Assessing the risk of blood donations in metropolitan France being infected with the Zika virus after sexual contamination, linked to travelers returning from an area affected by this virus (South America, Central America and the Caribbean)

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Introduction

Many countries are currently affected by the Zika virus in South America, Central America and the Caribbean, and to a lesser extent, countries in Asia, Africa, and the Pacific [1]. This virus is mainly transmitted by mosquitoes but may also be spread, albeit much more rarely, through sexual relations, maternal-fetal transmission. Furthermore it is very likely that transmission can occur through blood transfusions [1,2]. To date, several cases of sexual transmission have been published worldwide, all from infected male partners to a female or male partner [2-4]. In one published instance, sexual intercourse occurred only before the onset of symptoms [5]. The virus has been found in semen up to 62 days after onset of symptoms [2]. In France, to date, 5 cases of sexual transmission have been identified, all from infected male partners.

Although a deferral policy for prospective donors was implemented in France to prevent transmission of the Zika virus through transfusion (people returning from an endemic area are excluded for 28 days from donating blood), it does not cover the risk linked to a female donor who has not travelled to an endemic area, but who contracts the virus through sexual intercourse with a male partner returning from such an area.

Assessing the risk of a blood donation being infected with Zika after sexual transmission of the virus, in metropolitan France in 2016

In this assessment, the risk of contamination of a blood donation corresponds to the probability of taking blood from a prospective donor who has been infected through sexual intercourse, while he/she is viremic but shows no symptoms at the time of donation. We considered that symptomatic subjects will not go to give their blood after the onset of symptoms, or if they do go to give blood, they will be excluded at the pre-donation clinical selection stage.

Furthermore, we only took into account sexual transmission of the Zika virus from a man to a woman. Sexual transmission between men was not considered, since MSM are currently permanently excluded from making blood donations. From 10th July 2016, this ban will change to a deferral period of 12 months, which is much longer than the period the Zika virus has been documented in semen.

Given the many uncertainties surrounding the parameters used in this particular assessment of risk, we decided to use two types of estimation of incidence in travelers returning from affected areas (South America, Central America and the Caribbean), the first providing a maximum estimated risk, and the second a minimum estimated risk.

For the maximum estimate scenario (MAX), as a starting point for the estimation we used the proportion of donations which were positive for Zika RNA in blood donors screened in Martinique using individual-donation Nucleic Acid Testing (RealStar® the Zika virus RT-PCR 1.1 kit (Altona Diagnostics)) with an analytical sensitivity evaluated at 140 copies / ml for a 90% detection threshold. Between 19th January and 18th April 2016, of a total of 2,642 blood donations tested, 42 were positive for Zika RNA, that is 1.6% (0.9% in January, 1.7% in February, 1.4% in March and 2.1% in April) [6]. We used this proportion of 1.6% to estimate the daily incidence of Zika infection, applying it to all countries affected by the virus in South America, Central America and the Caribbean. It must be noted that this estimate was assessed during the epidemic phase in Martinique. Accordingly, it is too high in relation to the entire period covered by the estimate (January-December 2016) and to the combined area at risk (end of the epidemic or less intense transmission in some countries).This is why it constitutes a maximum estimate scenario.

For the minimum estimate scenario (MIN), as a starting point, we used the number of men aged 15 and over who contracted Zika after a trip to an affected area. More precisely, this is the number of imported cases in France reported to the French Public Health Agency between 1st February and 30th April, 2016, constituting a total of 88 men. Although we corrected that number to account for the fact that these 88 were all symptomatic cases (80% of people infected by Zika are assumed to be asymptomatic) the total number of cases obtained does not adequately reflect the total number of cases in France, because only symptomatic men who were seen by a doctor and whose infection was confirmed by laboratory tests were taken into account.

- **The hypotheses used in both scenarios:**

- 80% of people infected by Zika are asymptomatic.
- The duration of viremia in the blood is 7 days regardless of the presence or not of symptoms. In symptomatic patients, the duration of viremia prior to the onset of symptoms is 2 days
- Every man aged 15 or more infected with Zika has sexual relations with a woman in France, after returning from an affected area.
- The cumulative risk of sexual transmission from a man to a woman is 10% [1]
- The percentage of asymptomatic women infected with the Zika virus who give blood is the same as that for all women in France.
- The average monthly number of travelers returning from affected areas over the period February to April 2016 is the same as that for all the other months of the year.
- The number of travelers infected with Zika following a trip to an affected area other than South America, Central America or the Caribbean is negligible due to the more sporadic transmission of the virus and / or the low number of travelers.

