

**WEST NILE VIRUS AND BLOOD SAFETY
INTRODUCTION TO A PREPAREDNESS PLAN IN EUROPE**

Based on the EU Satellite Meeting
of the Working Group on Blood Safety and WNV,
Thessaloniki, 25-26 January 2012

FINAL WORKING DOCUMENT 2011 v.2.1.
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6 June 2012

[1]

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List of Acronyms

ABD:	Arthropod-Borne Disease
DG SANCO:	European Commission's Directorate General for Health and Consumer Policy
EBA:	European Blood Alliance
ECDC:	European Centre for Disease Prevention and Control
EID:	Emerging Infectious Diseases
EU	European Union
FDA:	Food and Drug Administration
ID:	Individual Donation
IgM	Immunoglobulin M
MP:	Mini Pool
NAT:	Nucleic Acid Testing
PCR:	Polymerase Chain Reaction
RNA:	Ribonucleic acid
RR:	Residual Risk
TMA:	Transcription-mediated Amplification Assay
TTA:	Transfusion Technology Assessment
WHO:	World Health Organisation
WNND:	West Nile Neuro-invasive Disease
WNV:	West Nile Virus

Acknowledgements

Special thanks to the members of the working group on West Nile Virus that worked hard to get this document ready and in particular to Dr Dina Politis from Greece, Dr Giuliano Grazzini from Italy , Dr Imad Sandid and Dr Elodie Pouchol from France, Dr Corina Posea and Alina Mirella from Romania

We would like to thank the colleagues working in ECDC for their valuable contribution and also the colleagues working in the Emerging infectious disease Monitor of European Blood Alliance for their contribution.

1 Introduction

It is expected that during 2012 and the coming years new human cases of West Nile Virus infection will be reported. Europe may see an endemic situation for WNV infection, though depending on multiple factors. In view of this, the joint meeting of the Competent Authorities and the Regulatory Committee on Blood and Blood Components decided on 27-28 October 2010 to create a working group to develop a preparedness plan for next year's expected outbreak. Elements to consider include impact on volume, geography, deferral criteria, cost and nucleic acid testing (NAT).

In the context of an expert consultation on WNV infection in Europe held in Thessaloniki on 25-26th January 2011 [1], organized by the European Centre for Disease Prevention and Control (ECDC) and the Greek Authorities (Hellenic Centre for Disease Control and Prevention), a satellite meeting of the EU working group on blood safety and WNV took place. In this first meeting of the working group, representatives from Austria, Denmark, France, Greece, Norway and Romania were present as well as, the ECDC, the European Blood Alliance (EBA), and observers from Israel. The discussion was mainly based on a draft working document prepared by Greece, Romania and Italy.

The objective of this document is to bring together experiences of Member States, assessing and managing risks for blood safety posed by WNV infection. This document can therefore guide competent authorities, both inside and outside affected areas, in decision making on how to assess and manage this risk.

Lessons learnt from the recent outbreak of WNV infection in humans have revealed a number of outstanding issues as well as major challenges to be met as next steps.

- Implementation of Directive 2004/33/EC [2] concerning deferral of all donors from areas with ongoing WNV transmission may have an impact on the blood supply

- Establishing geographic limits of the affected areas
- Affected area definition and triggering criteria to establish blood safety measures
- Best practices for screening blood donation (i.e. Nucleic Acid testing (NAT)[3,4,5])
- Guidance for Competent Authorities on how to conduct quantitative risk assessments
- Conducting a study on the evaluation and review of the risk of WNV for blood safety in travellers returning from endemic areas
- Documentation of experiences within EU Member States on WNV outbreaks in 2010 and 2011 (publications in scientific journals) is required.

The participants agreed on the key elements of the preparedness plan, which was further developed by the group.

In the context of May 2011 meeting of the Competent Authorities a protocol of the following measures on Blood Safety and WNV for affected, adjacent and non-affected areas as well as for travellers returning from WNV endemic areas was discussed:

- Surveillance and control strategy in the EU
- Continuous risk assessment
- Use of deferral criteria
- Testing strategy (NAT) and blood component pathogen inactivation
- Post-donation information and haemovigilance
- Impact of WNV on blood supplies and measures adopted

The preparedness plan has been finalized by mid July 2011. ECDC is now pilot testing the ECDC-coordinated risk assessment tool for assessing the contamination risk to blood products from infectious diseases which was submitted for expert review after summer 2011.

An audio conference was held on 18 January 2012. The four key points that were discussed during the meeting were: the situations in which NAT screening could be

implemented; the specific situations when pathogen inactivation procedures could be applied; the definition of affected area and an area of ongoing transmission to humans and the creation of a network for the exchange of alerts with an impact on blood safety in CIRCA.

