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West Nile Virus preparedness plan to ensure safe blood components in Switzerland: a risk-based approach

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Background In 2012, the Swiss Transfusion SRC founded a working group to develop a WNV preparedness plan for Switzerland in order to deal with expanding spread of WNV epidemics in Europe.

Materials and Methods The risk estimates were computed for various presumptive incidence scenarios and brought into relation to cost estimates for the introduction of a routine WNV-NAT screening programme. The costs to prevent one case per year and the number of donations which need to be tested to detect a WNV-RNA-positive donation were calculated.

Results With a theoretical postulated incidence of one West Nile virus meningoencephalitis (WNVME) case in Switzerland per year, approximately one WNV-RNA-positive case would be detected every 11 years. With 100 WNVME cases per year, approximately 8·8 donations would be detected every year. The additional cost burden of introducing WNV-NAT in Switzerland is 2·6 million euros per year. Costs to prevent one case per year are thus between 27 million and 0·28 million euros, depending on the incidence assumption.

Due to the geographical situation in Switzerland, it was decided to determine two potential risk regions, the southern part of the country and the remaining northern part. In addition, two risk levels and respective measures were defined.

Conclusions The risk for WNV transmission through blood products is low even when 100 autochthonous WNV cases would be detected. With this in mind, the blood transfusion services and the national health authorities established a cost-efficient WNV preparedness plan to prevent WNV transfusion–transmission and maintain self-sufficiency in the blood supply.

Introduction

West Nile virus (WNV), an emerging pathogen, is an arthropod-borne 50 nm enveloped positive-sense RNA virus belonging to the Flaviviridae family [1]. WNV is found primarily in an enzootic cycle between birds and mosquitos, mainly Culex species, but as well by Aedes and Anopheles. Humans, horses and other mammals on the other hand are considered incidental or dead-end hosts [2]. The first reported human WNV case was identified in 1937 from a human patient from the West Nile region of Uganda. Worldwide, it is the most widely distributed arbovirus, indigenously found in Africa, Asia, Europe and Australia [3–6]. The course of WNV infections in humans is most commonly nonsymptomatic (80%), while other cases present with mild influenza-like symptoms, such as fever and headache. Only in rare instances (<1%) does a serious neuro-invasive disease develop (West Nile encephalitis (WNVME) or neuritis) which has a potentially fatal outcome in elderly or immunocompromised patients.

In Europe, the first human WNV case was detected in 1958 from Albania [6]. Since then, several sporadic human and/or equine WNV infections have been reported in other European regions. Most were sporadic cases confined to

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rural populations, without huge human outbreaks, and seldom were they associated with a severe neurological disease [7]. The first major European outbreak in humans was reported in Romania in 1996 [8, 9]. Further notable outbreaks in the Mediterranean basin and southern Europe were followed in Tunisia in 1997, in Russia in 1999 and in Israel in 2000 [10]. In western Europe, several sporadic equine and/or human WNV cases were reported in France, Portugal and Spain since 1962, although no major human outbreaks were observed [11, 12]. This epidemiological situation changed in 2008 when in Italy, 10 years after the last epidemic in horses, there was a major outbreak in the North which spread rapidly over eight provinces [13, 14]. There have since been many re-occurrences in Italy from 2009 onwards; and there was a large outbreak in Greece during 2010 [13].

WNV infections came to the focus of blood transfusion services primarily when, in 2002, the first case of WNV transmission through blood transfusion was reported in the USA. The first human case of WNV in the USA was previously reported 1999 in New York during a meningoencephalitis epidemic. Thereafter, the virus spread rapidly across all of North America which in turn led, in 2003, to the implementation of a routine WNV-NAT screening programme for the release of blood products by the U.S. and Canadian blood suppliers [14].

The dramatic rapid spread of WNV across USA and the policies introduced by the American blood transfusion community certainly influenced the perception and the awareness of WNV in the western hemisphere leading to enhanced research efforts in this field and the introduction of extensive WNV surveillance programmes [15–17]. In Europe, deferral policies were introduced in many countries for blood donors returning from endemic regions. The Swiss health authorities introduced similar policies in 2003 [18].

In 2006, the Swiss Federal Office of Public Health (FOPH) declared WNV infections a reportable disease. Between 2006 and 2013, two WNV cases were reported. Based on the available information, FOPH considered both cases as nonautochthonous, as both cases referred to travellers returning from Kosovo [18, 19]. Further, Switzerland has adopted the WNV-disease case definition proposed by the European Union (Commission Decision 2008/426/EC) which was implemented in 2008 to facilitate data evaluation at the EU level [20].