[1] Cumulative risk of 10% used by blood transfusion establishments in Australia (Australian Red Cross), the Netherlands (Sanquin), the UK (UKBTS) and Canada (Canadian Blood Service) and to carry out similar Zika risk assessments

- **MAX scenario :**

Table 1 shows the assessment of risk, step by step, for this scenario.

The proportion of Zika RNA positive donations observed in donors in Martinique (line A) was corrected to reflect the fact that only asymptomatic prospective donors give blood (line B). After taking into account an average viremia duration in the blood of seven days, the daily incidence of infection by the Zika virus was estimated at 0.28% in Martinique (line D). Applying this value to the countries in South America, Central America and the Caribbean currently affected by Zika, and assuming an average stay of 16 days in these areas for people living in France traveling to these countries [7], the probability of being infected with Zika, during a stay in endemic areas was estimated at 4.6 % (line F).

Using data from the United Nations World Tourism Organization (UNWTO) and the French National Institute of Statistics and Economic Studies (INSEE), the number of travelers in the countries of South America, Central America and the Caribbean affected by Zika was estimated at 2.3 million over one year [8-11]. Assuming that half of these travelers are male, the number of infected men in 2016 was estimated at 52 362 (line I) and *in fine* the number of women infected through sexual relations would be 5 236 (line L). Considering that 3.6% of the latter would give blood in 2016, the number of Zika-infected donor women would be 191, corresponding to 344 potential donations (line O).

The likelihood of these donations occurring during the viremic phase was estimated at 0.0153 in asymptomatic female blood donors (P line) and 0.0011 in symptomatic female donors before the onset of symptoms (line Q).

The number of blood donations, in 2016, infected with Zika after sexual transmission was estimated in this MAX scenario at 5.6 in 2016 (line R), which corresponds to 1 in 490 000 donations (line T).

As the main objective is to prevent the occurrence of embryopathies after infection through a blood transfusion during pregnancy, we also estimated the risk of an infected donation being used in this circumstance. Based on 0.1% labile blood products (LBP) being specifically provided to pregnant women before the peripartum period birth [12 and French Blood Establishment (EFS) data] and assuming that two LBP are produced on average from a single blood donation [EFS data], 1 Zika-infected donation would be used in a transfusion to a pregnant woman every 90 years (0.011 donations per year) in the MAX scenario.

Table 1: Assessment of the risk of a blood donation being infected with Zika after sexual transmission in metropolitan France in 2016 - Scenario MAX –

Steps	Description	Value	Calculation, source and/or hypothesis
A	Proportion of Zika RNA-positive blood donations among donors in Martinique	1.6%	French Blood Establishment (EFS) source: Blood donation rates of zika RNA-pos. between 19th January 2016 and 18th April 2016 in Martinique
B	Proportion of Zika RNA-positive individuals in Martinique taking into account the fact that symptomatic persons do not give blood	2.0%	= [(1,6+0,4)/100,4] * 100 Hyp: 20% of infected people are symptomatic
C	Average duration of viremia in blood (days)	7	Source: [1,2]
D	Daily Incidence of Zika infection in Martinique	0.28%	= B / C
E	Average length of stay (days) in a country in South America, Central America or the Caribbean by persons living in France *	16	Source: Directorate General for enterprise -page 4 of the DGE n°45 July 2015
F	Probability of infection during a stay in a Zika-affected area	4.6%	= D x E Hyp: this probability, calculated from data from Martinique, is the same throughout all the areas infected with Zika
G	Number of French travelers in South America, Central America and the Caribbean ** (Zika affected area)	2 300 000	United Nations World Tourism Organisation and National Institute of Statistics and Economic Studies (INSEE)
H	Men having traveled in South America, Central America or the Caribbean	1 150 000	= G / 2
I	Men having traveled in South America, Central America or the Caribbean who were infected	52 362	= F x H
J	Women having sexual relations with a man infected with Zika	52 362	Hyp: 100% of infected men have sexual relations with women in metropolitan France
K	Probability of a woman being infected by sexual transmission	10.0%	Source: Sanquin, UKBTS, Canadian Blood Service, Australian Red Cross ***
L	Number of women infected by sexual transmission in 2016	5 236	= J x K
M	Proportion of women who give blood	3.6%	EFS data 2014
N	Number of female blood donors infected with Zika by sexual transmission in 2016	191	= L x M Hyp: the rate of blood donations by women infected with Zika (asymptomatic) is the same as that for all female donors in France
O	Number of donations from infected women in 2016	344	EFS data source: female donors give blood on average 1.8 times per year
P	Probability that donation occurs during the viremic and asymptomatic phase in asymptomatic donors	0.0153	= (7/365)*0,80 Hyp: 80% of infected persons are asymptomatic
Q	Probability that the donation occurs during the viremic and asymptomatic phase in symptomatic donors	0.0011	= (2/365)*0,20 Hyp: 20% are asymptomatic and the duration of viremia prior to onset of symptoms is 2 days
R	**Total Zika-infected donations after sexual contamination in 2016**	**5.6**	**= O x (P+Q)**
S	Number of blood donations in France	2 760 422	EFS data source: number of donations in 2014
T	**Risk of a blood donation being infected with Zika after sexual contamination**	**2.0456E-06**	**Or 1 in 490 000 donations**