2 Background

2.1 General information on West Nile Virus disease

West Nile virus (WNV) is an arthropod-borne 50 nm enveloped RNA virus belonging to the Flaviviridae family. It was first isolated in 1937 from a human patient in the West Nile region of Uganda. WNV have since been found in various parts of North America, Africa, Australia, Central and Southern Europe, and the Middle East. WNV infection recently emerged in North America where it is now endemic.

While birds are the natural host of WNV, the virus also infects other animals (e.g. horses and dogs) as well as humans who are considered dead-end hosts. Transmission is by mosquitoes, mainly *Culex spp.*, particularly *Culex pipiens*. Human-to-human transmission is not believed to occur in natural situations.

Most human WNV infections are asymptomatic. Approximately 20% of human infections will result in a mild febrile illness (West Nile fever) for 3-6 days while severe neuro-invasive disease (West Nile Neurological Disease - WNND) is reported in less than 1% of all infected persons. The case fatality in this group of patients is around 10%. Risk factors for this form of the disease include age greater than 50 years and immuno-compromised status. Long-term sequelae exist in persons with severe disease and might include memory loss, depression, difficulty walking and weakness.

Diagnosis is based on clinical evaluation and specific laboratory tests.

The incubation period of West Nile fever is between 3 and 14 days before clinical symptoms appear. According to the available data, viraemia occurs within 1-3 days after infection and lasts 1-11 days; thus, an infected person could be viraemic prior

to symptoms occurring, or may be viraemic but have an asymptomatic infection. Seroconversion (IgM) occurs 7-8 days post-infection.

2.2 Epidemiological situation in Europe

In 1996 there was a major outbreak in Romania, since then a few sporadic cases in humans have been identified in Europe in recent years in Portugal, Spain, France, Italy, Czech Republic, Romania and Hungary, and lately in Greece, mostly between the end of July and the end of September. The epidemiological framework of WNV infection in Europe is changing (see below). In the last three years outbreaks of human cases in different European countries have been reported at the same time.

The active surveillance of target bird species (natural virus reservoir), as well as sero-prevalence studies, demonstrate that in some European countries, such as in Italy, WNV also circulates in areas not regarded as at-risk for human infection.. In fact in 2010 the virus was detected in mosquitoes and birds in the Emilia-Romagna region but no human case was reported. Human cases of WNV infection are also imported into Europe.

Phylogenetically, WN viruses are assigned to two main lineages. Lineage 1 has been identified in the majority of the outbreaks in horses and humans in Europe. Lineage 2 was identified in Hungary in birds in 2004, spreading in 2008 for the first time into eastern Austria [6,7], and in humans in Southern Russia in 2007. Recently, a new lineage 2 strain genetically close to the WNV circulating in Hungary and eastern Austria was identified in *Cx. pipiens* mosquitoes during the 2010 outbreak in Greece, indicating that, most likely, descendants of the Hungary-2004 strain spread southward to the Balkan Peninsula and reached northern Greece [1]

2.3 The current epidemiological situation

The outbreak in Greece is the largest human outbreak of WNV infection in the EU since 1996. Taken together, the scale of this outbreak, the identification of lineage 2 virus in mosquitoes in Greece, and the geographical spread of reported cases in

Romania might all indicate an unusual development in the epidemiology of the disease, with co-circulation of viral strains from the two lineages, even though the situation in Hungary and Italy appears to be stable at the moment.

The reasons behind any possible epidemiological changes in the EU area remain to be elucidated. Changing ecological parameters and climate could be involved. Unfortunately we still do not completely understand the factors that influence each stage of the complex WNV transmission cycle.

2.4 West Nile Virus disease and blood safety.

2.4.1 EU legislation

Directive 2002/98/EC of the European Parliament and the Council of 27 January 2003, sets up the standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components [8].

In terms of blood safety, all EU Member States should apply the EU Directive 2004/33/EC[2]. Annex III of this Directive establishes the eligibility criteria for donors of whole blood and blood components, including the deferral criteria. After an infectious disease, donors shall be deferred for at least two weeks following the date of full clinical recovery. However, specific deferral period should be applied to the listed infectious diseases. Regarding infection with West Nile Virus, this Directive specifies a deferral period of 28 days after leaving an area with ongoing transmission of WNV to humans.