Different epidemiological grades (1a, 1b to 2 and 3), respective concepts and measures for increasing disease awareness, surveillance and prevention of WNV infections are described in the following documents: 'Lagebeurteilung West-Nil Fieber Januar bis November 2013' and 'Konzept zur Überwachung und Prävention von West-Nil Fieber' [21, 22]. Switzerland is considered scenario 1a country; that is, no autochthonous WNV cases as yet reported in humans, horses or (wild) birds and those human or equine/(wild) bird cases in neighbouring countries have not spread to Switzerland. However, a systematic surveillance system in Switzerland is only implemented for humans, but not for mosquitos, birds or horses. The assessment of the notified human cases is based on the availability of the information received from the physicians reporting a WNV case.

Since 2008, WNV cases in the EU are reported directly to an EU Early Warning Response System. This information is then used to prepare a yearly WNV respective risk assessment report by the European Centre for Disease Prevention and Control (ECDC) and is presented in their webpage. This information, in turn, is used as the basis for surveying the epidemiological situation for the Swiss Transfusion Swiss Red Cross (BTS SRC), the umbrella organization of the Swiss regional blood transfusion services, which is responsible for national recommendations in Switzerland. The EU deferral policy was adopted in Switzerland.

In May 2013, the BTS SRC and the board of directors of the Swiss regional blood transfusion services decided to set up a working party to propose a WNV preparedness plan. This was initiated due to imminent threat of WNV infection occurring in Switzerland because of the expanding number of regions or countries affected by WNV in Europe (Table 1), the presence of mosquitos and birds implicated in the transmission cycle in Switzerland [21] and because WNV recently became endemic in northern Italy. Particularly, the aim of the working group was to suggest a risk-based preparedness plan, taking into account a possible higher risk for the first human autochthonous WNV infection in the southern region of Switzerland (Ticino), as well as, to reflect on aspects of maintaining an adequate blood supply and the costs of the plan may entail.

Materials and methods

In May 2012, a working party from Greece, Italy, Romania and France published a report proposing a WNV preparedness plan for Europe 'West Nile Virus and Blood Safety – Introduction to a Preparedness Plan in Europe') [23]. This document provided the basis for discussions for the WNV preparedness plan for Switzerland. The Swiss working group firstly decided to perform specific risk assessment for Switzerland and then to combine calculated risk estimates with cost estimates. Once these estimates were analysed, the Swiss Federal Office of Public Health (FOPH) and Swissmedic (Swiss Health Authority for the admission of medical products and medical derivatives, including labile blood components) were

Table 1 Countries and regions affected by WNV infections between 2008 and 2014; according to ECDC[a]

	2008	2009	2010	2011	2012	2013	2014	2015
Albania				2				
Algeria					1			
Austria							1	3
Bulgaria					2			
Croatia					5	16		
Czech Republic						1		
France		1						1
Greece			262	100	161	86	15	
Hungary	19	7	19	3	17	31	11	13
Italy	3	18	5	14	50	69	24	60
Romania	2	2	57	11	14	24	23	19
Slovenia						1		
Bosnia and Herzegovina						3	13	
The Former Yugoslav Republic of Macedonia				4	6	1		
Israel				39	83	63	17	89
Kosovo					4			
Montenegro					1	4		
The Netherlands			1					
Occupied Palestinian territory					2			
Palestine							1	
Portugal								1
Russian Federation				153	447	177	29	39
Serbia					69	302	76	28
Spain			2					
Tunisia				3	63	6		
Turkey				3				
Ukraine				8	12	1		
Total	24	28	346	340	937	785	210	253
Number of affected countries	3	4	6	11	16	15	10	9

[a]Source: http://ecdc.europa.eu/en/healthtopics/west_nile_fever/West-Nile-fever-maps/Pages/historical-data.aspx (as of 10 January 2016). N.B. Historical data from 2008 to 2010 are unfortunately no longer available on the site. The data from this time period were taken from the site at that time.

brought into the decision-making process. Communication pathways were created to ensure optimal flow of relevant information between the FOPH and BTS SRC. Geographical areas within Switzerland at particular risk for WNV were defined, risk levels were proposed and options available to ensure blood safety at these risk levels were determined.

Mean risk estimates for transfusion-transmitted WNV in Switzerland

The mean risk of a WNV infectious donation per 10 000 donors in Switzerland was calculated using the model developed by Biggerstaff and colleagues (Fig. 1), a model established on the data collected from the first New York City epidemic in 1999 in conjunction with known viraemia distribution data [24].

The risk was calculated for various plausible incidence scenarios, such as 1, 2, 3, 5, 10 and 100 confirmed WNV cases per year in a population of eight million inhabitants [25].