* 15.6 days in America and 16.9 days in French Overseas Departments

** Bahamas, Belize, Bolivia , Brazil, Colombia , Costa Rica, Dominica Republican , Ecuador, Guadeloupe , Guatemala, Guyana , Haiti, Honduras, Jamaica , Martinique , Mexico, Nicaragua , Panama, Paraguay , Peru, El Salvador , Surinam , Venezuela

*** Cumulative risk of 10% used by the blood transfusion establishments in Australia, the Netherlands, the United Kingdom and Canada to carry out risk assessment of sexually acquired Zika infection among their blood donor population

- **MIN scenario :**

Table 2 shows the assessment of risk, step by step, for this scenario.

The only difference from Table 1 concerns lines A, B and C. The calculations for lines J to V are identical to those in Table 1.

A total of 88 men aged 15 and over contracted the Zika virus after a trip to an area affected by the virus and were reported to the French Public Health Agency between 1st February and 30th April, 2016 (line A). This number was corrected to reflect the fact that these 88 were symptomatic cases: the number of men infected during this period was estimated at 440 (line B), or 2 220 men for the whole year (line C). According to the same calculations as those in Table 1, the number of women infected through sexual relations equaled 220 in this scenario (line L). Considering that 3.6% of the latter would give blood in 2016, the number of women donating Zika-infected blood equaled 8, corresponding to 14 potential blood donations (line O).

As in Table 1, the probability that these donations occur during the viremic phase was estimated at 0.0153 in asymptomatic female blood donors (line P) and 0.0011 in symptomatic female donors before the onset of symptoms (line Q).

The number of Zika-infected blood donations after sexual contamination was estimated in the MIN scenario at 0.24 donations in 2016 (line R), which corresponds to 1 in 11 600 000 donations (line T).

Based on 0.1% labile blood products (LBP) being specifically provided to pregnant women before the peripartum period birth [12 and French Blood Service (EFS) data] and assuming that two LBP are produced on average from a single blood donation [EFS data], 1 Zika-infected donation would be used in a transfusion to a pregnant woman every 2 100 years (0.00047 donations per year) in the MIN scenario.

Table 2: Assessment of the risk of a blood donation being infected with Zika after sexual transmission in metropolitan France in 2016 - Scenario MIN –

Steps	Description	Value	Calculation, source and/or hypothesis
A	Number of (symptomatic) men infected with Zika during a trip in South America, Central America or the Caribbean: February-April 2016	88	Source: The French Public Health Agency: imported cases from area affected by Zika virus between 01/02/2016 and 30/04/2016
B	Total number of infected men: February 2016 - April 2016	440	= A x 5 Hyp: 80% of persons are asymptomatic
C	Total number of men infected with Zika virus in 2016	2 200	= B x 4
J	Women having sexual relations with a man infected with Zika	2 200	Hyp: 100% of infected men have sexual relations with women in metropolitan France
K	Probability of a woman being infected by sexual transmission	10.0%	Source: Sanquin, UKBTS, Canadian Blood Service, Australian Red Cross *
L	Number of women infected by sexual transmission in 2016	220	= J x K
M	Proportion of women who give blood	3.6%	EFS data 2014
N	Number of female blood donors infected with Zika by sexual transmission in 2016	8	= L x M Hyp: the rate of blood donations by women infected with Zika (asymptomatic) is the same as that for all female donors in France
O	Number of donations from infected women in 2016	14	EFS data source: female donors give blood on average 1.8 times per year
P	Probability that donation occurs during the viremic and asymptomatic phase in asymptomatic donors	0.0153	= (7/365)*0,80 Hyp: 80% of infected persons are asymptomatic
Q	Probability that the donation occurs during the viremic and asymptomatic phase in symptomatic donors	0.0011	= (2/365)*0,20 Hyp: 20% are asymptomatic and the duration of viremia prior to onset of symptoms is 2 days
R	**Total Zika-infected donations after sexual contamination in 2016**	**0.24**	**= O x (P+Q)**
S	Number of blood donations in France	2 760 422	EFS data source: number of donations in 2014
T	**Risk of a blood donation being infected with Zika after sexual contamination**	**8.59469E-08**	**or 1 in 11 600 000 donations**