WNV infection is a notifiable disease at EU level through Commission Decision 2007/875/EC[9]. Since 2008, there is a common case definition for WNV infection for reporting human cases at EU level to facilitate comparability of data at EU level

established by Commission Decision 2008/426/EC [11]. The criteria for the common case definition for West Nile virus are the following:

➤ **Clinical criteria:** Any person with fever OR at least one of the following two:

- Encephalitis
- Meningitis

➤ **Laboratory criteria**

Laboratory test for case confirmation

At least one of the following four:

- Isolation of WNV from blood or CSF
- Detection of WNV nucleic acid in blood or CSF
- WNV specific antibody response (IgM) in CSF— WNV IgM high titre AND detection of WNV IgG, AND confirmation by neutralisation

Laboratory test for a probable case

- WNV specific antibody response in serum

(Laboratory results need to be interpreted according to flavivirus vaccination status)

➤ **Epidemiological criteria**

At least one of the following two epidemiological links:

- Animal to human transmission (residing, having visited or having been exposed to mosquito bites in an area where WNV is endemic in horses or birds)
- Human to human transmission (vertical transmission, blood transfusion, transplants)

The Commission Decision 2008/426/EC establishes that a **confirmed case of West Nile Virus** is

any person meeting the laboratory criteria for case confirmation. This means that the clinical criteria are not taking into account for the cases confirmation therefore a human case of West Nile virus can be either asymptomatic, with fever or neuroinvasive.

2.4.2. Implementation

Enhanced surveillance in the countries currently reporting human cases could help to identify affected areas earlier in order to apply the deferral policy for blood donors. However, for other EU Member States, not experiencing WNV outbreaks, it would be opportune to ensure that blood donation screening questionnaires include questions on travel history in the previous 28 days, with a specific focus on the affected areas.

Furthermore it is an opportune moment for the interested countries to make an effort to document the steps employed to assess the risk to blood safety with the available epidemiological information, and to record the impact of implementing the EU Directive on their national blood supplies. This will assist other countries in strengthening their WNV preparedness and response plans in future transmission seasons.

The question of how to handle blood safety regarding WNV outbreaks is highly sensitive. The deferral measures that are implemented following WNV outbreaks can have a significant impact on a country's blood supply. In Hungary during the 2008 WNV outbreak, 19 WNND cases were reported from 12 counties. With the application of the Directive to this outbreak, blood donations would have been deferred from the majority of the country.

Blood safety requires the attention of a multi-sector group of stakeholders both at the national level and locally where the outbreak is occurring. These groups would include public health authorities (national and local), blood/plasma collection authorities and companies (national and local), clinical laboratories, veterinary authorities and the Institutes for Public Health Surveillance, blood donors, blood recipients and patients' associations. At the EU level, they would include DG SANCO and the ECDC without forgetting the World Health Organisation's (WHO) work in this field because there is a need to consider also neighbouring countries as well.

Before and during the implementation of control measures to ensure blood safety, the following information should be considered in the assessment:

- the potential number of donors/donations lost due to deferral;
- the impact of tourism, in terms of blood donations lost from returning travellers;
- the potential number of contaminated units due to the outbreak;
- the cost of implementing measures, including screening blood supplies, training laboratory staff and importing blood and blood components intended for transfusion;
- the geographical delineation of the affected areas;
- the need for adequate communication and information to the general population, blood donors and the recipients of blood and blood components intended for transfusion;
- whether high-risk recipients should receive selectively blood components that are ensured free of contamination;
- a continued balance of the supply of blood for patients against the impact of safety measures; and
- the need to report the outbreaks to the Commission and to other national competent authorities for blood, tissue and organ safety, to allow them to conduct their own risk assessments.

However, the decision to implement any control measures should depend on a thorough and continuous risk assessment of the epidemiological situation.

2.5 ECDC threat assessments for the European Union

Member States report human cases of WNV to the Commission through the EU Early Warning and Response System; and ECDC prepares disease risk assessment reports as stated in its mandate. ECDC undertook its first threat assessment for the EU in 2008 after human cases were reported from Romania (2 cases), Italy (3) and Hungary (14) between August and September.

This threat assessment highlighted the need for multidisciplinary approaches for risk analysis and preparedness related to clinical awareness, different case definitions,

existing diagnostic capacities, the risk of further spread in the EU and the potential impact on blood supplies.

Two other threat assessments were prepared in September 2009 and 2010 following human outbreaks in Hungary and Italy in 2009 and in Greece in 2010 [12, 13, 14].