The mean duration of asymptomatic viraemia was estimated using the data as presented in the publication; that is, for each WNV meningoencephalitis case (WNVME), there are 140 WNV-infected individuals in the population; 79% of these are not expected to develop symptoms but are viraemic for approximately 6·3 days; and those who develop symptoms are viraemic for at least 3 days before symptoms develop, which accordingly for the scenario of one autochthonous WNV case in Switzerland relates to a mean risk of 0·00268 (Fig. 1).

Cost estimates

The cost of introducing a routine nucleic acid test (NAT) screening strategy for WNV was calculated. Included in the calculation were the costs for the specific reagents, personal costs, amortization of the analysers,

$$\text{Mean risk} = \text{incidence}* \times 0{\cdot}1 \times \frac{\text{Mean duration of asymptomatic viraemia}**}{\text{Duration of the outbreak}***} = 0{\cdot}0125 \times 0{\cdot}1 \times \frac{784{\cdot}98}{365{\cdot}25} = 0{\cdot}00268$$

$$* \text{Incidence during the outbreak per } 100'000 = \frac{1}{8\ \text{Mio}} = 0{\cdot}0125$$

$$** 140 \times 0{\cdot}79 \times 6{\cdot}3 + 140 \times 0{\cdot}21 \times 3 = 784{\cdot}98 \text{ days}$$

$$*** 365{\cdot}25 \text{ days}$$

Fig. 1 Theoretical calculation of the mean risk for transfusion-transmitted WNV cases.

infrastructure and technical resources, as well as, consideration of purely a seasonal testing algorithm. These cost estimates were then expressed in relation to the costs required to prevent one WNV transmission case, taking into consideration the varying incidence rates and the number of donations required to be screened.

Decision-making at the level of the national authorities

After the risk calculations were determined and distributed to the FOPH and Swissmedic, the WNV preparedness plan working group together with the FOPH and Swissmedic began to deal with possible procedures. The aim was to increase the awareness in the blood donor population for influenza-like symptoms occurring post-donation, setting up strict deferral policies for all potentially WNV-exposed donors and to setup guidelines when and where to introduce routine WNV-NAT screening. Specific geographical regions of Switzerland at risk of WNV were defined and channels setup for the efficient and rapid flow of information between FOPH and Swiss regional blood transfusion services.

Results

The calculated mean risks for Switzerland for the different incidence scenarios are shown in Table 2.

When one autochthonous West Nile virus meningoencephalitis (WNVME) case is diagnosed in Switzerland per year, approximately one WNV-RNA-positive blood donation would be detected every 11 years. This increases in a linear fashion up to one WNV-RNA-positive donation every 40 days when 100 WNVME cases are detected yearly.

The overall estimated risk of infected blood donations per confirmed WNV infection in Switzerland with its eight million inhabitants and approximately 340 000 blood donations per year were calculated to lie around 0·09, a figure consistent with the estimate previously reported by Biggerstaff and colleagues [24].

A single WNV-NAT test costs 18 euros including reagents, personal and other overhead costs. Switzerland collects approximately 340 000 blood donations per year [26]. If the WNV-NAT is performed only seasonally during the expected WNV season from July to end of November, approximately 142 000 donations will be screened, resulting in 2·6 million euros additional costs per year. These calculations are used to extrapolate the costs incurred to prevent one WNV transmission case per year, as well as, the number of tests needed to detect a single WNV-RNA-positive donation, depending on the incidence of autochthonous WNV cases, as presented in Table 3.

Outcome of the meeting with FOPH and Swissmedic

The WNV preparedness plan elaborated by the working group in collaboration with the representatives of the national authorities is shown in Table 4. The discussions were based on the calculated risk and cost estimates

Table 2 Calculated risk estimates based on different incidences of confirmed autochthonous WNV cases in Switzerland

Incidence of WNVME per 8 million inhabitants	Mean Risk per 10 000 donations	Risk of an infectious donation in Switzerland per year (season) average 340 000 donations per year	Potential of a WNV transfusion-transmitted infection per year
1/8 million	0·00268	0·09	1/11 years
2/8 million	0·0054	0·18	1/5 years
3/8 million	0·008	0·27	1/3·7 years
5/8 million	0·013	0·46	1/2 years
10/8 million	0·026	0·8	1/1·25 years
100/8 million	0·26	8·8	1/0·11 years

Table 3 Calculated transmission per year and cost to prevent the occurrence of a positive WNV-RNA donation

