with the 28 day deferral period there could be an impact on donor supply in some areas at peak travel times, although it is anticipated that temporary shortages could be managed. An increase in the deferral period would inevitably have a greater effect, although the magnitude of this is unquantifiable.

4.2. General Factors Concerning Blood Donations in Europe

It is emphasised that the US position involves a period of deferral for those potential donors who provide a positive NAT test result or who have signs and symptoms of disease (predominantly fever and headache). This is different to a strategy that only involves deferral on the basis of travel to areas of risk without NAT or other screening procedures.

It is recognised that the testing for WNV in the USA is sensible and necessary. It should be noted, however, that no test is yet approved by the FDA and that uncertainty does exist with the effectiveness of the tests. A recent study suggests that tests may not detect all WNV-infected blood donors, that tests vary in sensitivity and that the procedures of pooling donations influence tests performance [19]. General technique-related issues with these tests have recently been discussed [20]. The test kits are also expensive and would add considerably to the cost of blood donations.

The question arises as to whether Member States within the European Union should consider testing donations from travellers returning from the USA. A recent survey by the European Commission, of September 6th 2004, did not reveal any plans by Member States to do this, although one Member State (UK) has recently announced in

a Press Release a test for the West Nile Virus [21] enabling blood donors returning from, for example, the USA to give blood without delay, at any season.

In the light of the possibility that regional and seasonal outbreaks could occur in Europe, consideration may be given to the testing of donations from inhabitants of the affected regions. In the south of France it is now the practice to consider deferral in an area where human cases are confirmed. It is possible that these measures could result in a temporary local shortage, although this should be manageable by distributing blood from adjacent regions.

4.3. Blood Products and Organ Transplantation

The SCMPMD Opinion of 2003 specified that there was no risk of WNV transmission through virus-inactivated plasma products, as confirmed in a European Medicines Agency (EMEA) statement [22]. There is no reason to alter that position. The Opinion also referred to the possibility of secondary WNV infections through organ transplantation, and indicated that WNV transmission had occurred in the USA arising in four recipients of organs originating from one donor. No specific recommendations were made about this matter. No further evidence is available. It is considered that within Europe the risk of such an occurrence is very low. It is noted that the introduction of a test for WNV on all organ donors might delay the use of the organs which could have implications for the effective use of organ transplants.

5. CONCLUSION

The viremia period for WNV is still considered to be 2-14 days. There are indications that in rare cases viremia may persist for a longer period of time but this may be attributed to exceptional reasons including concurrent medical conditions, and, therefore caution must be expressed over any extension of the deferral period. It is difficult to quantify the impact that this would have on the availability of blood from donors, but extension of the deferral period for those travelling to the US from one to two months must by definition have a direct impact on donations. Moreover, there is likely to be an unquantifiable negative effect in terms of individuals being turned away from donation simply because they had been to North America. The SCENIHR therefore concludes that there are no new grounds to amend the 2003 opinion of the SCMPMD concerning the 28 day deferral period.

One consequence of the changing situation concerning the incidence of WNV in both animals and humans is the uncertainty introduced into the geographical and seasonal basis for deferral for blood donors who have travelled to potentially infected areas. If this is the only basis for deferral, then constant vigilance is required with respect to the geographical locations.

In the European Union, where WNV is not endemic, the vast majority of individual donors could be considered to pose no risk of WNV transmission. However, with the possibility of WNV being found in Europe deferral on donations from individuals from affected regions should be considered whenever a human case is confirmed in a region of Europe.

In view of the possibility of an increase in the number of geographical areas of Europe affected by WNV, it is recommended that the Commission alerts Member States to the need for vigilance with respect to the identification of such areas and communication of this information between blood donation and other relevant authorities.

The SCENIHR concludes that the current scientific evidence does not support further action with respect to plasma products and organ transplantations.

6. MINORITY OPINION

There was no minority opinion.

7. REFERENCES

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