3. Risk Assessment

3.1. Data

In order to perform a risk assessment concerning the impact of WNV on blood safety, the following multi-sector surveillance data can be used:

- a. Veterinary (entomologic, wild birds, dead-end host animals)
 - i. to obtain information regarding WNV circulation

- b. Human (WNV disease incidence)
 - i. to assess the attack rate of WNV infection in the general population
 - ii. Overall length of the outbreak

- c. Blood donor epidemiological data collected in previous seasonal outbreaks
 - i. WNV NAT tested donations in the period [3,4,5]
 - ii. WNV NAT positive donations (“attack rate” in blood donor population)
 - iii. Seroprevalence study results
 - iv. Overall length of the outbreak

3.2. Geographical risk

In this section, the structured and common terminology for areas where an Arthropod-Borne Disease (ABD) is occurring, is the one recently published by ECDC [10]. This terminology is based on the analytical revision of terms and definitions and intended to be used mainly for the implementation of measures maintaining safety and sustainability of the supply with substances of human origin.

The key point in the proposal, is that every area where the chances of transmission of an ABD (here WNV) to humans are higher than zero is factually a risk area. This statement does not measure the level of the risk. The actual risk level in an area

depends on environmental conditions, the presence of arthropod vectors and pathogen, previous ABD transmission to humans, and the disease's seasonal recurrence in the area. The ECDC terminology and classification of risk areas are shown in the text and table below.

WNV human confirmed case: any person meeting the laboratory criteria for case confirmation as per EU case definition [11].

A **risk area** is an area where individuals are exposed to the risk (which can be small or large) of being infected with a locally acquired WNV. This is a generalised use of the term 'risk area' in order to prevent the imprecision linked to this term due to its use to signify a specific level of risk in an area.

The 4 categories of risk areas are defined as following:

A **predisposed area** is a risk area where existing conditions might facilitate the transmission of WNV to humans, but the respective pathogen has not been detected.

Conditions favouring transmission are receptivity and/or vulnerability of the area. The receptivity of an area is the presence and/or spread of arthropod vectors and the existence of other ecological and climatic factors favouring WNV transmission to humans. The vulnerability of an area means the proximity to areas where WNV infection is present or a frequent influx of infected individuals or groups and/or infective arthropods.

An **imperilled area** is a risk area where WNV has been detected in vectors, or transmission of WNV to animals has been detected, or the transmission of WNV to humans has occurred previously in the last 5 years.

An **affected area** is a risk area with ongoing transmission of WNV to humans. This means that at least one case of transmission of autochthonous WNV to a human has been confirmed in the area according to the agreed, standardised and disease-specific case definition. [11]. Under exceptional circumstances, a probable case can be used to determine transmission but only in specific and agreed situations when case confirmation cannot be performed within a reasonable time.

An **endemic area** is a risk area where transmission of WNV to humans is taking place over 5 seasonal cycles.

Risk area	Criteria			
	Conditions (a)	Pathogen (b)	Transmission(c)	Recurrence (d)
No risk	-	-	-	-
Predisposed	+	-	-	-
Imperilled	+	+	-	-
Affected	+	+	+	-
Endemic	+	+	+	+

(a) Environmental conditions favouring transmission of ABD to human.

(b) Presence of the pathogen in vectors and / or animals.

(c) Transmission of ABD to human

(d) Seasonal recurrences of ABD transmissions to human

The risk for WNV transmission to humans in an area should be re-evaluated for every season.

In addition to assigning a risk, an area must be accurately determined geographically, i.e. with name, location and boundaries. This should follow the biological and epidemiological findings (surveillance of human and animal cases, field investigation etc.) but be adapted to the administrative territorial divisions in order to allow epidemiological mapping and harmonisation and to avoid misunderstanding and imprecision. In an initial rapid risk assessment, broader administrative divisions should be applied cautiously to avoid unnecessary donor deferrals. The final geographical determination of an area where a WNV risk is present is possible after an epidemiological analysis and risk assessment have been performed. For practical reasons, simplification may be necessary regarding travel advice as well as for donors of substances of human origin returning from the area of exposure.

ECDC started in June 2011 to publish weekly an update of the list of affected areas on its website available at [http://ecdc.europa.eu/en/activities/diseaseprogrammes/emerging_and_vector_borne_diseases/Pages/West Niles fever Risk Maps.aspx](http://ecdc.europa.eu/en/activities/diseaseprogrammes/emerging_and_vector_borne_diseases/Pages/West_Niles_fever_Risk_Maps.aspx).

3.3. Estimation of the risk associated with collecting blood from asymptomatic donors

Based on available data, it is possible to apply the **method** proposed by Biggerstaff & Petersen [15, 16] for assessing the average risk involved in collecting donations from viremic asymptomatic donors.