WNV Incidence	Predicted transmissions per year	Cost to prevent 1 case per year[a]	Predicted number of donations screened per transmission
1/8 million	1/11 years	27	3 740 000
2/8 million	1/5 years	21·6	1 700 000
3/8 million	1/3·7 years	9·4	1 258 000
5/8 million	1/2 years	6·8	680 000
10/8 million	1/1·25 years	3·2	425 000
100/8 million	1/0·11 years	0·28	40 000

[a]Expressed in million euros.

provided by the working group of BTS SRC. Due to the natural geographical restrictions present in Switzerland, it was decided to propose two potential risk regions; Ticino, the southern region of the country below the Alps, and the remaining northern region of Switzerland. The Alps is a natural barrier, especially for the common WNV vector Aedes mosquitos. As no systematic surveillance systems for WNV-contaminated (wild-) birds and mosquitos are present in Switzerland, the FOPH relies primarily on active or suspected human WNV case reports as a trigger to inform BTS SRC. The time lag between initial viral detection and confirmation can last until 3 weeks. In addition, BTS SRC is informed on any incidental WNV cases in birds and mosquitos; however, these findings serve solely as early warning system and have no consequences. The risk estimates for WNV transmission through blood products are small, even if 100 autochthonous WNV cases would be diagnosed (Table 1). Except for Greece, most European countries have not reported such numbers. This observation led to the definition of two risk levels and respective measures for such low-risk regions.

Risk Level 1

It corresponds to the previous EU definition of an area with ongoing transmission (i.e. at least one transmission case of autochthonous WNV to a human has been confirmed in the area according to the standardized and disease-specific case definition) [22]. The Swiss preparedness plan, however, includes also transmission to horses. In level one, the blood donor population is encouraged to become actively aware of post-donation symptoms of a possible WNV infection. This recommendation is similar to the current measures in place for other potentially transfusion-transmitted diseases that are not routinely tested.

Risk Level 2

The detection of five WNV cases occurring within 4 weeks triggers the second risk level. The risk of WNV transmission through blood products when five WNV cases are detected is assumed to be comparable to the residual risk of HBV transmission calculated for Switzerland [27]. This level triggers the introduction of either countrywide WNV-NAT or WNV-NAT in a specific risk region and deferral of all donors returning from that region depending on the region the cases were detected.

Testing algorithms

The detection limit for the WNV-NAT systems used for the screening must fulfil the requirements of the Paul Ehrlich Institute (PEI). The assay may be performed in a mini-pool of six samples or individual donation approach, but 250 copies per ml in the individual donation must be achieved. Screening of all donations within one of the defined risk regions begins after five cases are confirmed within 4 weeks or in both regions as defined in the preparedness plan (Table 4). WNV-NAT screening will be stopped at the end of November if the epidemic has ceased, but can be extended. A negative test result is

Table 4 Risk-based WNV preparedness plan for the blood donor centres in Switzerland

Epidemiological situation	Measures
Single confirmed autochthonous WNV case in humans or horses in a 4-week period	Increased awareness for WNV within the donor population by the publication of posters, flyers, active information, etc. with the goal to alert the donors for possible post-donation infections
Five confirmed autochthonous WNV cases in horses/humans occurring within 4-week period in the southern part of Switzerland	1) Introduction of WNV-NAT in the southern region of the country 2) In the rest of the country: deferral of all donors for 28 days who have spent >24 h in the southern part of the country
Five confirmed autochthonous WNV cases in horses/humans occurring within 4-week period in Switzerland above the Alps	Introduction of WNV-NAT for the whole country

mandatory for the liberation of the corresponding blood components. In Switzerland, all platelet concentrates are compulsory pathogen-reduced with amotosalen and UVA, a treatment which reduces most pathogens between log 5–5·5 [28]. For this reason, apheresis platelets are not required to be screened for WNV-RNA during the epidemic.

Discussion

In Switzerland, the provision of the national donor selection guidelines and the testing algorithms and their regular update is covered by BTS SRC, in close collaboration with the regional blood transfusion services. In the light of the recent complex epidemiological WNV situation in Europe, BTS SRC and the board of directors of the regional blood centres decided to develop a strategy to deal with the probable WNV threat to Switzerland. A working party was consequently set up to formulate a written WNV preparedness plan particularly dealing with the threat to the national blood supply from autochthonous human WNV cases occurring in Switzerland. The goal of the consultations within the working party was to come up with the most cost-efficient approach to prevent WNV transmission through blood transfusion while maintaining self-sufficiency in the blood supply. The plan was approved by the board of directors of BTS SRC in May 2014, a year after the working party was assembled. The plan came up with a strategy in two distinct risk levels: firstly, the occurrence of the first autochthonous case in Switzerland as a trigger to activate increased post-donation awareness among donors of a potentially mild WNV infection symptoms; and secondly, after the identification of five autochthonous cases within 4 weeks as a trigger to implement a routine WNV-NAT screening of all donors.