* Cumulative risk of 10% used by the blood transfusion establishments in Australia, the Netherlands, the United Kingdom and Canada to carry out similar risk assessment of sexually acquired Zika infection among their blood donor population

Discussion – Conclusion:

The risk of a blood donation being infected by the Zika virus in metropolitan France after sexual contamination, by travelers returning from an area affected area (South America, Central America and the Caribbean) is low. More specifically, according to our 2 scenarios, this risk is between 1 in 11 600 000 and 1 in 490 000 donations, which corresponds to between 1 infected donation every 4 years and 5.6 infected donations every year.

These estimates provide an order of magnitude but the level of uncertainty is very high, as some parameters are still not well understood.

The main source of uncertainty is the incidence of Zika virus infection in travelers returning from affected countries. For the present analysis, the ideal situation would have been to have the incidence rate for each of the countries concerned. Each value would then have been applied to travelers returning from each of these countries to obtain a value for the number of men infected per country. As these incidence rates are not available, we used two data sources: the proportion of blood donations positive for Zika RNA, from donors screened between 19th January and 18th April 2016 in Martinique to estimate the daily incidence (which we applied to all travelers returning from all the areas affected by the Zika virus (MAX scenario)), and the reported number of men with confirmed infection returning to France following a trip to an affected area (MIN scenario).

Using the proportion of Zika RNA-positive donations from Martinique blood donors overestimates the real incidence, as in most affected countries either the peak of the epidemic has not arrived yet (for example Mexico) or it has already passed (northern Brazil in particular). One element which enabled us to confirm this overestimation is the distribution of imported cases of Zika in France. Only 6% of these cases were people returning from Brazil, and none from Mexico, while 70% were travelers returning from Martinique, despite the number of travelers to each of these two countries being approximately 3 times lower (200 000 per year) than the number traveling to Martinique (600,000 per year).

Conversely, the MIN scenario underestimates the number of infected travelers returning from affected areas, as only men who were seen by a doctor and whose infection was confirmed by laboratory tests were taken into account.

Another major source of uncertainty is the risk of sexually transmitted Zika infections: no data exist to estimate this risk, either for a singular sexual relation or for a period of repeated sexual intercourse. We therefore used a cumulative risk estimate of 10 %, considered a maximum, as this was the value chosen by the blood transfusion establishments in Australia, the Netherlands, the United Kingdom and Canada, and to carry out their own risk assessment of sexually acquired Zika infection among their blood donor populations [13,14]. A sensitivity analysis, performed for the MIN scenario showed that varying the rate of sexual transmission from 1% to 20% would increase the risk of a blood donation being infected after sexual contamination from 1 in 116 million to 1 in 6 million donations, highlighting the strong impact of this parameter on our estimates.

A further limitation of this study is that our estimates assume that men returning from their stay in an area affected by Zika, have only had sexual relations with one partner. In a sexual behaviour survey in France in 2006, 12% of heterosexual men had had at least two sexual partners in the previous 12 months [15]. Nevertheless, this fact would only increase the risk that a blood donation is infected with Zika after sexual transmission by approximately 10%. Moreover, we did not take into account the fact that in the same survey only 8.5 % of men had had no partner in the previous 12 months.

Finally, our estimates do not take into account the fact that a likely non-negligible proportion of men are accompanied by their female sexual partner during their travel in an affected area. One can assume that their partner would have the same risk of becoming infected through vector-borne transmission. She would then be immunized once the blood donation deferral period of 28 days after the return from travel was over, and would no longer be susceptible to sexual transmission. The real risk would therefore be lower than our estimates.

In conclusion, the risk of a blood donation being infected by the Zika virus in metropolitan France, after sexual transmission, is very low. Moreover, the risk that such a donation would be used for transfusion to a pregnant woman is even lower. If we focus only on donated blood used for transfusion during pregnancy, not including the time around childbirth, we find that one infected donation every 90 to 2100 years would be used.

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