Figure. 1 Method proposed by Biggerstaff & Petersen

$$\text{Mean Risk} = \text{Incidence during the outbreak (per 100,000 population)} \times \frac{\text{Mean duration of asymptomatic viraemia (days)}}{\text{Duration of the outbreak (days)}}$$

$$\text{Mean Duration of Asymptomatic viraemia} = (P_{\text{sympto}} \times V_{\text{sympto}}) + (P_{\text{asympto}} \times V_{\text{asympto}})$$

$$P_{\text{sympto}} = \text{Proportion of symptomatic cases}$$

$$V_{\text{sympto}} = \text{Duration of viraemia in symptomatic cases (days)}$$

$$P_{\text{asympto}} = 1 - P_{\text{sympto}} = \text{Proportion of asymptomatic cases}$$

$$V_{\text{asympto}} = \text{Duration of viraemia in asymptomatic cases (days)}$$

In **Italy** a retrospective risk assessment in the affected areas carried out both in 2009 and in 2010, showing that the estimated risk of introducing viremic donations from asymptomatic donors into the blood stock was, respectively, 1.4 and 0.5-0.9 per 10,000 donations. The WNV NAT yield subsequently obtained in tested blood donors (respectively 1.5 and 0.5 per 10,000 donations) confirmed these estimates.

In **Greece** the risk of infected blood donations in the affected area of Central Macedonia for 2010 was 2.95 per 10,000. The highest frequency of viremic asymptomatic donors tested with ID-NAT was observed in August (1 per 619 blood

donations) whereas in the next month the WNV-NAT yield was 1 per 5,279 blood donations. Based on the Biggerstaff & Petersen mathematical model the estimated risk of one infected blood donation per 100,000 donations is 3.17.

In **Romania**, a calculation of the average contamination risk per 100,000 blood units collected from asymptomatic donors with viremic donations in the affected areas of Constanta, Bucuresti, Iasi and Brasov showed considerable variation ranging from 1.3 to 13.

In **France**, an alternative model for assessing the residual risk (RR) according to the window period has been proposed by Pillonel [17].

Quantitative risk assessment of blood donation contamination can contribute to guiding the implementation of preventive measures such as the introduction of blood testing.

Currently ECDC, the Transfusion Technology Assessment (TTA) Group, and Julius Centre for Health Science and Primary Care of the University Medical Centre, Utrecht, are cooperating to build a **risk estimating tool** (EUFRAT) to quantify the potential outbreaks of emerging infectious diseases (EID) including WNV and the associated risk for the recipients. The risk assessment tool portrays entities and transition phases, starting from the risk of blood donors in the affected population getting the infection up until the risk of recipients getting the infection through receiving the end blood and blood components intended for transfusion. In this tool the estimated risk outcomes are: prevalence of infection in the (donor) population, number of infected donations, number of potentially infected released components, number of potentially infected end blood and blood components intended for transfusion, risk of infection in blood and blood components recipients.

Regarding the estimation of the risk of infected donation in the affected area and in travelers returning from an affected area, the European Centre for Diseases control and Prevention published an online tool that can be found on the following link: <http://ewrstest.ecdc.europa.eu/blood/>, this tool is based on the methodology of Biggerstaff and Petersen.

4 Measures

The options for ensuring blood safety include:

- deferral of potentially exposed blood donors and discard of infectious donations;
- implementation of laboratory screening methods, such as nucleic acid testing (NAT);
- use of pathogen inactivation procedures;
- asking donors to report any symptoms after donation (enhancement of post-donation information);
- post –transfusion haemovigilance

4.1. Deferral period for blood donors

Blood collection in non-affected areas (No-Risk, Predisposed and Imperilled areas)

- Deferral of potential blood donors for a period of 28 days after leaving an affected area with ongoing transmission of WNV to humans (based on Directive 2004/33/EC)
- To provide updated maps with human cases distribution to the Blood Establishments

http://ecdc.europa.eu/en/activities/diseaseprogrammes/emerging_and_vector_borne_diseases/Pages/West_Niles_fever_Risk_Maps.aspx

Blood collection in affected and endemic areas

- Geographical donor deferral: Define a deferral season in cooperation with national public health authorities and other stakeholders for the citizens living in affected areas during the transmission season, unless WNV NAT screening is implemented as an alternative measure.

4.2. Screening strategies

WNV infection can be detected in blood donations using either Nucleic Acid Testing (NAT) or antibody based technologies. As antibodies are not detectable at the earliest stages of infection, and can persist long after the virus is cleared, NAT has been determined to be the only relevant method for primary WNV blood screening.

Two diagnostic assays bearing CE-mark and FDA approval are available for the detection of WNV-RNA by NAT. They can be performed either on mini-pools (MPs) of 6 or 8 to 16 specimens respectively for each diagnostic method, or on individual donations (IDs).