The peak of the European WNV awareness occurred in 2012 (Table 1). The number of WNV confirmed cases and affected countries within the EU and neighbouring regions has since decreased. This observation was not taken into consideration in formulating the plan for the following reasons: during this period, Italy, and particularly northern region adjoining Ticino, constantly reported new WNV infections; furthermore, the reported cases represent only a small proportion of WNV infections in the population since most are asymptomatic or present with mild flu-like symptoms, thus making predictions where the next case will occur challenging. This situation was highlighted by the transfusion-transmitted WNV case that was reported in Vienna, Austria, during 2014, which is the first published European case of a WNV transmission through blood transfusion [29].

A major stumbling block which the working party dealt with was what would be an acceptable risk and to which cost. For instance, is it reasonable to implement systematic WNV-NAT testing after the occurrence of a single human autochthonous WNV case, or perhaps should the WNV-NAT screen begin even after a single equine autochthonous WNV case? The risk of transmitting WNV by transfusion in Switzerland based on the data submitted to the Biggerstaff and Peterson model is currently very low, but will increase with a greater incidence in the population [24]. To define the threshold to implement WNV-NAT screening, the residual risk of transfusion-transmitted HBV infection occurring in Switzerland was chosen. HBV was particularly preferred because it represents the current highest residual risk of the compulsory NAT-screened transfusion-transmitted viruses. The theoretically calculated residual risk for HBV is currently estimated to be around 1:600 000 in Switzerland. This residual risk was then extrapolated for potential WNV autochthonous cases [27]. The choice of using residual risk level of HBV as acceptable trigger for the implementation of WNV-NAT testing is a pragmatic approach without respecting epidemiology, severity or clinical significance of the two viruses.

The risk to acquire WNV infection during an ongoing epidemic is considered to be higher from a mosquito bite than through blood transfusion. As mainly older and immunocompromised blood recipients are at risk to develop symptoms after transfusion, a selective testing for these patients was considered but rejected due to the lack of practicability within the blood transfusion services.

WNV-NAT screening has been in place in the USA since 2003 as a consequence of the high-risk levels reported from the USA epidemic which began in 2002 (i.e. 1·46–21·33 transmissions/10 000 transfusions and an incidence between 2·79 and 10·71 WNV infections/10 000 individuals [24]. The risks for WNV calculated from this USA epidemic were believed to be between 200–2000 times higher than those for HBV, HIV and HCV, respectively [24]. In Europe, lower risk levels have been described. For instance, in Italy and Greece between 1·4 and 3·17 transmissions/10 000 donations were reported, with an incidence between 0·5 and 0·9 WNV infections/10 000 individuals. The EU Directive 2004/33/EC proposes to implement a WNV-NAT screen after a single autochthonous WNV case in humans within a distinct region. Based on the low-risk calculations for Switzerland, the preparedness plan defined, in contrast to the EU Directive 2004/33/EC, to implement WNV-NAT screening not after a single autochthonous WNV case in humans, but the fifth autochthonous case. Furthermore, the trigger to screen requires five cases to be detected within a 4-week period. Moreover, the model does not take into account for higher risks in specific geographical regions

of Switzerland, as the risk calculations included data from the whole of the country. It was thus argued that because Ticino has a higher risk than the rest of the country, a two-tiered strategy (i.e. below and above the Alps) should be incorporated into the plan. Thus, if the five cases are found below the Alps, the WNV-NAT screening is to be begun in this region only, whereas the rest of Switzerland would introduce a 28-day-deferral policy of all donors returning from Ticino.

It is noteworthy to mention that policy to defer all blood donors returning from a WNV risk area outside Switzerland with proven ongoing transmission for 28 days is maintained despite the adoption of the prepared plan. However, the BTS SRC proposes when the deferral policy jeopardizes the blood supply, for instance when too many donors are deferred, WNV-NAT screening should be introduced regardless of the occurrence of autochthonous WNV cases. This may particularly important in Ticino where many people commute to-and-from the northern regions in Italy.

In summary, a WNV preparedness plan is presented with the aim of preventing potential TTM WNV cases in Switzerland. The plan, recommended by the Swiss BTS SRC, defines measures to deal with two different WNV risk levels proposed within the country. This two component plan was approved by the Swiss health authorities FOPH and Swissmedic.

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Conflict of interests

None of the authors has received a grant, speakers fees or similar remunerations from a commercial body within the last 2 years.

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