Both WNV assays are qualitative in vitro tests with high sensitivity and specificity and are able to detect lineage 1 and lineage 2 WNV.

However, pooling donations may reduce assay sensitivity and increase the possibility of missing donors with low-level viremia.

Large studies in the USA determined that if ID-NAT were implemented early in a region with a severe epidemic, 5-10% of the units detected would be MP-NAT negative but ID-NAT positive, and therefore potentially infectious[19,20].

These considerations led most US blood collection agencies to adopt a testing strategy referred to as "targeted" ID-NAT. This aimed to balance the residual risk of transfusion transmission from units screened with MP NAT against the limitations in testing capacity for performing ID-NAT.

ID-NAT would be triggered for all donations in a region upon reaching a predetermined initiation trigger, which was an absolute number of detected MP reactive donations combined with an MP-NAT detection rate of >1 per 1000 donations. Against this targeted strategy some US and European centres have decided to perform ID-NAT on all donations. Haemovigilance data in the USA, Canada and in Europe are favourable to the ID-NAT strategy. Furthermore, tail-end viremia accompanied by the presence of IgM is detectable only by ID-NAT.

Additionally, screening donor blood for WNV may be complicated by the need for the switch from mini-pool to ID screening in times of severe epidemic outbreaks.

Italy has recently conducted a study on the two CE-marked diagnostic methods for the detection of WNV-RNA by NAT in order to provide to participating testing laboratories a valuable tool for monitoring the quality of analytical performance and competence of operators. Extension of this to a European quality assessment inter-laboratory study on diagnostic methods for the detection of WNV-RNA by NAT is proposed by Italy for discussion.

Along these lines, the Reference Laboratory for Hemorrhagic Fever and Arboviruses of Aristotle University in Thessaloniki, could be networked with other European laboratories for serological and molecular combined with sequencing analysis as well as research purposes in studying other Arboviruses and other new emerging or as yet undiscovered agents that may also pose a transfusion safety risk.

4.3. Other Measures

- Persons with diagnosis of WNV infection may be accepted for blood donation 120 days after diagnosis (Guide to the Preparation, Use and Quality Assurance of Blood and Blood Components of the Council of Europe 16th Edition, 2011);
- Apply “look-back procedures” in case of confirmed or suspected post transfusion transmission for a period dating back 120 days prior to the donation that was ID-NAT reactive (FDA Guidance for industry 2009) ;
- Fever, flue like or other symptoms within 15 days after donation to be reported to blood establishments;
- Quarantine measures for blood components collected before a reported outbreak of WNV. Retrieve and quarantine blood components from prior collections dating back 120 prior to the donation that was ID-NAT reactive. (FDA Guidance for industry 2009)
- The stocks of plasma samples to be retrospectively tested.
- Implement viral inactivation procedures for platelets and plasma blood components.

4.4. Algorithm of measures for blood safety depending on the level of risk
(to be applied by the Competent Authority and the Blood Establishment)

a. Measures to ensure blood safety during the WNV season

Measures	No Risk Area/ Predisposed Area	Imperilled Area	Affected Area/ Endemic Area
1. Deferral of inhabitants	No	No	No blood collection, until NAT testing is implemented
2. Deferral of travellers who return from affected areas	28 days, unless NAT testing is performed	28 days, unless NAT testing is performed	28 days, unless NAT testing is performed
3. NAT screening for donors when a lot of travellers come back from affected areas in order to ensure the blood supply	To consider, if available	To consider, if available	Recommended, to ensure blood supply
4. NAT screening of quarantine blood collected and retrospective NAT testing of plasma samples stock	No	To consider, if available	Yes
5. Pathogen inactivation procedures (plasma and platelets)	Not necessary	To be evaluated	To be evaluated
6. Activate crisis management team (CMT) within the CA	No, unless high numbers of donors return from affected areas	Not applicable; CMT proceeds until the area becomes a free area	Yes, activate
7. Inform other MS (CA) when NAT testing is activated	Yes	Yes	Yes

4.5 Key elements of a preparedness plan

With the objective of performing a rapid response, in the event of a WNV outbreak, a set of measures and activities should be included in the national preparedness plans on WNV in order to ensure the safety and quality of the blood transfusion chain. It would be recommended that national preparedness plans are annually updated and re-evaluated.

These preparedness plans should include activities to be implemented by national competent authorities, blood establishments (BE) and other actors responsible for the safety and quality of blood and blood products. Moreover, some of the activities could also be performed at EU level to strengthen cooperation and to ensure a coordinated response.

A multidisciplinary approach is recommended and should include public health, animal health and entomologist surveillance in collaboration with the national competent authorities on blood and the haemovigilance services.

The following activities should be taken into account:

A. Activities for the National competent authorities

- Continuous quantitative risk assessment of the epidemiological situation both for autochthonous WNV cases and imported cases.
- To develop guidelines and specific contingency plans including precautionary measures to ensure blood safety and blood supply.
- To update the blood transfusion establishment list.
- Continuous assessment of the effectiveness of the communication channels with BE.
- Dissemination of WNV information to BE and feedback from BE to CA.
- Quantitative risk assessment of transfusion transmitted infection of WNV.
- To evaluate the impact of implemented measures on blood supply.
- To monitor the maps of WNV vector distribution, ECDC
- To monitor the maps of WNV human cases, ECDC
- Development of prediction models for outbreaks of WNV in different areas
- Cost-effectiveness analysis of screening tests.
- Promote research on alternative screening strategies
- Communication strategies:

- To raise awareness among doctors and healthcare institutions about the threat of WNV.
- Procedures to coordinate and to communicate clear and common messages to the general population and to specific risk groups.
- Cooperation between national public health authorities, blood transfusion services and other stakeholders (e.g. blood donor associations, epidemiological services, animal health services, entomological services, experts, researchers, patient associations, etc)
- Circulate on CIRCA platform or the system in place at that moment, the information collected from BE using the reporting template (Annex I) on implemented measures in affected areas and in non-affected areas in periods of WNV ongoing transmission to humans (Directive 2005/61/EC).

B. Activities for the blood establishments

- Establishment and continuous quality check of the Haemovigilance system (post-donation information; look-back procedures (traceability))
- Verify protocols for blood donation, and blood testing.
- Assessment of the effectiveness of the communication of information and education materials in donor population
- Optimal use of blood components and appropriate management of the blood supply to ensure self-sufficiency in affected areas and also in potentially impacted non affected areas.
- To develop and monitor the maps of WNV vector distribution. (If feasible and indicated)
- To develop and monitor the maps of WNV human cases, ECDC
- Assessment of the Implementation of the blood testing and labelling procedures.
- Implementation of precautionary measures to ensure blood safety and to ensure blood supply.
- Communication:
 - Communicate information to CA using the reporting template (Annex I) on implemented measures in affected areas and in non-affected areas

in periods of WNV ongoing transmission to humans (Directive 2005/61/EC).

C. Activities at EU level (EC, ECDC, coordination between MS)

- Continuous quantitative risk assessment of the epidemiological situation both for autochthonous WNV cases and imported cases. (ECDC)
- Guidelines and specific contingency plans with precautionary measures for blood safety.
- Quantitative risk assessment of transfusion transmitted infection of WNV (ECDC)
- Monitor Maps with vector distribution ECDC
- Monitor Maps with human cases, (if necessary)
- Development of prediction models for outbreaks of WNV in different areas
- Promote research on alternative screening strategies
- Cost-effectiveness analysis of screening tests.
- Communication strategies:
 - Procedures to coordinate and to communicate clear and common messages to the general population and to specific risk groups.
 - Cooperation with national public health authorities, blood transfusion services and other stakeholders (e.g. blood donor associations, epidemiological services, animal health services, entomological services, experts, researchers, patient associations, etc)
 - Development of an EU Rapid Alert system for the exchange of information of alerts with an impact on blood safety and consequential measures. This network should benefit from the participation of Experts from BE as well.
 - Adopt the definition of affected areas agreed in this document.

5 Further experiences with WNV and control measures for blood safety

Deferral of potentially exposed individuals is required in the European Union under Commission Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards to certain technical requirements for blood and blood components. As set out in Annex III of Directive 2004/33/EC, the deferral procedures should be consistent with the epidemiological situation and should be notified by the national Competent Authority to the European Commission with a view to Community action. Specifically for WNFV, Directive 2004/33/EC sets a minimum deferral period of 28 days after leaving an area with ongoing transmission of WNV to humans. **Nucleic acid testing (NAT)** screening procedures are universally used in the United States and Canada for screening pools of blood donations. If a pool is NAT positive for WNV, then each individual donation is tested.

In **France**, NAT will be deployed in area with notified human autochthonous cases. NAT will be used for two issues : i) in order to test retrospectively the stored blood products collected before the human case notifications and ii), in order to screen blood donations collected from donors living in the affected area..

Depending on the geographic spread of the viral transmission, pathogen inactivation procedures on blood components can be implemented on donor platelet concentrates and plasma.

In **Italy**, NAT screening techniques on blood supplies were initiated during the 2008 outbreak in order to offset the reduced blood donations available at the national level. In Israel, NAT screening was considered but not implemented due to financial limitations. Deferral procedures for ill persons continue to be implemented in Israel, although so far no post-transfusion WNV infection has been detected.

In both, **France and Italy**, an Action Plan for protecting the Blood System against the WNV was developed. It is based on a crisis management teams which have been set up with a single agency as the main coordinating body to deal specifically with blood, tissue and organ questions in the event of WNV outbreaks. They discuss the relevant epidemiological data, the quantitative risk assessment of the situation in

terms of public health, which deferral and screening measures can be implemented, and what impact these measures will have on blood supplies.

Similarly, in **Greece**, an Action Plan for protecting the Blood System against the WNV was developed. In this context, a crisis management team was set up in order to develop a communication strategy with blood services, and other stakeholders as well as the National Transplant Organization. The team also cares for the surveillance of WNV on blood donors and multi-transfused patients with thalassaemia, quantitative risk assessment and haemogilance.

The impact on the blood supply was 10% reduction in the affected areas of Central Macedonia and Larissa and less than 2% in the rest of the country.

In **Romania**, the impact of the measures on blood collection in the county of Constanta was estimated 1% decrease.

Even though the true risk to blood supplies in the EU from WNV remains low at present, political and media attention to this disease is high and it is therefore important that public health and blood authorities put in place clear communication strategies to explain the risk, both to the public and to policy makers.

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ANNEX 1. TEMPLATE FOR REPORTING BLOOD SAFETY MEASURES UNDERTAKEN.

Template for a rapid exchange of information on West Nile Virus (WNV) and Blood Safety

This document is intended to facilitate communication, information sharing and cooperation relating to blood safety and WNV at EU level. The first part is dedicated to WNV affected areas (at least 1 autochthonous WNV case). The second part concerns non affected areas in periods of WNV ongoing transmission to humans elsewhere. Please fill it and update it when appropriate. Filled document and updates should be sent to your competent authority:

Thanks for your help to maintain a safe blood supply for patients.

Country /Name and institution of the communicating person	
Date of communication / update	

Information from countries with affected area(s)

<p>Triggering criteria to share information</p> <ul style="list-style-type: none"> • One or more confirmed autochthonous WNVD case: please specify date of the 1st case; number up to now; geographic area(s). Please attach a map. • Number of positive tested blood donation in case of screening on WNV. • Other criteria (e.g. circulation of WNV in mosquitoes, bird, horses...)? If yes please specify 	
<p>Use of model (eg Biggerstaff-Petersen; Pillonel, ECDC website) for assessing the risk to collect viremic donations from asymptomatic donors in affected area(s): Y/N? If Y please specify and give the today's number of expected cases /10,000 donations (or a range)</p>	
<p>Please indicate (Y/N) the measures taken for ensuring blood safety in affected area(s) and for each date of implementation (and later suppression)</p> <ul style="list-style-type: none"> • Deferral of donor candidates (DC) 	

for 28 days <ul style="list-style-type: none"> • Cancelling blood donor sessions • Deferral of DC for 120 days after diagnosis (asymptomatic) or after recovery (symptomatic) • Fever, flue like or other symptoms within 15 days after donation to be reported • Quarantine measures for blood components collected before outbreak • Specific measures for high risk patients eg multi-transfused (please specify) • "Look-back procedures" in case of confirmed or suspected post transfusion transmission • NAT, individual/ minipool (please specify) • Pathogen reduction (please specify) • Other (please specify) 	
Impact on blood supply (please specify) When appropriate, measures taken to maintain adequate blood supply (please specify)	
Media and political communication measures / difficulties (please specify)	
Please add any information / data you deem useful	

Information from unaffected countries / unaffected area(s) in affected countries

Countries / areas considered for measures concerning travelers For each country or area please indicate date of information receipt	
Use of model (eg adapted Biggerstaff-Petersen, ECDC website) for assessing the risk to collect viremic donations from asymptomatic donors having left affected area(s): Y/N? If Y please specify and give the today's number of expected cases /10,000 donations (or a range)	
Please indicate (Y/N) the measures taken for ensuring blood safety from donors having stayed in affected	

area(s) and for each date of implementation (and later suppression)	
<ul style="list-style-type: none"> • Deferral of potential blood donors for 28 days after leaving an affected area • Other (please specify) 	
Impact on blood supply (please specify) When appropriate, measures taken to maintain adequate blood supply (please specify)	
Please add any information / data you deem useful	

Commento [r1]: Same list as affected area(s) can be used. And added dot: surveillance in (donor)population.

***Source: European Blood Alliance (EBA)**